DNA-BASED POPULATION SCREENING FOR PRECISION PUBLIC HEALTH

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DNA-BASED POPULATION SCREENING FOR PRECISION PUBLIC HEALTH

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Editorial: DNA-based population screening for precision public health

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DNA, population screening, precision public health, health equity, implementation science, genome sequencing, expanded newborn screening

Editorial on the Research Topic
DNA-based population screening for precision public health

Introduction

Rapid advances, increasing availability, decreasing costs of sequencing technologies, computational pipelines for variant interpretation, and training of clinical personnel, are accelerating the integration of genomic sequencing into routine health care.

Although genomic sequencing has demonstrated utility as an indication-based diagnostic tool for certain diseases, the full potential of DNA sequencing as a non-diagnostic tool for population-level screening is not yet realized. DNA-based population screening has enormous potential to identify people with underlying genetic predisposition to serious diseases such as cancer and heart disease, who represent 1–2% of the population (Murray et al., 2020). Early detection, disease prevention, and timely treatment can improve health outcomes and equity, and usher in a new era of precision public health (Khoury et al., 2018a).

Nevertheless, the ascertainment of otherwise apparently healthy individuals with underlying genetic risk will necessitate a departure from the traditional model of familial or personal risk-based genetic testing in specialty settings to a population-based model of screening in primary care or community settings (Bean et al., 2021). Additionally, adoption of a population-level genomic screening strategy requires dismantling barriers to equitably enact such an approach in the context of clinical care, design and conduct, to develop a sufficient evidence base for clinical utility and cost-effectiveness (Roberts et al., 2019).

Given the low frequency of individuals with a heritable genetic risk, sharing of study methods and data from evidence-gathering pilot studies are needed to foster collaborative linkage of observations and outcomes to address these gaps (Khoury et al., 2018b). With

the ever-increasing number of settings carrying out DNA-based screening, this Research Topic of the journal commissioned articles to highlight the breadth of perspectives and approaches that comprise the current state of knowledge about DNA-based population screening, including genome sequencing data and interpretation, data governance and stewardship issues, stakeholder engagement, patient and provider education, and clinical outcomes from ongoing clinical and research programs in a variety of settings.

Utilizing implementation science frameworks

DNA-based population screening is increasingly viewed through the lens of implementation science methods and frameworks (Bangash and Kullo, 2020). Use of rigorous methods to mitigate barriers to equitable uptake, evaluation of the impact on providers and health systems, and aggregation and sharing of patient health outcome data are increasingly relied upon to support the translation of effective DNA-based screening practices into routine clinical care to improve public health.

In this Research Topic of the journal, (Wildin et al.) describes feasibility testing of the Genomic Population Health Pilot Program within the University of Vermont Health Network using the well-known Consolidated Framework for Implementation Research (CFIR). The article details the barriers to and facilitators of this unique program that was among the first non-research DNA-based screening pilots. (Jones et al.) detail the use of the RE-AIM implementation science framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) to conduct separate pragmatic program evaluations of two different Geisinger DNA screening pilots, the MyCode community health research program and a primary care clinical DNA screening pilot, based on their most relevant and informative domains.

The systematic review by (Shen et al.) of multi-level barriers, facilitators, stakeholder perceptions, and outcomes of implementing DNA-based population screening supports the need for more research to address significant barriers to health equity, ethical, legal, and social implications (ELSI), readiness for implementation in primary care, and evidence gaps regarding clinical utility and long-term outcomes. Emphasis on the development of metrics for the collection and sharing of aggregated patient, health service, and intervention outcomes is critically important for evaluating the public health impact and cost-effectiveness of DNA-based population screening.

Maximizing clinical utility

Currently available evidence does not provide support for the widespread use of predictive genomic screening in healthy populations. Thus, an inherent challenge for DNA-based population screening programs is determining which disease-causing genes and genomic variants to screen for to maximize clinical utility and minimize undue harms to healthy individuals. Incomplete penetrance and variable expressivity of genetic variants can result in a broad spectrum of phenotypes, from subclinical manifestations to severe disease, even among relatives harboring the same disease-causing genotypes. Our current understanding of the natural history of many genetic diseases is based on small cohorts of clinically diagnosed individuals, which raises valid concerns about overdiagnosis and overtreatment in unselected populations. (Kingdom and Wright) address this urgent need for a broader genotype-based understanding of risk identification with a comprehensive review of emerging clinical studies of common and rare genetic variation and its effect on human diseases.

Longitudinal data from clinical cases with positive results are also needed to reclassify potential pathogenic variants and link successful standards of clinical care to ascertainment by population-scale implementation of DNA-based screening. The work of (Wilhelm et al.) illustrates the value of combining longitudinal health information from follow-up genetic testing of screen-positive newborns with accompanying clinical information to inform genotype-phenotype correlations and reevaluate the clinical relevance of genetic variant data. (Ashenhurst et al.) highlight the predictive utility and complementarity of polygenic scores combined with other types of screening data such as family health histories, for providing an earlier and more precise diagnosis in high-risk individuals.

Cascade screening in blood relatives for a variant that confers an inherited disease predisposition is an important and cost-effective strategy for identifying and improving health outcomes of other at-risk individuals; however, there are substantial barriers to widespread acceptance of this beneficial process. In their manuscript (Schmidlen et al.) describe the impact of a proband indication on the uptake of cascade testing by family members based on two settings, one in which the proband has a clinical condition and presents for testing in a diagnostic setting as well as a non-diagnostic scenario where the proband was detected *via* proactive screening. (Haas et al.) evaluate whether an alternative approach to population genomic screening—automated sharing of family health history *via* the electronic health record (EHR)—offers an efficient and cost-saving method to facilitate cascade testing.

Understanding public perceptions and values

Understanding the factors that affect public interest in participating in genomic research will ultimately support informed decision-making and minimize enrollment barriers in clinical offerings. (Roberts et al.) observe an association between awareness of genetic testing and educational attainment level and public interest in participating in genomic screening to learn about inherited predisposition to cancer. (Kaphingst et al.) investigate about whether offering genomic screening as part of routine health visits would stimulate interest and participation by ethnically diverse young women. (Brown et al.) explore the perceptions of parents who belong to underrepresented groups in genomic research in making an urgent and difficult choice about whether to enroll in the prenatal arm of the California-based Program in Prenatal and Pediatric Genome Sequencing (P3EGS), part of the Clinical Sequencing Evidence-Generating Research (CSER) consortium. Building on this work, (Outram et al.) reports on the expectations of the parents who ultimately did decide to enroll in the P3EGS study and the subsequent value to them of the prenatal genomic sequencing results they received.

Prioritizing health equity in population screening

As (Azriel et al.) note in their article, the implementation of any health care innovation is generally accompanied by concerns about adequate reach and representation of medically underserved individuals. DNA-based population screening is subject to these concerns due to stark inequities posed by numerous barriers at the patient, provider, and policy levels. However, if the implementation of DNA-based population screening can be effectively moored to public health screening frameworks and community partnerships that center equity and justice as Azriel et al. describe, there is tremendous potential to improve outcomes for all individuals with inherited predispositions to certain actionable medical conditions, add to our knowledge base about the natural history and spectrum of disease in underrepresented populations, and potentially reduce the access gap to clinical and genetic services. In the article by (Powell et al.), a collaborative team of parents and researchers illustrate the development of a bidirectional partnership in which community stakeholders are integrated in the design, implementation, and dissemination of knowledge throughout the lifespan of the Age-Based Genomic Screening (ABGS) project. Engagement marketing concepts can foster these types of trust-based relationships with communities that have been historically marginalized in biomedical research to ensure that health disparities are not perpetuated in DNA-based population screening programs, as (Lewis et al.) describe from their engagement experiences with the *All of Us* program. (Rahimzadeh V. et al.) share a protocol for understanding public beliefs and values about stewardship of cloud-based human genomic data that can help to assuage concerns about data access and privacy.

Expanding newborn screening to include genomic screening

Newborn screening (NBS) is a highly successful public health screening program for which early detection and effective interventions have resulted in established health benefits over many decades. Implementing DNA-based screening could significantly expand the number of conditions that NBS could screen for, and the gap between enhanced diagnostic capability and available, effective treatments is rapidly closing. However, effective and equitable implementation of expanded NBS incurs an even higher burden of evidence than screening healthy adults. (Armstrong et al.) examines the perspectives of parents of healthy newborns in the BabySeq Project who were surveyed about various aspects of newborn genome sequencing, including whether it should be state-mandated and accompanied by informed consent, and the return of different types of genetic information. (Brower et al., 2022) reports findings from the NBS Expansion Study and (Chan et al.) highlights opportunities for modeling to address the challenges of accelerating the process of adjudicating candidate conditions. (Pichini et al.) describe the development of an ethics- and engagement-informed Genomics England-sponsored Newborn Genomes Program to explore the utility of offering whole genome sequencing (WGS) in the newborn period.

Addressing informed consent, education, and ELSI for expanded genomic NBS

Despite the expected benefit of rapidly emerging new therapies and the critical importance of early initiation of treatment for maximizing health benefits, widespread clinical integration of expanded genomic NBS has been effectively stalled due to substantial ethical, social, and practical challenges inherent in sequencing newborns. Historically, NBS has employed an "opt-out" model of consent due to its vast public health importance; however, expanding NBS by hundreds of conditions will concomitantly expand the range, relevance, and recommendations for the results parents might receive and will likely require parents to "opt-in" to expanded genomic NBS. This paradigm shift will entail educating parents on a broad array of relatively complex topics in preparation for informed decision-making and consent. Health care practitioners will require education and innovative resources for facilitating informed

decision-making, parental consent and return of results. (Peay et al.) describe the development and evaluation of an electronic and patient-centered education and informed consent approach for the large-scale expanded NBS Early Check study. (Rahimzadeh V. et al.) balance the potential benefits against the possible harms in their assessment of unresolved challenges associated with using universal sequencing as a methodology for population screening of newborns. (Spencer and Fullerton) explore the ethical rationale for coinciding age of screening implementation for highly actionable genetic conditions with the age of maximum clinical utility in the general population.

Building effective governance and infrastructure

DNA-based population screening has the potential to transform the practice of health care from reactively treating disease symptoms to proactively identifying at-risk individuals in the population and delivering precision care to prevent the onset of disease. Encapsulated in this Research Topic are articles describing broad advancement in research and clinical integration of DNA-based population screening. Creating and utilizing effective infrastructure to translate research to clinical practice remains crucial to realizing actual improvements in public health. The EHR features prominently in patient-centered healthcare as an important data tool for sharing results between providers and patients, monitoring clinical follow up, and, more recently, providing passive and active clinical decision support. (Elhanan et al.) describe barriers to relevant clinical action following the delivery by the Healthy Nevada Program of important genetic findings directly into participants' EHR and proposes potential solutions centered on providing additional education and support for healthcare providers.

Advances in EHR functionality notwithstanding, the necessary infrastructure to enable learning healthcare systems remains elusive. Fertile settings for discussion and problem solving are needed to harmonize collection, analysis, and reporting of data and outcomes. The National Human Genome Research Institute's Genomic Medicine XIV virtual meeting entitled; "Genomic Learning Healthcare Systems" provides promising support for priority research areas. (Roberts et al.) highlight outcomes from *The Transdisciplinary Conference for Future Leaders in Precision Public Health,* a participatory forum to accelerate solutions for precision public health challenges. Finally, (Onstwedder et al.) summarize necessary translational improvements required in practice and policymaking to operationalize the promise for DNA-based population screening for precision public health.

In conclusion, while currently available evidence does not provide support for the widespread use of predictive genomic screening in healthy populations the scientific, ethical and implementation foundation for such an endeavor is slowly being built. However, there is a significant need for more research to address significant barriers to health equity, ethical, legal, and social implications (ELSI), readiness for implementation in primary care, and evidence gaps regarding clinical utility and long-term outcomes. This research should use an implementation science framework and build effective governance and infrastructure. We hope our readers find the collection of papers herein useful in advancing the dialogue on DNA-based population screening towards a new era of precision public health.

Author contributions

LM and MK drafted and edited the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Bangash, H., and Kullo, I. J. (2020). Implementation science to increase adoption of genomic medicine: An urgent need. *J. Pers. Med.* 11, 19. doi:10.3390/jpm11010019

Bean, L. J. H., Scheuner, M. T., Murray, M. F., Biesecker, L. G., Green, R. C., Monaghan, K. G., et al. (2021). DNA-Based screening and personal health: A points to consider statement for individuals and health-care providers from the American college of medical genetics and genomics (ACMG). *Genet. Med.* 23, 979–988. doi:10.1038/s41436-020-01083-9

Brower, A., Chan, K., Williams, M., Berry, S., Currier, R., Rinaldo, P., et al. (2022). Population-based screening of newborns: Findings from the NBS expansion study (Part One). *Front. Genet.* 13, 867337. doi:10.3389/fgene.2022.867337

Khoury, M. J., Bowen, M. S., Clyne, M., Dotson, W. D., Gwinn, M. L., Green, R. F., et al. (2018a). From public health genomics to precision public health: A 20-year journey. *Genet. Med.* 20, 574–582. doi:10.1038/gim.2017.211

Khoury, M. J., Feero, W. G., Chambers, D. A., Brody, L. C., Aziz, N., Green, R. C., et al. (2018b). A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health. *PLoS Med.* 15, e1002631. doi:10.1371/journal.pmed.1002631

Murray, M. F., Evans, J. P., and Khoury, M. J. (2020). DNA-based population screening: Potential suitability and important knowledge gaps. *JAMA* 323, 307–308. doi:10.1001/jama.2019.18640

Roberts, M. C., Mensah, G. A., and Khoury, M. J. (2019). Leveraging implementation science to address health disparities in genomic medicine: Examples from the field. *Ethn. Dis.* 29, 187–192. doi:10.18865/ed.29.S1.187

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Parental Guidance Suggested: Engaging Parents as Partners in Research Studies of Genomic Screening for a Pediatric Population

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Recent advances in genomic sequencing and genomic medicine are reshaping the landscape of clinical care. As a screening modality, genetic sequencing has the potential to dramatically expand the clinical utility of newborn screening (NBS), though significant barriers remain regarding ethical, legal, and social implications (ELSI) and technical and evidentiary challenges. Stakeholder-informed implementation research is poised to grapple with many of these barriers, and parents are crucial stakeholders in this process. We describe the formation and activities of a Community Research Board (CRB) composed of parents with diverse backgrounds assembled to participate in an ongoing research partnership with genomic and public health researchers at the University of North Carolina. The mission of the CRB is to provide insight into parental perspectives regarding the prospect of adding genomic sequencing to NBS and collaboratively develop strategies to ensure its equitable uptake. We describe how these contributions can improve the accessibility of research and recruitment methods and promote trust and inclusivity within diverse communities to maximize the societal benefit of population genomic screening in healthy children.

Keywords: genomic sequencing, newborn screening, community research board, engaging parents, stakeholders, public health, equity, accessibility

INTRODUCTION

Clinical genomic sequencing is increasingly used for diagnosis and management of newborns and children with suspected genetic conditions, but has not been adopted for screening in healthy populations (Biesecker and Green, 2014; Willig et al., 2015; Strande and Berg, 2016). Genomic sequencing has the potential to greatly expand universal newborn screening (NBS) through early diagnosis of rare genetic conditions at birth, thereby enabling early health actions to prevent or ameliorate adverse health outcomes before symptoms develop (Remec et al., 2021). However, substantial ethical, legal, and social implications (ELSI) and practical and policy challenges must be addressed before this technology can be widely adopted for public health screening (Committee on Bioethics et al., 2013; Botkin et al., 2015; Brothers et al., 2019; Ross and Clayton, 2019; Sen et al.,

2021). While translational research studies are evaluating various methods of integrating sequencing into NBS (Berg et al., 2017; Holm et al., 2018; Milko et al., 2018; Petrikin et al., 2018; Adhikari et al., 2020; Andrews et al., 2022), effective working partnerships between researchers and community stakeholders are also vitally important to ensure research and future clinical offerings are inclusive, accessible, and beneficial for all (Goldenberg, 2019; Downie et al., 2021; Halley et al., 2022).

Conventional NBS exemplifies the model of public health screening to detect individuals for whom early diagnosis and treatment of "clinically actionable" conditions offers unambiguous health benefits (Berg and Powell, 2015; Hendricks-Sturrup and Lu, 2019; Powell, 2020; Woerner et al., 2021). Expanding NBS via genomic sequencing could dramatically increase the number of clinically actionable conditions that states could effectively screen for, from several dozen to several hundred (Ceyhan-Birsoy et al., 2019; Milko et al., 2019). Rapidly proliferating clinical trials for new gene therapies and pharmaceutical products also promise life-altering interventions for previously untreatable genetic conditions (Tambuyzer et al., 2020). There is growing advocacy for expanding NBS to include genomic sequencing because of the expected impact on health outcomes, and because early initiation of treatment often maximizes health benefits (Kingsmore, 2016; Powell, 2018; Bailey et al., 2021). Public health access to "expanded NBS" could aid efforts to reduce existing disparities in genetic testing and increase equity in potential benefits of a genetic diagnosis, including avoidance of a diagnostic odyssey, access to clinical management and counseling, and reproductive decision-making (Friedman et al., 2017). However, the inherent ambiguity of these benefits, such as enrollment in clinical trials for unproven treatments, and the concomitant potential for harm would likely disrupt the current NBS "opt-out" model and necessitate parental consent (Ross et al., 2013; Botkin et al., 2015).

Studies of stakeholder perspectives about genomic screening indicate that persistent apprehension could impede broad parental consent for expanded NBS, particularly among historically underserved and underrepresented populations (Borry et al., 2008; Shkedi-Rafid et al., 2015; Ulm et al., 2015; Kerruish, 2016; Moultrie et al., 2020; Tutty et al., 2021; Halley et al., 2022). Parental areas of concern include 1) anxiety regarding choices about what information they wish to have disclosed or about the security or potential misuse of their child's genetic data, 2) the potential for large out-of-pocket expense, 3) future discriminatory implications for their child, and 4) the psychosocial effects of learning about health conditions without affordable or effective treatments (Howard et al., 2015; Paquin et al., 2018). Effectively and equitably integrating genomic sequencing into NBS will require building trust with community partners in diverse settings to understand what genomic information should be returned to parents and how best to communicate that information. Without this crucial insight, limited uptake of genome-scale sequencing is likely and could endanger public trust in the current public health NBS system (Johnston et al., 2018).

Despite these substantial issues and gaps in the clinical evidence base, direct-to-consumer genetic testing has begun targeting healthy infants and children, raising questions about the nature of the information provided to parents (DeCristo et al., 2021). There are currently no standards or guidelines governing disclosure of genomic screening results or follow-up clinical care for those who test positive. Poorly regulated genetic testing poses a significant risk to uninformed parents as well as to primary care providers who will increasingly bear the burden of parental requests for education and information, interpretation of widely variable results, and clinical care among those testing positive for highly heterogeneous conditions (Cohidon et al., 2021; Majumder et al., 2021). Practice-based and stakeholder-informed implementation research is urgently needed to inform and safeguard future public health access to expanded NBS in the face of increasing commercialization.

This article highlights the importance of parent/caregiver engagement in ongoing pediatric genomic screening research and presents a collaborative approach to stakeholder-researcher partnership. As a team, we represent the Community Research Board (CRB), comprising parents from diverse communities in central North Carolina and multidisciplinary genetics professionals (researchers, clinicians, educators, and stakeholder engagement experts) at the University of North Carolina at Chapel Hill (UNC-CH). Together we seek to collaboratively address challenges in designing and broadly implementing research studies of genomic screening and public health offerings for a pediatric population. Here we describe the processes we followed to build a functionally integrated research group of community members and academicians and the activities, and initial outcomes of the CRB. We highlight successes and challenges, as well as key advantages and lessons learned from such a collaboration early in the research process.

DEFINING MEANINGFUL STAKEHOLDER ENGAGEMENT

Stakeholder engagement is a critical component in translational research and includes patients, parents and caregivers, research participants, health care providers, payers, policy makers, advocacy groups and community leaders (Kost et al., 2012; Wilkins et al., 2013; Yarborough et al., 2013; Lemke and Harris-Wai, 2015; Griesemer et al., 2020). Stakeholder engagement in research is defined as the iterative process of actively soliciting the knowledge, experience, judgment, and values of individuals selected to represent a broad range of interests in a particular issue, for the dual purposes of creating a shared understanding and making relevant, transparent, and effective decisions (Deverka et al., 2012). Meaningful engagement empowers stakeholders from the group(s) responsible for or impacted by health and/or healthcare decisions (Concannon et al., 2012) to affect the research process and resulting outcomes (Arnstein, 1969). In this way, stakeholders partner with researchers to collaboratively outline research questions and refine protocols and approaches to address issues that impact their communities.

A well-developed and carefully established bi-directional community research partnership fosters a trusting and

mutually beneficial relationship for the research study and the community. In such a collaboration, both researchers and community members are actively involved in the design and implementation of the project as well as the interpretation and dissemination of the findings. Engaged Participation is one category of stakeholder engagement in which community health stakeholders (who traditionally have limited power) collaborate in decision-making and resource allocation with an equitable balance of power that values input from the community health stakeholders (Goodman and Sanders Thompson, 2017). *Transparency, honesty,* and *trust* are key principles of effective engagement when major decisions are made inclusively, information is openly shared, and patients/community members and researchers are committed to open and honest communication (Rawl et al., 2021). The CRB was established following these key principles, with the goal of informing the effective and equitable integration of genomic screening in newborns and children.

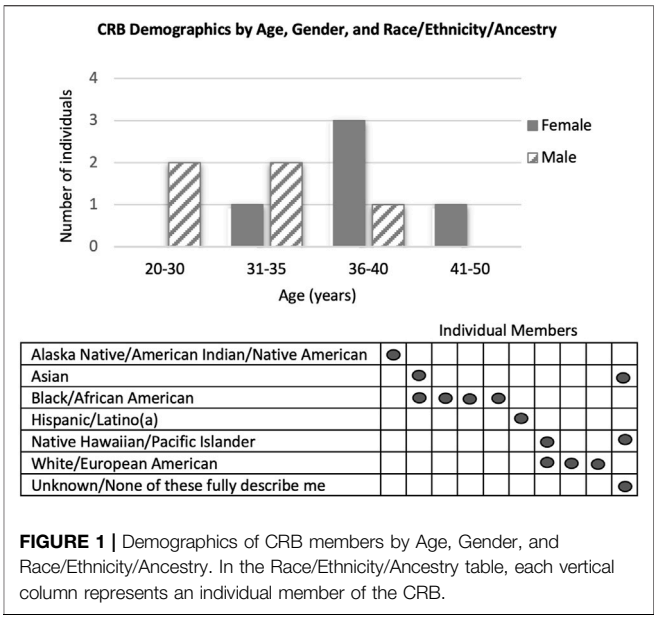

FIGURE 1 | Demographics of CRB members by Age, Gender, and Race/Ethnicity/Ancestry. In the Race/Ethnicity/Ancestry table, each vertical column represents an individual member of the CRB.

INFORMING EFFECTIVE AND EQUITABLE INTEGRATION OF GENOMIC SCREENING IN NEWBORNS AND CHILDREN

Recruitment challenges faced by the Newborn Sequencing In Genomic medicine and public HealTh consortium, including the North Carolina Newborn Exome Sequencing for Universal Screening (NC NEXUS) (Roman et al., 2020), NSIGHT1 (Petrikin et al., 2018), and BabySeq (Pereira et al., 2021), suggest substantial stakeholder engagement is necessary to improve enrollment of underrepresented communities in research involving expanded NBS research. Authentic bidirectional involvement with parents from diverse communities is also needed to navigate larger issues and challenges inherent to expanded NBS. Toward this end, we established the CRB as a community-based arm of a research team that also includes investigators and staff from the Program for Precision Medicine in Health Care (PPMH) in the UNC-CH School of Medicine. CRB members were recruited with the expectation that they would be engaged throughout the lifecycle of a research process: 1) developing the research questions, processes, and methods; 2) designing and disseminating informational and educational study materials; 3) participating in community outreach events; and 4) interpreting and disseminating the results from a community perspective.

Recruitment

Recruitment for a socio-demographically diverse CRB began in May 2020. Consultation with the Community and Stakeholder Engagement (CaSE) team at the North Carolina Translational and Clinical Sciences Institute (NC TraCS) at UNC-CH helped to optimize the design and reading-level of the recruitment materials. The CRB members were recruited over approximately six months from the Children's Research Institute at UNC, a local church, online parent groups (Facebook and Reddit), and regional message boards (Reddit). Interested members were asked to complete a survey designed to invite members who could represent diverse communities and perspectives. CRB members (5M/5F; avg. 33.8 years see **Figure 1**) are parents (15 children; 0–16 years), represent urban, suburban, and rural communities, have diverse racial/ethnic backgrounds, varying health insurance coverage, a high school education or above, and views that ranged from "strongly supporting" to "not supporting" genomic screening of children as reported on the interest survey.

Based on review of interest survey responses, our recruitment methods were biased for individuals with positive or neutral attitudes towards genomic screening in childhood. While targeted messaging and snowball recruitment methods enabled successful recruitment of many diverse characteristics, we were only able to recruit one member who self-identified as "not supporting" genomic screening. Therefore, we continue to seek members with more critical views. Challenges related to COVID-19 were addressed via exclusively virtual participation.

Formation and Relationship-Building

Initially, meetings focused heavily on building trust and familiarity, and creating a sense of community through a group resume activity that encouraged the team to recognize and share their knowledge, experiences, and motivations with the group. UNC investigators acknowledged historic neglect and abuse of racial and ethnic minorities in genetic and genomic science and shared their ongoing commitment to promoting diversity and inclusion in genomic research. The CRB and UNC team discussed their individual and shared goals, expectations, and timeline. Broad thought formation questions prompted the CRB to share their initial opinions of augmenting NBS with genomic sequencing. These included general excitement about potential benefits, as well as concerns about impact on insurance and the need for informed consent if sequencing of newborns

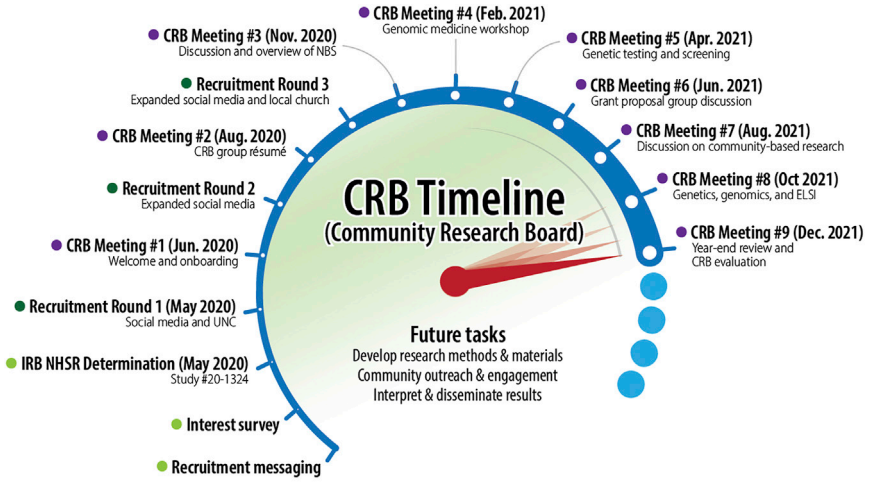

FIGURE 2 | Timeline of CRB establishment and activities in 2020 and 2021.

became routine. As valued members of the research team who contribute invaluable insight, lived experience, and expertise, they are compensated at a rate of $50/hr.

Capacity Building and Initial Activities

After an initial formative period, the CRB met every other month in 2021 in the evenings *via* Zoom (see **Figure 2**). To facilitate bidirectional capacity building, the UNC-based AGBS investigators led a series of presentations to provide relevant background information for the CRB members. Topics included: newborn screening, genomic medicine and screening, ELSI, community-based participation, and academic research grant proposal development. Each topical presentation was followed by group discussion of key themes and questions. This enabled the CRB and UNC members to develop a mutual foundation of terms and concepts as well as issues of importance and concern for CRB members. Meetings were recorded and transcribed for later analysis. They were also summarized in a bimonthly newsletter that also included relevant news and information from the UNC team to maintain engagement between meetings.

Group discussions in 2021 focused on sharing knowledge and perspectives about a research proposal to develop a clinical pilot implementation of genetic screening for a healthy pediatric population. A research study with this aim and scope will require working closely with stakeholders, including parents, guardians, and caretakers, on many aspects of study design and development. We also discussed how the CRB would help to design accessible research tools and measures (e.g., interview guides and surveys) for mixed methods research to explore parental preferences for: 1) which conditions to screen for; 2) when and where screening should be done; 3) what and how results should be returned; and 4) educational strategies to facilitate the process of informed decision-making and parental consent.

In meetings over the course of 18 months, the CRB has shared their perspectives about thorny and contentious issues related to genomic sequencing of children. CRB members responded to discussion questions in the context of being offered screening for childhood-onset, medically actionable conditions for a healthy newborn. These early insights, shared below, will inform our ongoing research in this area including methods to elicit perspectives from broader stakeholder groups.

Perspectives on Select Topics

Opt-In Versus Opt-Out

CRB members expressed frustration about the lack of information about NBS and agreed that transparency about issues such as false positives and false negatives, and privacy and data security, could improve their confidence about participating in expanded NBS.

"There are so many decisions made for people . . . without really consulting them . . . and there are so many people who do not recall being given any information . . . couldn't there be a pamphlet or something at the doctor's office?"

"I think the false positives prospect is why the follow ups need to be easily accessible. It is still stressful but easy to get a definitive answer."

Other parents said they would rely on their doctors to help them make informed decisions.

"My gut reaction is yes, I'd like to pick the conditions, but honestly, not knowing exactly what conditions are being researched, and knowing that I may not know what 10 of those conditions even are, I think testing for as many as possible is best."

A range of answers from the group illustrates a need to better understand the issues to choose effective and appropriate strategies for educating parents and facilitating informed decision-making.

Community Engagement

CRB members felt strongly that accessible alternatives (community-based and group offerings) to pediatric and family medicine clinics were needed.

"Working in the school system a lot of the families that I work with just don't have the capacity to do anything extra . . . partnering with community agencies that have groups of people that already feel comfortable with one another could . . . reach a wide group of people that might typically not come for these kinds of information sessions."

"Maybe something worth considering . . . is possibly illustrating these analogies and explaining these points through comics or something that the general public is not afraid of."

Community-based strategies used in other contexts (e.g., mobile vaccination buses) have clinical limitations for genomic screening, but the point was well made that creative engagement strategies are imperative for broad accessibility.

Insurance coverage for the cost of the screening test and other downstream costs also concerned the CRB members, both as parents and community representatives.

"I always go back to cost . . . to the patient [and] what's covered by insurance."

Privacy and Data Security

CRB members expressed trust in doctors and researchers and were open to providing their child's de-identified DNA for research with a well-explained reason, though some noted they would need to be assured that their child's data would not be misused.

"I'm uncomfortable with giving my child's genetic info/DNA without having some sort of assurance that it will only be used for the sequencing and possibly anonymous data research."

Members noted more concerns about providing DNA samples to companies and the government. One member identified perceived lack of transparency as a potential reason for declining to participate.

Which Conditions to Screen for and How to Deliver the Genetic Information?

In the context of early onset, medically actionable conditions, some CRB members were very concerned about severe conditions.

"I would want to know all of it. In the case of a package, I would want to know which ones create more of a strain on lifestyle. The name of the game is severity."

Others were more concerned about having flexible options.

"I think it makes sense to have as many options as possible, so what works for one person might not work for another. . ."

DISCUSSION AND FUTURE DIRECTIONS

Engaged Scholarship seeks to achieve health equity through shared decision making with stakeholder members of communities about research that is likely to impact the groups they represent (Goodman and Sanders Thompson, 2017). Engaging the CRB early in the research cycle has benefited all members. Parents have reported that their participation has given them a stronger sense of ownership of and advocacy in their own health care decision making. Parents and researchers report that the formative sessions contributed to a deeper trust and a sense of community and purpose. The research study benefits from an insightful model for education and outreach strategies that can be extrapolated to a broader population and a foundation from which to develop accessible and appropriate research tools and measures to address the significant variability in parental preferences, values, and beliefs about expanding NBS with genomic sequencing.

Parental engagement will be critically important to democratize access to expanded NBS. There is relevant concern that worsening health disparities contradict the principle that public health interventions should serve as equalizers. (Borry et al., 2009; Tarini and Goldenberg, 2012; Lewis et al., 2016; Evans et al., 2019; Moultrie et al., 2020; Peinado et al., 2020; Miller et al., 2021). Routine well-child interventions such as vaccinations and periodic screening for hearing, vision, and environmental exposures can have a profound effect on preventing individual morbidity and mortality and are also widely accepted because of their public health impact. Pediatric genomic screening has the potential to be adopted in a similar fashion if feedback from diverse parent stakeholders is sought and incorporated into the research process.

Willingness to participate in research is frequently shaped by cultural beliefs and personal and group experiences with health systems and research. CRB members are strategically positioned to build bridges between their communities and researchers, simultaneously increasing awareness of community perspectives and the benefits of participating in genomic research. Looking toward the future, we believe that engaging parents as partners throughout the genomic screening research process will reduce barriers to the uptake of highly actionable genetic information with the best chance of societal benefit.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

LM, GB, SP, AB, TO, EJ-C, JS, HO and JO contributed to the conception and design of the manuscript. SP, GB, TO, JS, AB, EJ-C, and LM wrote the first draft of the manuscript. AB, EJ-C, HO, AF, LH, and TO edited early drafts of the manuscript. JS conceptualized and designed **Figure 2**. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

Adhikari, A. N., Gallagher, R. C., Wang, Y., Currier, R. J., Amatuni, G., Bassaganyas, L., et al. (2020). The Role of Exome Sequencing in Newborn Screening for Inborn Errors of Metabolism. *Nat. Med.* 26, 1392–1397. doi:10.1038/s41591-020-0966-5

Andrews, S. M., Porter, K. A., Bailey, D. B., and Peay, H. L. (2022). Preparing Newborn Screening for the Future: A Collaborative Stakeholder Engagement Exploring Challenges and Opportunities to Modernizing the Newborn Screening System. *BMC Pediatr.* 22, 90. doi:10.1186/s12887-021-03035-x

Arnstein, S. R. (1969). A Ladder of Citizen Participation. *J. Am. Inst. Planners* 35, 216–224. doi:10.1080/01944366908977225

Bailey, D. B., Porter, K. A., Andrews, S. M., Raspa, M., Gwaltney, A. Y., and Peay, H. L. (2021). Expert Evaluation of Strategies to Modernize Newborn Screening in the United States. *JAMA Netw. Open* 4, e2140998. doi:10.1001/jamanetworkopen.2021.40998

Berg, J. S., Agrawal, P. B., Bailey, D. B., Beggs, A. H., Brenner, S. E., Brower, A. M., et al. (2017). Newborn Sequencing in Genomic Medicine and Public Health. *Pediatrics* 139 (2), e20162252. doi:10.1542/peds.2016-2252

Berg, J. S., and Powell, C. M. (2015). Potential Uses and Inherent Challenges of Using Genome-Scale Sequencing to Augment Current Newborn Screening. *Cold Spring Harb. Perspect. Med.* 5, a023150. doi:10.1101/cshperspect.a023150

Biesecker, L. G., and Green, R. C. (2014). Diagnostic Clinical Genome and Exome Sequencing. *N. Engl. J. Med.* 370, 2418–2425. doi:10.1056/NEJMra1312543

Borry, P., Evers-Kiebooms, G., Cornel, M. C., Clarke, A., and Dierickx, K.Public and Professional Policy Committee (PPPC) of the European Society of Human Genetics (ESHG) (2009). Genetic Testing in Asymptomatic Minors: Background Considerations towards ESHG Recommendations. *Eur. J. Hum. Genet.* 17, 711–719. doi:10.1038/ejhg.2009.25

Borry, P., Goffin, T., Nys, H., and Dierickx, K. (2008). Attitudes Regarding Predictive Genetic Testing in Minors: A Survey of European Clinical Geneticists. *Am. J. Med. Genet.* 148C, 78–83. doi:10.1002/ajmg.c.30165

Botkin, J. R., Belmont, J. W., Berg, J. S., Berkman, B. E., Bombard, Y., Holm, I. A., et al. (2015). Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am. J. Hum. Genet.* 97, 6–21. doi:10.1016/j.ajhg.2015.05.022

Brothers, K. B., Vassy, J. L., and Green, R. C. (2019). Reconciling Opportunistic and Population Screening in Clinical Genomics. *Mayo Clinic Proc.* 94, 103–109. doi:10.1016/j.mayocp.2018.08.028

Ceyhan-Birsoy, O., Murry, J. B., Machini, K., Lebo, M. S., Yu, T. W., Fayer, S., et al. (2019). Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project. *Am. J. Hum. Genet.* 104, 76–93. doi:10.1016/j.ajhg.2018.11.016

Cohidon, C., Cardinaux, R., Cornuz, J., Chenal, R., Desvergne, B., Guessous, I., et al. (2021). May Direct-To-Consumer Genetic Testing Have an Impact on General Practitioners' Daily Practice? a Cross-Sectional Study of Patients' Intentions towards This Approach. *BMC Fam. Pract.* 22, 79. doi:10.1186/s12875-021-01428-6

Committee on Bioethics, Committee on Genetics, The American College of Medical Genetics (ACMG), and Social Ethical and Legal Issues Committee (2013). Ethical and Policy Issues in Genetic Testing and Screening of Children. *Pediatrics* 131, 620–622. doi:10.1542/peds.2012-3680

Concannon, T. W., Meissner, P., Grunbaum, J. A., McElwee, N., Guise, J.-M., Santa, J., et al. (2012). A New Taxonomy for Stakeholder Engagement in Patient-Centered Outcomes Research. *J. Gen. Intern. Med.* 27, 985–991. doi:10.1007/s11606-012-2037-1

DeCristo, D. M., Milko, L. V., O'Daniel, J. M., Foreman, A. K. M., Mollison, L. F., Powell, B. C., et al. (2021). Actionability of Commercial Laboratory Sequencing Panels for Newborn Screening and the Importance of Transparency for Parental Decision-Making. *Genome Med.* 13, 50. doi:10.1186/s13073-021-00867-1

Deverka, P. A., Lavallee, D. C., Desai, P. J., Esmail, L. C., Ramsey, S. D., Veenstra, D. L., et al. (2012). Stakeholder Participation in Comparative Effectiveness Research: Defining a Framework for Effective Engagement. *J. Comp. Eff. Res.* 1, 181–194. doi:10.2217/cer.12.7

Downie, L., Halliday, J., Lewis, S., and Amor, D. J. (2021). Principles of Genomic Newborn Screening Programs: A Systematic Review. *JAMA Netw. Open* 4, e2114336. doi:10.1001/jamanetworkopen.2021.14336

Evans, A., LeBlanc, K., Bonhomme, N., Shone, S. M., Gaviglio, A., Freedenberg, D., et al. (2019). A Newborn Screening Education Best Practices Framework: Development and Adoption. *Int. J. Neonatal. Screen.* 5, 22. doi:10.3390/ijns5020022

Friedman, J. M., Cornel, M. C., Goldenberg, A. J., Lister, K. J., Sénécal, K., and Vears, D. F. (2017). Genomic Newborn Screening: Public Health Policy Considerations and Recommendations. *BMC Med. Genomics* 10, 9. doi:10.1186/s12920-017-0247-4

Goldenberg, A. J. (2019). Considering Equity in Assessing Familial Benefit from the Return of Genomic Research Results. *Pediatrics* 144 (6), e20193111. doi:10.1542/peds.2019-3111

Goodman, M. S., and Sanders Thompson, V. L. (2017). The Science of Stakeholder Engagement in Research: Classification, Implementation, and Evaluation. *Behav. Med. Pract. Pol. Res.* 7, 486–491. doi:10.1007/s13142-017-0495-z

Griesemer, I., Staley, B. S., Lightfoot, A. F., Bain, L., Byrd, D., Conway, C., et al. (2020). Engaging Community Stakeholders in Research on Best Practices for Clinical Genomic Sequencing. *Personalized Med.* 17, 435–444. doi:10.2217/pme-2020-0074

Halley, M. C., Young, J. L., Fernandez, L., Kohler, J. N., Bernstein, J. A., Wheeler, M. T., et al. (2022). Perceived Utility and Disutility of Genomic Sequencing for Pediatric Patients: Perspectives from Parents with Diverse Sociodemographic Characteristics. *Am. J. Med. Genet. A.* 2022, 1–14. doi:10.1002/ajmg.a.62619

Hendricks-Sturrup, R. M., and Lu, C. Y. (2019). When Should Genomic and Exome Sequencing Be Implemented in Newborns? A Call for an Update to Newborn Screening Guidelines. *Genet. Med.* 22, 809–810. doi:10.1038/s41436-019-0707-7

Holm, I. A., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., Frankel, L. A., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18, 225. doi:10.1186/s12887-018-1200-1

Howard, H. C., Knoppers, B. M., Cornel, M. C., Wright Clayton, E., Sénécal, K., and Borry, P.European Society of Human Genetics, P3G International Paediatric Platform, and Human Genome Organisation; and the PHG Foundation (2015). Whole-Genome Sequencing in Newborn Screening? A Statement on the Continued Importance of Targeted Approaches in Newborn Screening Programmes. *Eur. J. Hum. Genet.* 23, 1593–1600. doi:10.1038/ejhg.2014.289

Johnston, J., Lantos, J. D., Goldenberg, A., Chen, F., Parens, E., and Koenig, B. A. (2018). Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies. *Hastings Cent. Rep.* 48 (Suppl. 2), S2–S6. doi:10.1002/hast.874

Kerruish, N. (2016). Parents' Experiences 12 Years after Newborn Screening for Genetic Susceptibility to Type 1 Diabetes and Their Attitudes to Whole-Genome Sequencing in Newborns. *Genet. Med.* 18, 249–258. doi:10.1038/gim.2015.73

Kingsmore, S. F. (2016). Newborn Testing and Screening by Whole-Genome Sequencing. *Genet. Med.* 18, 214–216. doi:10.1038/gim.2015.172

Kost, R. G., Reider, C., Stephens, J., and Schuff, K. G.Clinical and Translational Science Award Research Subject Advocacy Survey Taskforce (2012). Research Subject Advocacy: Program Implementation and Evaluation at Clinical and Translational Science Award Centers. *Acad. Med.* 87, 1228–1236. doi:10.1097/ACM.0b013e3182628afa

Lemke, A. A., and Harris-Wai, J. N. (2015). Stakeholder Engagement in Policy Development: Challenges and Opportunities for Human Genomics. *Genet. Med.* 17, 949–957. doi:10.1038/gim.2015.8

Lewis, M. A., Paquin, R. S., Roche, M. I., Furberg, R. D., Rini, C., Berg, J. S., et al. (2016). Supporting Parental Decisions about Genomic Sequencing for Newborn Screening: the NC NEXUS Decision Aid. *Pediatrics* 137 (Suppl. 1), S16–S23. doi:10.1542/peds.2015-3731E

Majumder, M. A., Guerrini, C. J., and McGuire, A. L. (2021). Direct-to-Consumer Genetic Testing: Value and Risk. *Annu. Rev. Med.* 72, 151–166. doi:10.1146/annurev-med-070119-114727

Milko, L. V., O'Daniel, J. M., DeCristo, D. M., Crowley, S. B., Foreman, A. K. M., Wallace, K. E., et al. (2019). An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screening. *J. Pediatr.* 209, 68–76. doi:10.1016/j.jpeds.2018.12.027

Milko, L. V., Rini, C., Lewis, M. A., Butterfield, R. M., Lin, F.-C., Paquin, R. S., et al. (2018). Evaluating Parents' Decisions about Next-Generation Sequencing for Their Child in the NC NEXUS (North Carolina Newborn Exome Sequencing for Universal Screening) Study: A Randomized Controlled Trial Protocol. *Trials* 19, 344. doi:10.1186/s13063-018-2686-4

Miller, B. C., Goldenberg, A. J., and Bonhomme, N. F. (2021). Digital Peer-to-Peer Information Seeking and Sharing: Opportunities for Education and Collaboration in Newborn Screening. *Am. J. Med. Genet.* 187, 64–69. doi:10.1002/ajmg.c.31884

Moultrie, R. R., Paquin, R., Rini, C., Roche, M. I., Berg, J. S., Powell, C. M., et al. (2020). Parental Views on Newborn Next Generation Sequencing: Implications for Decision Support. *Matern. Child. Health J.* 24, 856–864. doi:10.1007/s10995-020-02953-z

Paquin, R. S., Peinado, S., Lewis, M. A., Biesecker, B. B., Rini, C., Roche, M., et al. (2018). A Behavior-Theoretic Evaluation of Values Clarification on Parental Beliefs and Intentions toward Genomic Sequencing for Newborns. *Soc. Sci. Med.* 271, 112037. doi:10.1016/j.socscimed.2018.11.017

Peinado, S., Paquin, R. S., Rini, C., Roche, M., Butterfield, R. M., Berg, J. S., et al. (2020). Values Clarification and Parental Decision Making about Newborn Genomic Sequencing. *Health Psychol.* 39, 335–344. doi:10.1037/hea0000829

Pereira, S., Smith, H. S., Frankel, L. A., Christensen, K. D., Islam, R., Robinson, J. O., et al. (2021). Psychosocial Effect of Newborn Genomic Sequencing on Families in the Babyseq Project: A Randomized Clinical Trial. *JAMA Pediatr.* 175, 1132–1141. doi:10.1001/jamapediatrics.2021.2829

Petrikin, J. E., Cakici, J. A., Clark, M. M., Willig, L. K., Sweeney, N. M., Farrow, E. G., et al. (2018). The NSIGHT1-Randomized Controlled Trial: Rapid Whole-Genome Sequencing for Accelerated Etiologic Diagnosis in Critically Ill Infants. *NPJ Genom. Med.* 3, 6. doi:10.1038/s41525-018-0045-8

Powell, C. M. (2020). Newborn Screening and Long-Term Outcomes. *Pediatrics* 146 (5), e2020023663. doi:10.1542/peds.2020-023663

Powell, C. M. (2018). What Genomic Sequencing Can Offer Universal Newborn Screening Programs. *Hastings Cent. Rep.* 48 (Suppl. 2), S18–S19. doi:10.1002/hast.878

Rawl, S. M., Bailey, S., Cork, B., Fields, M., Griffin, T., Haunert, L., et al. (2021). Partnering to Increase Colorectal Cancer Screening: Perspectives of Community Advisory Board Members. *West. J. Nurs. Res.* 43, 930–938. doi:10.1177/0193945921993174

Remec, Z. I., Trebusak Podkrajsek, K., Repic Lampret, B., Kovac, J., Groselj, U., Tesovnik, T., et al. (2021). Next-Generation Sequencing in Newborn Screening: A Review of Current State. *Front. Genet.* 12, 662254. doi:10.3389/fgene.2021.662254

Roman, T. S., Crowley, S. B., Roche, M. I., Foreman, A. K. M., O'Daniel, J. M., Seifert, B. A., et al. (2020). Genomic Sequencing for Newborn Screening: Results of the NC NEXUS Project. *Am. J. Hum. Genet.* 107, 596–611. doi:10.1016/j.ajhg.2020.08.001

Ross, L. F., and Clayton, E. W. (2019). Ethical Issues in Newborn Sequencing Research: The Case Study of Babyseq. *Pediatrics* 144 (6), e20191031. doi:10.1542/peds.2019-1031

Ross, L. F., Saal, H. M., David, K. L., and Anderson, R. R.American Academy of Pediatrics, and American College of Medical Genetics and Genomics (2013). Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children. *Genet. Med.* 15, 234–245. doi:10.1038/gim.2012.176

Sen, K., Harmon, J., and Gropman, A. L. (2021). Select Ethical Aspects of Next-Generation Sequencing Tests for Newborn Screening and Diagnostic Evaluation of Critically Ill Newborns. *Int. J. Neonatal. Screen.* 7, 76. doi:10.3390/ijns7040076

Shkedi-Rafid, S., Fenwick, A., Dheensa, S., and Lucassen, A. M. (2015). Genetic Testing of Children for Adult-Onset Conditions: Opinions of the British Adult Population and Implications for Clinical Practice. *Eur. J. Hum. Genet.* 23, 1281–1285. doi:10.1038/ejhg.2014.221

Strande, N. T., and Berg, J. S. (2016). Defining the Clinical Value of a Genomic Diagnosis in the Era of Next-Generation Sequencing. *Annu. Rev. Genom. Hum. Genet.* 17, 303–332. doi:10.1146/annurev-genom-083115-022348

Tambuyzer, E., Vandendriessche, B., Austin, C. P., Brooks, P. J., Larsson, K., Miller Needleman, K. I., et al. (2020). Therapies for Rare Diseases: Therapeutic Modalities, Progress and Challenges Ahead. *Nat. Rev. Drug Discov.* 19, 93–111. doi:10.1038/s41573-019-0049-9

Tarini, B. A., and Goldenberg, A. J. (2012). Ethical Issues with Newborn Screening in the Genomics Era. *Annu. Rev. Genom. Hum. Genet.* 13, 381–393. doi:10.1146/annurev-genom-090711-163741

Tutty, E., Amor, D. J., Jarmolowicz, A., Paton, K., and Downie, L. (2021). Personal Utility of Genomic Sequencing for Infants with Congenital Deafness. *Am. J. Med. Genet.* 185, 3634–3643. doi:10.1002/ajmg.a.62411

Ulm, E., Feero, W. G., Dineen, R., Charrow, J., and Wicklund, C. (2015). Genetics Professionals' Opinions of Whole-Genome Sequencing in the Newborn Period. *J. Genet. Counsel* 24, 452–463. doi:10.1007/s10897-014-9779-3

Wilkins, C. H., Spofford, M., Williams, N., McKeever, C., Allen, S., Brown, J., et al. (2013). Community Representatives' Involvement in Clinical and Translational Science Awardee Activities. *Clin. Translational Sci.* 6, 292–296. doi:10.1111/cts.12072

Willig, L. K., Petrikin, J. E., Smith, L. D., Saunders, C. J., Thiffault, I., Miller, N. A., et al. (2015). Whole-Genome Sequencing for Identification of Mendelian Disorders in Critically Ill Infants: A Retrospective Analysis of Diagnostic and Clinical Findings. *Lancet Respir. Med.* 3, 377–387. doi:10.1016/S2213-2600(15)00139-3

Woerner, A. C., Gallagher, R. C., Vockley, J., and Adhikari, A. N. (2021). The Use of Whole Genome and Exome Sequencing for Newborn Screening: Challenges and Opportunities for Population Health. *Front. Pediatr.* 9, 663752. doi:10.3389/fped.2021.663752

Yarborough, M., Edwards, K., Espinoza, P., Geller, G., Sarwal, A., Sharp, R., et al. (2013). Relationships Hold the Key to Trustworthy and Productive Translational Science: Recommendations for Expanding Community Engagement in Biomedical Research. *Clin. Translational Sci.* 6, 310–313. doi:10.1111/cts.12022

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Interest in Cancer Predisposition Testing and Carrier Screening Offered as Part of Routine Healthcare Among an Ethnically Diverse Sample of Young Women

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Sequencing technologies can inform individuals' risks for multiple conditions, supporting population-level screening approaches. Prior research examining interest in genetic testing has not generally examined the context of population-based approaches offered in routine healthcare or among ethnically diverse populations. Cancer predisposition testing and carrier screening could be offered broadly to women of reproductive age. This study therefore examined interest in these tests when offered as part of routine care, and predictors of interest, among an ethnically diverse sample of women aged 20–35. We conducted an online English-language survey of 450 women; 39% identified as Latina. We examined predictors of interest for two outcomes, interest in testing in the next year and level of interest, in multivariable logistic regression models and stratified analyses by Latina ethnicity. More than half of respondents reported being interested in cancer predisposition testing (55%) and carrier screening (56%) in the next year; this did not differ by ethnicity. About 26% reported being very interested in cancer predisposition testing and 27% in carrier screening. Latina respondents (32%) were more likely to be very interested in cancer predisposition testing than non-Latina respondents (22%; $p < 0.03$). In multivariable models, having higher worry about genetic risks, higher genetic knowledge, and higher perceived importance of genetic information were associated with higher interest across multiple models. Predictors of interest were generally similar by ethnicity. Our findings show substantial interest in both cancer predisposition testing and carrier screening among young women as part of routine healthcare with similar interest between Latina and non-Latina women. Efforts to broadly offer such testing could be important in improving access to genetic information. It will be critical to develop tools to help healthcare providers communicate about genetic testing and to address the needs of those who have less prior knowledge about genetics to support informed decision making.

Keywords: population screening, genetic testing, cancer predisposition testing, carrier screening, ethnicity

1 INTRODUCTION

DNA-based population screening of unaffected individuals has been identified as an important future approach to inform individual disease risks and direct screening and prevention efforts (Murray et al., 2021). Currently, genetic testing is generally targeted based on medical history factors, such as family history and personal history of disease (Murray et al., 2019). However, increasing evidence shows that medical history-based genetic testing approaches do not identify the majority of individuals at increased inherited risk for cancer and heart disease (Abul-Husn et al., 2016; Manickam et al., 2018; Khoury and Dotson, 2021). These gaps in identification, combined with decreasing costs of sequencing technologies, have led to heightened consideration of population screening approaches (Murray et al., 2019; Murray et al., 2021). Tier 1 genomic applications, which are hereditary breast and ovarian cancer, Lynch Syndrome, and familial hypercholesterolemia, have received particular consideration for future implementation of population screening (Khoury et al., 2018; Khoury and Dotson, 2021).

A number of recent commentaries have outlined key questions that need to be addressed prior to launching population screening efforts (Murray et al., 2019; Bean et al., 2021; Khoury and Dotson, 2021; Murray et al., 2021). Although previous research studies have begun to explore population-based testing approaches in defined populations, such as BRCA testing among an Ashkenazi Jewish population (Manchanda et al., 2020a; Manchanda et al., 2020b), limited data exist to inform the implementation of population screening more broadly and the potential impact on health outcomes (French et al., 2018; Phillips et al., 2020). Related data that are available suggest that population screening could have several behavioral benefits, such as increased screening in women at high risk of breast cancer without major adverse emotional effects (French et al., 2018). However, substantial gaps have been identified in data related to how individuals would make decisions related to offers of population screening (French et al., 2018). One important need is to understand individuals' interest in population screening for various disease outcomes, and the factors that influence their interest. These findings are critical to developing effective approaches to offering population screening and supporting individuals' informed decision making. The importance of these issues is likely to increase as the public becomes more interested in obtaining their genomic information (Bean et al., 2021).

In considering potential future population screening initiatives, pre-pregnancy may offer a unique opportunity to engage women and their reproductive partners in genetic testing. Pre-pregnancy has been identified as a key window for health promotion activities (Johnson et al., 2006; Barker et al., 2017; American College of Obstetrics and Gynecology, 2019a; van Elten et al., 2019; Hill et al., 2020; Moholdt and Hawley, 2020). While definitions of pre-pregnancy vary (Hill et al., 2020), women who are intending a pregnancy in the future may be particularly interested in various types of genetic information. The Centers for Disease Control and Prevention have identified genetic conditions and family history as specific areas for pre-pregnancy risk assessment (Johnson et al., 2006). Carrier screening is a recommended genetic test to identify couples at risk for conceiving a fetus affected with a serious health condition that can be offered pre-pregnancy (Porter et al., 2018). Currently, the American College of Obstetricians and Gynecologists (ACOG) and American College of Medical Genetics and Genomics (ACMG) recommend that all couples be offered carrier screening for cystic fibrosis and spinal muscular atrophy, and other targeted screening based on ethnicity (Edwards et al., 2015; American College of Obstetrics and Gynecology, 2017a; American College of Obstetrics and Gynecology, 2017b). However, expanded carrier screening, which potentially screens for hundreds of conditions, could be offered more broadly at a population level.

While carrier screening is ideally offered prior to pregnancy, it is often not offered until a pregnancy when results could increase anxiety to a greater extent due to the high likelihood of carrier status for one or more conditions and time for partner results (Grody, 2016). In considering population screening efforts for expanded carrier screening, therefore, some research has examined interest among women, as well as their reproductive partners, in receiving this genetic testing prior to pregnancy (Capalbo et al., 2021). Wide variability in interest and uptake of expanded carrier screening has been observed across available studies (van Steijvoort et al., 2020). A systematic review of 12 published studies found that 32%–76% of respondents were interested in a hypothetical expanded carrier screening test, while actual uptake rates for expanded carrier screening ranged from 8% to 50% (van Steijvoort et al., 2020). While the highest uptake rate was observed in a study with pregnant women (van Steijvoort et al., 2020), another study that compared uptake rates found that 69% of women counseled pre-pregnancy chose to have expanded carrier screening, which was significantly higher than the 35% choosing to have screening during pregnancy (Larsen et al., 2019).

This wide range of interest and uptake observed in different studies with different populations heightens the importance of examining factors affecting interest if expanded carrier screening were offered pre-pregnancy to a broad population. A few studies have examined women's reasons for choosing to have or declining pre-pregnancy carrier screening. In one survey of the general Dutch population, the primary motivation for receiving expanded carrier screening was to spare a child from a life with a severe hereditary disorder, while lack of a hereditary disorder in the family was identified as a reason to decline screening (Nijmeijer et al., 2019). Another survey identified the desire for reassurance and making informed decisions about future pregnancies as drivers of interest in expanded carrier screening (Rabkina et al., 2021). Interestingly, in one study, women who declined offers of preconception genomic carrier screening did so for logistical issues (e.g., time) rather than the rationale for testing (Gilmore et al., 2017). Limited prior research has examined psychological predictors of interest in preconception carrier screening, although one study in Western Australia found that higher genetic knowledge and more positive attitudes were correlated with screening interest (Ong et al., 2018).

Use of sequencing technologies for expanded carrier screening could allow for informing risks for other health conditions among those receiving genetic testing (Lindor et al., 2017; Machini et al., 2019). Routine gynecology visits may be an ideal time for women to consider both expanded carrier screening and genetic testing for cancer predisposition, as these are both clinical genetic tests that are highly relevant to women of reproductive age. ACOG recommends that assessing for hereditary cancer risk and offering carrier screening are within the roles of obstetrics/gynecology providers (American College of Obstetrics and Gynecology, 2017c; American College of Obstetrics and Gynecology, 2019a; American College of Obstetrics and Gynecology, 2019b), and that familial cancer risk assessment be part of routine gynecological visits (Gavin et al., 2014). Returning multiple types of genetic information may bring substantial communication challenges due to greater information volume and complexity but returning multiple results may also increase the perceived value of genetic testing to individuals (Lindor et al., 2017; Kaphingst et al., 2018; Sapp et al., 2018; Delanne et al., 2019; Horowitz et al., 2019; Bartley et al., 2020). While studies have begun to explore interest in offers of pre-pregnancy genomic carrier screening (Kauffman et al., 2017b; van Steijvoort et al., 2020), research is needed to assess women's interest in receiving additional genetic tests that would provide information about their own health at the same time and whether predictors of interest are the same between different types of genetic tests. One prior study related to participating in genome sequencing for carrier status showed that a primary motivating factor was to obtain general health information for oneself (Kauffman et al., 2017a). Additional research is needed to examine whether interest in both of these types of genetic tests would be high in a routine clinical setting as well.

Prior related research conducted outside of the pre-pregnancy and carrier status context has shown that patients are often interested in receiving multiple types of genetic information from genome sequencing, including cancer risk information (Kaphingst et al., 2016a; Kaphingst et al., 2018; Delanne et al., 2019; Hoell et al., 2020). Many of these studies have been conducted in the context of genome sequencing research rather than routine clinical contexts, finding high levels of interest in secondary findings related to various health conditions among the general public and patient populations (Kaphingst et al., 2019). Studies have found strong interest in receiving secondary findings among cancer patients, with the strongest interest in actionable findings and those with reproductive significance (Kaphingst et al., 2016a; Kaphingst et al., 2018; Bijlsma et al., 2020). Members of the general public have also perceived genome sequencing results as having high personal utility (Goranitis et al., 2020). A number of different factors affecting interest in various types of sequencing results have been identified (Mighton et al., 2019), including understanding and impact on quality of life (Bollinger et al., 2012; Mighton et al., 2020). Early adopters of genome sequencing have expressed various health-related and non-health-related motivations (Sanderson et al., 2016), and participants in genetic research have highlighted the importance of offers of personal genomic risk information being based on individual preferences (Smit et al., 2020).

Our prior work has examined possible predictors of interest in various types of findings from genome sequencing informed by a model of risk information and processing (Griffin et al., 1999), examining both genetic-related and general health-related predictors. In one study with 1,080 women who had been diagnosed with breast cancer at a young age, we found that the same psychological factors (i.e., higher knowledge about sequencing benefits, greater worry about genetic risks, and stronger orientation toward health information) predicted a high level of interest in learning about six different types of genome sequencing findings, including carrier status (Kaphingst et al., 2018). In other research conducted with primary care patients offered genetic susceptibility testing for multiple health conditions, we found that social influence from family and friends impacted interest in seeking information about genes (Hay et al., 2012). Additional possible predictors of interest in different types of genetic testing are suggested by related theories of how individuals cope with the uncertainty inherent in risk information (Brashers, 2001; Hillen et al., 2017), particularly the importance of examining individuals' tolerance for uncertainty information (Carleton et al., 2007; Hillen et al., 2017).

Issues of equity must be considered when assessing interest in population screening, as well as predictors of interest, so that these technologies do not further exacerbate health disparities (Institute of Medicine, 2002; Halbert and Harrison, 2018; Pierle and Mahon, 2019; Murray et al., 2021). There has been limited research on the access and use of genetic technologies among diverse patients (Canedo et al., 2019; Kaphingst et al., 2019), particularly with Latinx patients (Canedo et al., 2020; Chavez-yenter et al., 2021a). For example, people from racial and ethnic minority groups are often interested in testing (Kaphingst et al., 2015; Hay et al., 2019; Turbitt et al., 2019), but have lower access to and use of cancer genetic services in the US (Hall and Olopade, 2005; Hall and Olopade, 2006; Fisher et al., 2019), even when cost barriers are minimized (Alford et al., 2011). These disparities have been linked to both individual-level (e.g., lower knowledge) (Singer et al., 2004; Pagan et al., 2009; Kinney et al., 2010; Bloss et al., 2018; Canedo et al., 2019) and system-level factors (e.g., unmet needs for discussion of testing with providers) (Peters et al., 2004; Singer et al., 2004; Jagsi et al., 2015; Kaphingst and Goodman, 2016; Roberts et al., 2019; Southwick et al., 2020). However, these critical issues need to be examined within the context of population screening approaches.

Prior related research has indicated that a broad population sample may be interested in receiving genetic testing for multiple health conditions, including cancer predisposition testing and carrier status, with at least some support for expanded cancer screening offered pre-pregnancy. However, these studies have not generally been conducted in a clinical setting and little is known about individuals' interest in genetic testing offered as part of routine healthcare. In addition, research examining predictors of interest in different types of genetic testing among racially and ethnically diverse populations is limited. To address these identified research gaps, this study examined interest, and predictors of interest, in population-based carrier screening and cancer predisposition testing offered as part of routine gynecologic care among an ethnically diverse sample of women aged 20–35.

2 METHODS

2.1 Participants

We conducted an online English-language survey in order to investigate these research questions (see **Supplemental File**). A convenience sample of US adults was recruited by Qualtrics Panel Services in June 2021 to participate in the survey. Because of our focus on genetic testing pre-pregnancy, we recruited respondents who identified as female and were between the ages of 20–35 years. Because of the limited prior data for Latinx individuals related to use of genetic technologies, as described above, and because of the substantial and growing Latinx community in the catchment area for our healthcare system, we also set an a priori threshold of at least 25% of respondents identifying as Latina so that we could examine the effect of ethnicity on interest. The minimum survey sample size was set at 425 respondents in order to examine the effect of ethnicity on interest in genetic testing. Individuals were removed if they did not meet the gender ($n = 41$) or age ($n = 34$) criteria in the pre-screener questions, did not complete the consent acceptance question at the beginning of the survey ($n = 51$), or were below the 6-min speed threshold pre-set for time to complete the survey ($n = 52$). This resulted in a final sample of 450 respondents. The survey was approved as an exempt protocol by the University of Utah Institutional Review Board.

2.2 Measures

2.2.1 Interest Outcome Variables

We began the survey with an educational component that described different types of genetic testing and then asked participants a series of questions about their interest in the different types. Because of our prior work showing that predictors of interest may vary depending upon item wording (Guo et al., 2020), we assessed interest in genetic testing with two different item formats. Five items assessed respondents' level of interest in genetic testing for cancer predisposition testing (i.e., "How interested would you be in doing genetic testing to learn about your risk of developing a cancer that may be able to be prevented or treated") and carrier status information (i.e., "How interested would you be in doing genetic testing to learn about a gene variation that does not affect your health but might affect the health of your children"), as well as testing to learn about the risk of a preventable/treatable disease, risk of an unpreventable/untreatable disease, and medication response. To assess delivery preferences, we also had two items assessing the level of interest in genetic testing as part of a general check-up either "with a health care provider" or "through your gynecologist's office." These items were scored on a seven-point Likert scale from "not at all" to "very" interested. The responses were dichotomized as "very" interested vs. all other categories in order to characterize a high level of interest (Kaphingst et al., 2018). A second set of interest items assessed interest in the next year in having the same five types of genetic testing if offered ("If it were offered, would you be interested in having the following types of genetic testing in the next year"). Respondents answered yes, no, or not sure to each item. Responses were dichotomized as yes vs. no/not sure for analysis.

2.2.2 Predictor Variables

Selection of hypothesized predictors was informed by a conceptual framework based on the model of Risk Information and Processing and Uncertainty Management Theory (Griffin et al., 1999; Brashers, 2001).

2.2.2.1 Worry About Genetic Risks

We assessed genetic worry with three items (e.g., "On a scale from 1 to 7 where 1 is not at all worried, and 7 is extremely worried, please describe how worried you are about the following: your genes put you at increased risk for developing a common disease, like heart disease or diabetes") (Biesecker et al., 2009). Response options were on a seven-point Likert-type scale from "not at all" to "extremely" worried. We calculated an average genetic worry score (Cronbach's α of 0.83), which was treated continuously in analysis.

2.2.2.2 Genetic Self-Efficacy

We assessed genetic self-efficacy (i.e., individuals' confidence in their ability to use genetic information) using a three-item measure on which participants indicated the extent to which they agreed with each item on a five-point Likert-type scale from strongly disagree to strongly agree (i.e., "I can explain genetic issues to people") (Parrott et al., 2004). Scores on these items were averaged (Cronbach's α of 0.76) and modeled as a continuous variable in analysis.

2.2.2.3 Genetic Knowledge

To assess general knowledge about genetics, we utilized an 18-item (e.g., "Altered" (mutated) genes can cause disease") measure (Fitzgerald-Butt et al., 2016). Each item was answered as true, false, or not sure. Correct answers were summed (Cronbach's α of 0.81) and the sum score was treated as a continuous variable for analysis.

2.2.2.4 Importance of Genetic Information

We used two items to assess the perceived importance of genetic information, one focused on cancer predisposition testing (i.e., "Please mark how important it is to you to learn more about how your genes may affect your chance of getting cancer") and one on carrier screening, adapted from our prior work (McBride et al., 2009; Kaphingst et al., 2016b). Both items were answered on a seven-point scale from "not at all important" to "very important." Responses were dichotomized (Cronbach's α of 0.69) as very important vs. other categories for analysis.

2.2.2.5 Health Consciousness

Participants' degree of health consciousness was assessed with five items (e.g., "my health depends on how well I take care of myself"), which were answered on a five-point Likert-type scale from "strongly disagree" to "strongly agree" (Dutta-Bergman, 2003). The responses were averaged (Cronbach's α of 0.83) and treated continuously in analysis. Higher scores indicated a stronger health consciousness.

2.2.2.6 Health Information Orientation

The importance placed on health information was assessed with eight items (e.g., "It is important to me to be informed about health issues"), which were answered on a five-point Likert-type scale from "strongly disagree" to "strongly agree" (Dutta-Bergman, 2003). The responses were averaged (Cronbach's α of 0.86) and treated continuously in analysis. Higher scores indicated a stronger health information orientation.

2.2.2.7 Health Information Seeking

One item was used to assessed health information seeking (i.e., "In the past 30 days, how often would you say you have looked for information about ways to stay healthy or to feel better?"), which respondents answered on a four-point Likert-type scale from "Not at all" to "Very often" (Kaphingst et al., 2012; National Cancer Institute, 2015). Responses were treated as categorical in analysis.

2.2.2.8 Risk Perceptions

We assessed relative risk perceptions for breast, ovarian, and colon cancer with three items (e.g., "Based on this information, compared to most people your age and sex, would you say that you are. . .,)" which was answered on a five-point scale from "a lot less likely" to "a lot more likely" to get the disease (Wertz et al., 1986; Lipkus et al., 2000). Risk perceptions were treated dichotomized as "somewhat" or "a lot" more likely vs. other categories for analysis.

2.2.2.9 Social Influences

We assessed social influences on learning more about health (i.e., normative beliefs) and motivation to comply using two items from our prior research (Hay et al., 2012): "The people who mean the most to me think I should learn more about ways I can keep myself healthy" and "On a scale from 1 to 7 where 1 is not at all motivated and 7 is very motivated, how motivated you would say you are to do what these people want you to do?" These items were answered on seven-point Likert-types scales from "strongly agree" to "strongly disagree" and "not at all" to "very" motivated, respectively. Responses (Cronbach's α of 0.72) were dichotomized as strongly agree or very motivated vs. other categories for analysis.

2.2.2.10 Intolerance for Uncertainty

We utilized the 12-item short version of the intolerance of uncertainty scale (i.e., "I always want to know what the future has in store for me") (Carleton et al., 2007). Respondents answered each item on a five-point Likert-type scale from "Not at all" to "Entirely" characteristic of me. Following scoring rules, we summed the responses (Cronbach's α of 0.89) and treated as continuous in analysis.

2.2.2.11 Numeracy

We assessed numeracy using the Subjective Numeracy Scale, a self-report measure with two four-item subscales: perceived ability to perform mathematical tasks and preference for the use of numeric versus verbal information (Fagerlin et al., 2007). Each item was answered on a six-point Likert-type scale (e.g., "not at all good" to "extremely good" and "always prefer words" to "always prefer numbers/percentages"). Following standard scoring, we averaged the responses (Cronbach's α of 0.85), and treated the average score as continuous in analysis. Higher scale scores reflected greater perceived ability and stronger preference for numeric information.

2.2.2.12 Health Literacy

Health literacy was assessed with a three-item screener (e.g., "How confident are you filling out medical forms by yourself?") (Chew et al., 2008). Each item was answered on five-point Likert-type scales. Responses were summed and treated as continuous in analysis.

2.2.3 Sociodemographic Characteristics

We also assessed the following characteristics as potential covariates: age, race, ethnicity, Jewish ancestry, educational attainment, marital status, having biological children, planning to become pregnant in next year, urban vs. rural residence, household income, health insurance status, personal history of cancer, family history of cancer, and having had prior genetic testing.

2.3 Analysis

Descriptive statistics were calculated for each variable. We used chi-squared tests to evaluate whether Latina women differed from non-Latina women in their level of interest in various types of genetic testing. Because of sociodemographic differences by ethnicity, we also examined the effect of Latina ethnicity in multivariable logistic regression models. To identify potential predictors of interest in cancer predisposition testing and carrier status testing, which were the areas of focus for this analysis, we used chi-squared tests for associations with categorical variables, t-tests for continuous variables, and the Wilcoxon Rank Sum Test for non-normal continuous variables. Of these predictors, those with a bivariate association of $p < 0.10$ were included in multivariable logistic regression models (Hildalgo and Goodman, 2013). Sociodemographic covariates (i.e., age, race, Jewish ancestry, educational attainment, marital status, having biological children, planning to become pregnant in the next year, urban vs. rural residence, household income, health insurance status, personal history of cancer, family history of cancer, having had prior genetic testing) were also assessed in these models, and those covariates with a $p < 0.10$ were retained in final multivariable logistic regression models. An interaction variable between ethnicity and intolerance for uncertainty was also tested for entry in these models. However, since the interaction term was not significant in any of the models we present the final models without the interaction term. We re-fit the final multivariable models on samples stratified by ethnicity to examine whether predictors of the interest outcome variables were the same for Latina vs. non-Latina women. For final models, we present odds ratios along with their corresponding 95% confidence intervals. R was used for all analyses (R Core Team, 2019). The statistical significance level was set at $p < 0.05$.

TABLE 1 | Sociodemographic characteristics of 450 female respondents by ethnicity.

Characteristics	*Latina*/Hispanic (*n* = 176)		Non-Hispanic/non-*Latina*/other (*n* = 274)		*p*-value
	N	%	*N*	%	
Educational attainment					0.29
High school degree/junior high	44	25.1	86	31.5	
Some college/associate degree	76	43.4	102	37.4	
College degree or higher	55	31.4	85	31.1	
Married/living as married	72	41.1	104	38.4	0.63
Have biological children	94	53.7	114	41.9	**0.019**
Race					<**0.001**
White/Caucasian	77	44.0	147	53.8	
Black/African-American	26	14.9	83	30.4	
Asian/Pacific Islander/Native Hawaiian	16	9.1	23	8.4	
Multi-racial	22	12.6	19	7.0	
Other	34	19.4	1	0.4	
Have Ashkenazi (Eastern European) Jewish ancestry	46	26.3	30	11.1	<**0.001**
Planning to become pregnant in the next year					**0.048**
Yes	60	34.5	65	23.8	
No	85	48.9	158	57.9	
Not sure	29	16.7	50	18.3	
Geographic location					<**0.001**
Urban	11	6.4	56	21.1	
Rural/Frontier	161	93.6	210	78.9	
Household income					0.067
<$25,000	38	21.7	82	29.9	
$25,000–$49,999	44	25.1	62	22.6	
$50,000–$74,999	43	24.6	57	20.8	
>$74,999	46	26.3	56	20.4	
Prefer not to answer	4	2.3	17	6.2	
Health insurance					0.17
Private insurance	89	50.9	126	46.2	
Public insurance	66	37.7	98	35.9	
No	20	11.4	49	17.9	
Have had genetic testing	60	37.7	63	26.2	**0.02**
Have personal history of cancer	27	15.3	19	7.0	**0.007**
Have family history of cancer	90	57.0	141	58.0	0.915
	Mean	SD	Mean	SD	
Current age	25.0	4.5	26.1	5.0	**0.02**

SD, standard deviation.

3 RESULTS

3.1 Participant Characteristics

The mean age of respondents was 25.7 years (SD = 4.8). About 50% of respondents identified as white/Caucasian, 39% as Latina/Hispanic, and 24% as Black/African-American. The majority had not completed college; 29% had a high school degree or less and 40% had some college education. Respondents had a moderate level of self-reported numeracy ability (M = 3.9; SD = 1.2) and health literacy (M = 9.5; SD = 1.8). About half (50%) had a household income of <$50,000. Less than half were married or living as married (40%). About 47% had biological children, and 28% reported that they were planning to become pregnant in the next year. Few respondents (10%) reported a personal history of cancer, although 58% had a family history of cancer. Less than half (31%) reported having had prior genetic testing. As shown in **Table 1**, having had biological children, race, having Ashkenazi Jewish ancestry, planning to become pregnant in the next year, rural vs. urban residence, having had genetic testing, having a personal history of cancer, and age differed significantly between Latina and non-Latina respondents.

In terms of possible psychosocial predictors of interest in genetic testing (**Table 2**), approximately 27% of participants reported that cancer genetic information was very important to them and 35% thought that carrier status information was very important. Most (65%) sought health information either somewhat often or very often. About half of respondents believed that important others strongly valued keeping oneself healthy (48%). Respondents had a moderate level of health consciousness (M = 3.7; SD = 0.9), health information orientation (M = 3.6; SD = 0.8), and intolerance for uncertainty (M = 39.8; SD = 10.1). Less than one-third perceived themselves as more likely to develop breast (24%), ovarian (32%), or colon (31%) cancer than the average woman of their race. They had moderate worry about their genetic risks (M = 4.3; SD = 1.6), and a moderate degree of genetic self-efficacy (M = 9.5; SD = 3.1) and genetic knowledge (M = 9.1; SD = 4.3).

TABLE 2 | Psychosocial characteristics of 450 female respondents.

Characteristics	*N*	%
High importance of cancer genetic information (*n* = 449)	121	26.9
High importance of carrier status information (*n* = 449)	155	34.5
Health information seeking (n = 447)		
Very often	104	23.3
Somewhat often	186	41.6
Not very often	126	28.2
Not at all	31	6.9
Risk perception (Somewhat more likely/a lot more likely)		
Breast cancer (*n* = 445)	108	24.3
Ovarian cancer (*n* = 446)	142	31.8
Colon cancer (*n* = 446)	139	31.2
Strongly agree that the people who mean the most to me think I should learn more about ways I can keep myself healthy. (*n* = 447)	214	47.9
Very motivated to do what these people want you to do. (*n* = 447)	194	43.4
	Mean (SD)	Range
Numeracy Ability subscale (*n* = 446)	3.9 (1.2)	1–6
Numeracy Preference subscale (*n* = 447)	3.9 (1.1)	1–6
Health Literacy (*n* = 450)	9.5 (1.8)	0–13
Worry about genetic risks (*n* = 450)	4.3 (1.6)	1–7
Genetic self-efficacy (*n* = 450)	9.5 (3.1)	0–15
Genetic knowledge (*n* = 450)	9.1 (4.3)	0–18
Health consciousness (*n* = 448)	3.7 (0.9)	1–5
Health information orientation (*n* = 448)	3.6 (0.8)	1–5
Intolerance for uncertainty (*n* = 450)	39.8 (10.1)	0–60

SD, standard deviation.

TABLE 3 | Interest in cancer predisposition testing and carrier screening among respondents (*n* = 450).

Outcome	*N*	%
Very interested in genetic testing as part of a general check-up		
With your health care provider (*n* = 450)	110	24.4
Through your gynecologist's office (*n* = 450)	103	22.9
Very interested in genetic testing to learn about		
Your risk of developing a disease that may be able to be prevented or treated (*n* = 447)	110	24.6
Your risk of developing a *cancer* that may be able to be prevented or treated (*n* = 447)	116	26.0
Your risk of developing a disease that cannot be prevented or treated (*n* = 447)	87	19.5
How you would respond to a medication for a disease (*n* = 447)	95	21.3
A gene variation that does not affect your health but might affect the health of your children (*n* = 447)	119	26.6
Yes, Interested in having the following types of genetic testing in the next year		
Your risk of developing a disease that may be able to be prevented or treated (*n* = 450)	246	54.7
Your risk of developing a *cancer* that may be able to be prevented or treated (*n* = 449)	222	49.4
Your risk of developing a disease that cannot be prevented or treated (*n* = 450)	203	45.1
How you would respond to a medication for a disease (*n* = 449)	239	53.2
A gene variation that does not affect your health but might affect the health of your children (*n* = 449)	249	55.5

SD, standard deviation.

3.2 Interest in Different Types of Genetic Testing

We assessed how interested respondents would be in having each type of genetic testing in the next year if it were offered (**Table 3**). More than half reported that they would be interested in receiving genetic testing in the next year to learn information about carrier status (56%), risk of a preventable or treatable disease (55%), and medication response (53%). A slightly lower proportion reported that they would be interested in receiving genetic testing to learn about their risk of a preventable or treatable cancer (49%), and the lowest level of interest was in having genetic testing to learn about the risk of an unpreventable or untreatable disease (45%).

To further investigate women's level of interest in genetic testing, we also examined the proportion of respondents having a high level of interest (i.e., reporting being "very interested"). When asked about genetic testing as part of a general check-up, 24% were very interested in receiving testing with their healthcare provider and 23% through a gynecologist. For different types of testing, we found the highest proportions were very interested in genetic testing to learn about their risk of developing a preventable or treatable cancer (26%) and learn about carrier status (27%). Similarly, about 25%

TABLE 4 | Bivariate associations between genetic testing interest and ethnicity (n = 450).

		Latina	Non-Latina	*p*-value
		***n* = 176**	***n* = 274**	
Interest in genetic testing to learn about				
Your risk of developing a disease that may be able to be prevented or treated	Very interested	51 (29.1)	59 (21.7)	*0.094*
	Other categories	124 (70.9)	213 (78.3)	
Your risk of developing a *cancer* that may be able to be prevented or treated	Very interested	56 (32.0)	60 (22.1)	**0.026**
	Other categories	119 (68.0)	212 (77.9)	
Your risk of developing a disease that cannot be prevented or treated	Very interested	45 (25.7)	42 (15.4)	**0.011**
	Other categories	130 (74.3)	230 (84.6)	
How you would respond to a medication for a disease	Very interested	41 (23.4)	54 (19.9)	0.43
	Other categories	134 (76.6)	218 (80.1)	
A gene variation that does not affect your health but might affect the health of your children	Very interested	56 (32.0)	63 (23.2)	*0.051*
	Other categories	119 (68.0)	209 (76.8)	
Interest in genetic testing as part of a general check-up				
With your health care provider	Very Interested	47 (26.7)	63 (23.0)	0.43
	Other categories	129 (73.3)	211 (77.0)	
Through your gynecologist's office	Very Interested	48 (27.3)	55 (20.1)	*0.097*
	Other categories	128 (72.7)	219 (79.9)	
Interested in having the following types of genetic testing in the next year				
Your risk of developing a disease that may be able to be prevented or treated	Yes	107 (60.8)	139 (50.7)	**0.046**
	No/Not sure	69 (39.2)	135 (49.3)	
Your risk of developing a *cancer* that may be able to be prevented or treated	Yes	89 (50.6)	133 (48.7)	0.78
	No/Not sure	87 (49.4)	140 (51.3)	
Your risk of developing a disease that cannot be prevented or treated	Yes	87 (49.4)	116 (42.3)	0.17
	No/Not sure	89 (50.6)	158 (57.7)	
How you would respond to a medication for a disease	Yes	99 (56.6)	140 (51.1)	0.30
	No/Not sure	76 (43.4)	134 (48.9)	
A gene variation that does not affect your health but might affect the health of your children	Yes	103 (58.9)	146 (53.3)	0.29
	No/Not sure	72 (41.1)	128 (46.7)	

p-*value by Chi-square Test; Significant results are bolded.*

were very interested in learning about their risk of preventable or treatable diseases more generally. A slightly lower proportion reported being very interested in genetic testing to learn about pharmacogenomic variants (21%) or risk of an unpreventable or untreatable disease (20%).

3.3 Differences in Interest in Testing by Ethnicity

Interest in different types of testing was generally similar between Latina respondents and non-Latina respondents, as was interest in genetic testing as part of a general check-up (**Table 4**). However, for interest in having genetic testing in the next year if offered, we found that Latina respondents (60.8%) were more likely to say that they would be interested in testing for risk of a preventable or treatable disease than non-Latina respondents (51%; p = 0.046). For level of interest in different types of genetic testing, we found that Latina respondents (32.0%) were more likely to be very interested in learning about their risk of a preventable or treatable cancer compared with non-Latina respondents (22.1%; p = 0.03). Latina respondents (25.7%) were also more likely to be very interested in learning about their risk of an unpreventable or untreatable disease compared with non-Latina respondents (15.4%; p = 0.01). There was a trend toward a greater proportion being very interested in carrier status information (32.0% among Latina participants vs. 23.2% among non-Latina participants, p = 0.051).

3.4 Bivariate Predictors of Interest in Genetic Testing

We next examined the bivariate relationships of hypothesized predictors and ethnicity with interest in genetic testing for cancer predisposition and carrier status. As shown in **Table 5**, being interested in both types of genetic testing in the next year if it were offered was associated with higher worry about genetic risks (both $p < 0.001$), higher genetic self-efficacy (both $p < 0.05$), higher genetic knowledge (both $p < 0.001$), greater perceived importance of cancer genetic information (both $p < 0.001$) and carrier status information (both $p < 0.001$), greater health consciousness (both $p < 0.001$), stronger health orientation (both $p < 0.001$), greater health information seeking (both $p < 0.05$), stronger social influence (both $p < 0.001$), higher intolerance for uncertainty (both $p < 0.001$), and higher subjective numeracy (both $p < 0.001$). Higher breast cancer risk perceptions were significantly associated with interest in cancer predisposition testing ($p < 0.05$) but not carrier status testing, and ovarian and colorectal cancer risk perceptions were not significantly related with interest in either type of genetic testing in the next year.

We found similar patterns of bivariate associations for the outcome of being very interested in genetic testing, with the exception of risk perceptions. Being very interested in both types of genetic testing was associated with higher worry about genetic risks (both $p < 0.001$), higher genetic self-efficacy (both $p < 0.001$), higher genetic knowledge (both $p < 0.001$), greater perceived importance of cancer genetic information (both $p < 0.001$) and

TABLE 5 | Bivariate predictors of interest in receiving cancer predisposition testing and carrier screening (n = 450).

Predictor	Cancer predisposition testing		Carrier status	
	Very interested[a]	Yes, interested in next year[b]	Very interested[a]	Yes, interested in next year[b]
	n = 116	*n = 222*	*n = 119*	*n = 249*
Worry about genetic risks, median [IQR]	**6.0 [4.0–7.0]**	**5.0 [3.8–6.3]**	**5.7 [4.0–7.0]**	**5.0 [3.7–6.3]**
Genetic self-efficacy, mean (SD)	**10.4 (3.9)**	**9.8 (3.3)**	**10.3 (3.8)**	**9.8 (3.2)**
Genetic knowledge, median [IQR]	**11.0 [8.0–13.0]**	**11.0 [9.0–14.0]**	**11.0 [8.0–13.0]**	**11.0 [7.0–13.0]**
Importance of cancer genetic information, n (%)				
Very important	**76 (65.5)**	**88 (39.6)**	**72 (60.5)**	**91 (36.5)**
Other categories	**40 (34.5)**	**134 (60.4)**	**47 (39.5)**	**158 (63.5)**
Importance of carrier status information, n (%)				
Very important	**91 (78.4)**	**110 (49.5)**	**86 (72.3)**	**115 (46.2)**
Other categories	**25 (21.6)**	**112 (50.5)**	**33 (27.7)**	**134 (53.8)**
Health consciousness, median [IQR]	**4.4 [4.0–5.0]**	**4.0 [3.4–4.6]**	**4.2 [3.6–5.0]**	**3.8 [3.2–4.4]**
Health orientation, median [IQR]	**4.4 [3.8–4.9]**	**3.9 [3.3–4.5]**	**4.3 [3.6–4.9]**	**3.8 [3.1–4.4]**
Health information seeking, n (%)				
Very often	**47 (40.5)**	**62 (27.9)**	**48 (40.3)**	**68 (27.4)**
Somewhat often	**46 (39.7)**	**93 (41.9)**	**47 (39.5)**	**104 (41.9)**
Not very often	**17 (14.7)**	**57 (25.7)**	**16 (13.4)**	**59 (23.8)**
Not at all	**6 (5.2)**	**10 (4.5)**	**8 (6.7)**	**17 (6.9)**
Risk perceptions				
Breast cancer, n (%)				
Somewhat more likely/a lot more likely	**45 (38.8)**	**65 (29.5)**	**48 (40.3)**	69 (27.8)
About as likely	**38 (32.8)**	**80 (36.4)**	**34 (28.6)**	88 (35.5)
A lot less likely/somewhat less likely	**33 (28.4)**	**75 (34.1)**	**37 (31.1)**	91 (36.7)
Ovarian cancer, n (%)				
Somewhat more likely/a lot more likely	**50 (43.1)**	73 (33.0)	**51 (42.9)**	80 (32.3)
About as likely	**37 (31.9)**	81 (36.7)	**34 (28.6)**	93 (37.5)
A lot less likely/somewhat less likely	**29 (25.0)**	67 (30.3)	**34 (28.6)**	75 (30.2)
Colon cancer, n (%)				
Somewhat more likely/a lot more likely	35 (30.2)	61 (27.6)	32 (26.9)	72 (29.0)
About as likely	31 (26.7)	74 (33.5)	35 (29.4)	75 (30.2)
A lot less likely/somewhat less likely	50 (43.1)	86 (38.9)	52 (43.7)	101 (40.7)
Motivation				
Normative beliefs, n (%)				
Strongly Agree	**91 (78.4)**	**141 (63.5)**	**89 (74.8)**	**141 (56.9)**
Other categories	**25 (21.6)**	**81 (36.5)**	**30 (25.2)**	**107 (43.1)**
Motivation to comply, n (%)				
Very motivated	**79 (68.1)**	**118 (53.2)**	**79 (66.4)**	**125 (50.4)**
Other categories	**37 (31.9)**	**104 (46.8)**	**40 (33.6)**	**123 (49.6)**
Intolerance for uncertainty, mean (SD)	**45.1 (10.9)**	**41.6 (10.0)**	**44.4 (11.0)**	**41.5 (10.3)**
Subjective numeracy, mean (SD)	**4.5 (1.1)**	**4.2 (1.0)**	**4.4 (1.2)**	**4.1 (1.1)**

Bold indicates p < *0.05; SD: standard deviation; IQR: interquartile range;* p-*value by Wilcoxon Rank Sum Test for the following variables: Worry about genetic risks, Genetic knowledge, Health consciousness, and Health orientation;* p-*value by T-test for Genetic self-efficacy, Intolerance for uncertainty, and Subjective numeracy;* p-*value by Chi-squared Test for: Importance of cancer genetic information, Importance of carrier status information, Health information seeking, and Risk perceptions (breast, ovarian, and colon cancers).*

[a]*Very interested vs. other categories.*

[b]*Yes vs. no/not sure.*

carrier status information (both $p < 0.001$), greater health consciousness (both $p < 0.001$), stronger health orientation (both $p < 0.001$), greater health information seeking (both $p < 0.001$), higher breast cancer risk perceptions (both $p < 0.001$), higher ovarian cancer risk perceptions (both $p < 0.01$), stronger social influence (both $p < 0.001$), higher intolerance for uncertainty (both $p < 0.001$), and higher subjective numeracy (both $p < 0.001$).

3.5 Multivariable Predictors of Interest in Genetic Testing

In multivariable logistic regression models, Latina ethnicity was not associated with any interest outcome (**Table 6**). In multivariable models, respondents who were interested in being tested for cancer predisposition in the next year had higher worry about genetic risks (OR = 1.44; 95% CI: 1.22–1.72) and higher genetic knowledge (OR = 1.26; 95% CI: 1.18–1.35). They were also more likely to report that they did not seek health information very often compared to those who said not at all (OR = 2.97; 95% CI: 1.05–8.93). Respondents who were interested in receiving carrier screening in the next year had also higher worry about genetic risks (OR = 1.39; 95% CI: 1.17–1.64) and higher genetic knowledge (OR = 1.11; 95% CI: 1.05–1.18). They were also more likely to perceive carrier status information as very important (OR = 2.46; 95% CI: 1.24–4.97), although

TABLE 6 | Multivariable logistic regression models showing predictors of interest in receiving cancer predisposition testing and carrier screening.

Tested predictors	Cancer predisposition testing		Carrier status	
	Very interested[a] (*n* = 440)	Yes, interested in next year[b] (*n* = 442)	Very interested[a] (*n* = 442)	Yes, interested in next year[b] (*n* = 431)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Worry about genetic risks	**1.29 (1.06, 1.57)**	**1.44 (1.22, 1.72)**	1.12 (0.93, 1.35)	**1.39 (1.17, 1.64)**
Genetic self-efficacy	0.95 (0.86, 1.05)	1.01 (0.92, 1.10)	0.98 (0.89, 1.08)	0.98 (0.90, 1.07)
Genetic knowledge	1.02 (0.94, 1.11)	**1.26 (1.18, 1.35)**	1.09 (1.00, 1.18)	**1.11 (1.05, 1.18)**
Importance of cancer genetic information	**2.71 (1.35, 5.46)**	1.44 (0.72, 2.90)	**2.58 (1.29, 5.15)**	1.21 (0.61, 2.42)
Importance of carrier status information	**3.53 (1.69, 7.44)**	1.53 (0.78, 3.02)	**3.00 (1.44, 6.30)**	**2.46 (1.24, 4.97)**
Health consciousness	**1.89 (1.06, 3.42)**	0.82 (0.54, 1.24)	0.95 (0.55, 1.63)	**0.60 (0.39, 0.91)**
Health orientation	1.21 (0.65, 2.29)	1.47 (0.90, 2.42)	1.31 (0.73, 2.41)	1.46 (0.91, 2.37)
Health information seeking[c]				
Not very often	0.64 (0.17, 2.58)	**2.97 (1.05, 8.93)**	0.28 (0.08, 1.01)	0.68 (0.26, 1.75)
Somewhat often	0.60 (0.17, 2.32)	2.03 (0.73, 5.98)	0.40 (0.13, 1.33)	0.70 (0.27, 1.80)
Very often	0.60 (0.15, 2.49)	1.78 (0.58, 5.67)	0.53 (0.15, 1.95)	0.72 (0.24, 2.08)
Breast Cancer Risk Perception[d]				
About as likely	1.32 (0.54, 3.29)	1.21 (0.71, 2.07)	0.98 (0.45, 2.17)	
Somewhat more likely/a lot more likely	1.53 (0.60, 3.92)	1.29 (0.70, 2.38)	1.95 (0.85, 4.51)	
Ovarian Cancer Risk Perception[d]				
About as likely	1.15 (0.46, 2.84)		0.83 (0.37, 1.86)	
Somewhat more likely/a lot more likely	1.29 (0.48, 3.46)		1.17 (0.49, 2.80)	
Normative beliefs	1.34 (0.64, 2.78)	1.69 (0.99, 2.91)	1.48 (0.76, 2.88)	1.08 (0.63, 1.83)
Motivation to comply	1.03 (0.50, 2.11)	0.80 (0.45, 1.40)	1.24 (0.64, 2.38)	1.08 (0.62, 1.86)
Intolerance for uncertainty	1.00 (0.96, 1.04)	0.98 (0.95, 1.01)	1.00 (0.97, 1.04)	1.00 (0.97, 1.03)
Subjective numeracy	1.32 (0.94, 1.86)	1.18 (0.89, 1.58)	0.99 (0.71, 1.36)	1.13 (0.85, 1.50)
Covariates				
Non-Hispanic/Non-Latina/Other[e]	0.56 (0.30, 1.04)	0.97 (0.60, 1.58)	0.64 (0.36, 1.14)	1.01 (0.63, 1.62)
Health Literacy	**1.38 (1.13, 1.70)**			
Educational attainment[f]				
Some college/associate degree			**0.46 (0.22, 0.96)**	1.52 (0.87, 2.68)
College degree or higher			1.20 (0.55, 2.63)	1.07 (0.56, 2.02)
Household income[g]				
$25,000–$49,999			0.69 (0.31, 1.52)	**2.42 (1.30, 4.57)**
$50,000–$74,999			2.02 (0.90, 4.58)	**2.31 (1.19, 4.58)**
>$74,999			1.09 (0.47, 2.54)	1.90 (0.96, 3.77)
Prefer not to answer			0.15 (0.01, 0.94)	2.74 (0.91, 8.66)
Geographic location: Urban[h]				**2.02 (1.06, 3.88)**
Health Insurance[i]				
Public insurance				1.15 (0.58, 2.29)
Private insurance				1.59 (0.80, 3.19)

Significant results are bolded.
[a]*Very interested vs. other categories.*
[b]*Yes vs. no/not sure.*
[c]*Compared with not at all.*
[d]*Compared with a lot less likely/somewhat less likely.*
[e]*Compared with Latina/Hispanic.*
[f]*Compared with High school degree/junior high.*
[g]*Compared with <$25,000.*
[h]*Compared with Rural/Frontier.*
[i]*Compared with no insurance.*

those with lower health consciousness were more interested in genetic testing for carrier status (OR = 0.60; 95% CI: 0.39–0.91).

For the outcome of high level of interest, being very interested in genetic testing for cancer predisposition was associated with higher worry about genetic risks (OR = 1.29; 95% CI: 1.06–1.57), higher perceived importance of cancer genetic information (OR = 2.71; 95% CI: 1.35–5.46), higher perceived importance of carrier status information (OR = 3.53; 95% CI: 1.69–7.44), and higher health literacy (OR = 1.38; 95% CI: 1.13–1.70). Being very interested in genetic testing for carrier status was associated with higher perceived importance of cancer genetic information (OR = 2.57; 95% CI: 1.29–5.12) and higher perceived importance of carrier status information (OR = 3.00; 95% CI: 1.44–6.29). In this model, respondents with some college were less likely to report being very interested than those with a high school degree (OR = 0.46; 95% CI: 0.22–0.95).

In models stratified by Latina ethnicity, predictors of interest in having cancer predisposition genetic testing in the next year were similar between strata (**Table 7**), although normative

TABLE 7 | Multivariable logistic regression models, stratified by ethnicity, showing predictors of interest in receiving cancer predisposition testing and carrier screening in the next year.

Tested predictors	Interest in receiving genetic testing for cancer predisposition testing in next year[a]		Interest in receiving genetic testing for carrier status in next year[a]	
	Latina/Hispanic (*n* = 170)	Non-Hispanic/non-*latina*/other (*n* = 272)	Latina/hispanic (*n* = 168)	Non-hispanic/non-latina/other (*n* = 263)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Worry about genetic risks	**1.68 (1.22, 2.40)**	**1.34 (1.09, 1.66)**	**1.48 (1.08, 2.08)**	**1.35 (1.10, 1.67)**
Genetic self-efficacy	1.03 (0.87, 1.23)	1.00 (0.89, 1.11)	1.05 (0.89, 1.23)	0.92 (0.83, 1.03)
Genetic knowledge	**1.28 (1.13, 1.47)**	**1.25 (1.15, 1.36)**	**1.14 (1.02, 1.28)**	1.07 (1.00, 1.15)
Importance of cancer genetic information	1.46 (0.41, 5.02)	1.47 (0.61, 3.55)	0.69 (0.20, 2.27)	1.35 (0.56, 3.30)
Importance of carrier status information	1.31 (0.38, 4.59)	1.41 (0.62, 3.27)	1.61 (0.45, 6.02)	**3.06 (1.33, 7.38)**
Health consciousness	1.00 (0.45, 2.19)	0.82 (0.49, 1.37)	0.80 (0.37, 1.67)	0.62 (0.36, 1.04)
Health orientation	1.48 (0.61, 3.74)	1.50 (0.81, 2.81)	1.90 (0.81, 4.63)	1.32 (0.71, 2.48)
Health information seeking[b]				
Not very often	3.93 (0.44, 88.71)	2.85 (0.86, 10.04)	0.08 (0.00, 0.82)	1.38 (0.46, 4.29)
Somewhat often	2.52 (0.28, 56.86)	1.96 (0.61, 6.68)	0.10 (0.00, 0.99)	1.29 (0.43, 3.97)
Very often	2.38 (0.22, 58.06)	1.79 (0.49, 6.80)	0.09 (0.00, 1.02)	1.61 (0.44, 5.94)
Breast Cancer Risk Perception[c]				
About as likely	1.13 (0.44, 2.92)	1.26 (0.65, 2.44)		
Somewhat more likely/a lot more likely	1.32 (0.46, 3.83)	1.28 (0.58, 2.81)		
Normative beliefs	1.34 (0.52, 3.43)	**2.02 (1.01, 4.07)**	1.23 (0.52, 2.89)	1.03 (0.52, 2.03)
Motivation to comply	1.46 (0.58, 3.59)	0.49 (0.22, 1.04)	0.84 (0.33, 2.04)	1.08 (0.52, 2.21)
Intolerance for uncertainty	0.95 (0.90, 1.01)	0.99 (0.95, 1.03)	1.01 (0.96, 1.07)	0.99 (0.95, 1.03)
Subjective numeracy	0.91 (0.48, 1.69)	1.30 (0.93, 1.83)	0.99 (0.56, 1.69)	1.15 (0.82, 1.62)
Educational attainment[d]				
Some college/associate degree			1.03 (0.38, 2.78)	1.74 (0.87, 3.56)
College degree or higher			0.74 (0.22, 2.42)	1.45 (0.66, 3.20)
Household income[e]				
$25,000-$49,999			1.56 (0.52, 4.76)	**2.82 (1.27, 6.45)**
$50,000-$74,999			2.56 (0.80, 8.48)	1.75 (0.74, 4.19)
>$74,999			1.31 (0.41, 4.25)	2.18 (0.90, 5.36)
Prefer not to answer			3.24 (0.35, 52.01)	1.82 (0.50, 6.79)
Geographic location: Urban[f]			2.44 (0.57, 11.24)	2.04 (0.99, 4.26)
Health Insurance[g]				
Public insurance			1.69 (0.45, 6.75)	1.03 (0.45, 2.39)
Private insurance			2.23 (0.60, 8.80)	1.42 (0.62, 3.29)

Significant results are bolded.
[a]*Yes vs. no/not sure.*
[b]*Compared with not at all.*
[c]*Compared with a lot less likely/somewhat less likely.*
[d]*Compared with High school degree/junior high.*
[e]*Compared with <$25,000.*
[f]*Compared with Rural/Frontier.*
[g]*Compared with no insurance.*

beliefs were a predictor of interest only among non-Latina respondents (OR = 2.02; 95% CI: 1.01–4.07). For predictors of interest in testing to learn carrier status information, worry about genetic risks was a significant predictor in both strata. However, higher genetic knowledge was a predictor of interest among Latina women (OR = 3.06; 95% CI: 1.33–7.38), and greater importance of carrier status information and income were predictors only among non-Latina respondents (OR = 2.82; 95% CI: 1.27–6.45). For predictors of a high level of interest in genetic testing (**Table 8**), higher worry about genetic risks was a significant predictor of being very interested in cancer predisposition testing only among non-Latina respondents (OR = 1.38; 95% CI: 1.06–1.79). Higher perceived importance of cancer genetic information was a significant predictor of being very interested in both cancer predisposition testing (OR = 3.85; 95% CI: 1.24–11.88) and carrier screening (OR = 3.60; 95% CI: 1.10–11.82) among Latina respondents, while higher perceived importance of carrier status information was related to these outcomes among non-Latina respondents (OR = 7.53; 95% CI: 2.64–21.46 and OR = 3.34; 95% CI: 1.32–8.43, respectively).

4 DISCUSSION

In this study, we examined interest, and predictors of interest, in carrier screening and cancer predisposition testing offered as part of routine care among an ethnically diverse sample of 450 women aged 20–35. We found substantial interest in both types of genetic testing, with about half of respondents reporting that they would have each type of testing in the next year if it were offered. The proportion interested in testing for carrier status is consistent

TABLE 8 | Multivariable logistic regression models, stratified by ethnicity, showing predictors of being very interested in cancer predisposition testing and carrier screening.

Tested predictors	Very interested in cancer predisposition testing[a]		Very interested in genetic testing for carrier status[a]	
	Latina/Hispanic (*n* = 169)	Non-Hispanic/non-*latina*/other (*n* = 271)	Latina/hispanic (*n* = 169)	Non-hispanic/non-latina/other (*n* = 270)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Worry about genetic risks	1.18 (0.85, 1.66)	**1.38 (1.06, 1.79)**	1.03 (0.72, 1.47)	1.11 (0.89, 1.38)
Genetic self-efficacy	0.88 (0.75, 1.03)	1.01 (0.88, 1.15)	0.98 (0.82, 1.16)	0.98 (0.87, 1.10)
Genetic knowledge	1.00 (0.87, 1.13)	1.09 (0.98, 1.23)	1.10 (0.97, 1.25)	1.07 (0.97, 1.18)
Importance of cancer genetic information	**3.85 (1.25, 11.88)**	2.37 (0.92, 6.13)	**3.60 (1.10, 11.82)**	1.82 (0.75, 4.39)
Importance of carrier status information	1.41 (0.43, 4.64)	**7.53 (2.64, 21.46)**	2.03 (0.55, 7.41)	**3.34 (1.32, 8.43)**
Health consciousness	1.84 (0.78, 4.35)	1.52 (0.63, 3.67)	0.77 (0.32, 1.87)	1.17 (0.59, 2.35)
Health orientation	1.02 (0.41, 2.51)	1.47 (0.57, 3.79)	1.20 (0.46, 3.11)	1.12 (0.52, 2.39)
Health information seeking[b]				
Not very often	0.91 (0.04, 23.77)	0.70 (0.14, 3.59)	0.58 (0.02, 15.59)	0.29 (0.08, 1.15)
Somewhat often	1.57 (0.06, 38.90)	0.33 (0.07, 1.63)	1.46 (0.06, 37.76)	0.35 (0.10, 1.23)
Very often	1.08 (0.04, 29.43)	0.38 (0.06, 2.23)	2.06 (0.07, 57.66)	0.43 (0.10, 1.81)
Breast cancer risk perception[c]				
About as likely	1.72 (0.47, 6.23)	0.87 (0.25, 3.00)	1.62 (0.45, 5.81)	0.82 (0.32, 2.11)
Somewhat more likely/a lot more likely	2.90 (0.82, 10.26)	0.71 (0.17, 2.93)	**3.99 (1.11, 14.40)**	0.86 (0.29, 2.60)
Ovarian cancer risk perception[c]				
About as likely	1.16 (0.32, 4.19)	0.98 (0.27, 3.58)	0.32 (0.09, 1.15)	1.63 (0.57, 4.64)
Somewhat more likely/a lot more likely	0.78 (0.21, 2.84)	2.45 (0.57, 10.57)	0.51 (0.15, 1.75)	2.61 (0.82, 8.30)
Normative beliefs	1.42 (0.52, 3.85)	0.92 (0.31, 2.75)	0.83 (0.29, 2.39)	1.96 (0.85, 4.50)
Motivation to comply	0.79 (0.29, 2.18)	1.80 (0.61, 5.28)	1.03 (0.37, 2.89)	1.37 (0.57, 3.27)
Intolerance for uncertainty	1.01 (0.95, 1.07)	1.00 (0.95, 1.05)	1.04 (0.97, 1.10)	0.99 (0.95, 1.03)
Subjective numeracy	1.12 (0.64, 1.95)	1.23 (0.79, 1.94)	0.83 (0.46, 1.47)	1.01 (0.69, 1.48)
Health Literacy	**1.36 (1.03, 1.79)**	1.29 (0.97, 1.73)		
Educational attainment[d]				
Some college/associate degree			0.41 (0.13, 1.26)	0.73 (0.29, 1.82)
College degree or higher			1.38 (0.38, 5.00)	1.11 (0.42, 2.98)
Household income[e]				
$25,000-$49,999			0.72 (0.20, 2.61)	0.74 (0.27, 2.02)
$50,000-$74,999			1.50 (0.42, 5.40)	1.88 (0.65, 5.46)
>$74,999			0.97 (0.27, 3.54)	1.22 (0.41, 3.65)
Prefer not to answer			0.14 (0.00, 8.28)	0.43 (0.06, 2.90)

Significant results are bolded.
[a]*Very interested vs. other categories.*
[b]*Compared with not at all.*
[c]*Compared with a lot less likely/somewhat less likely.*
[d]*Compared with High school degree/junior high.*
[e]*Compared with <$25,000.*

with the proportions found to be interested in a hypothetical expanded carrier screening test in prior studies (van Steijvoort et al., 2020; Nijmeijer et al., 2019). The findings also add to our knowledge about interest in cancer predisposition testing in this population if conducted as part of routine clinical care, indicating support from survey respondents for offering genetic testing as part of routine clinical care. Little prior research has examined interest in population-based genetic testing as part of routine care, although in one prior survey conducted in the Netherlands about half of respondents preferred that pre-pregnancy cancer screening be offered via a general practitioner (Plantinga et al., 2016) and another survey found that participants felt that offering personal genomic risk information to the general population to inform prevention and early detection recommendations is acceptable (Smit et al., 2020).

Of note, however, about half of respondents were not interested in testing in the next year, or were not sure, and many did not indicate the highest level of interest in either type of genetic test. It is therefore critical to develop effective decision support tools so that women can make informed decisions about testing if population-based genetic testing efforts are initiated. Better understanding of the predictors of interest is essential to developing effective decision support tools. Consistent with our prior research conducted with women who had been diagnosed with breast cancer at a young age, we found that women's worry about their broader genetic risks was an important predictor of interest in genetic testing. Notably, worry about genetic risks was predictive, while risk perceptions for breast, ovarian, and colorectal cancer were not predictive of interest in either type of genetic testing in multivariable models. This finding suggests the importance of focusing on information that could be provided about inherited risks, rather than disease risks more generally, in approaches to informed decision making. Also consistent with our prior work, as well as other studies (Kaphingst et al., 2018; Ong et al., 2018), those with higher genetic knowledge were more likely to be interested in both types of testing in the next year. These findings indicate determining key components of genetic knowledge and providing information about these topics is also

important in decisional support so that individuals can make informed decisions about genetic testing.

Unlike the findings from our prior work with women who had been diagnosed with breast cancer at a young age (Kaphingst et al., 2018), in this population health information orientation was not predictive of any interest outcomes. Instead, perceived importance of genetic information, either for cancer predisposition testing or carrier status, was related to a number of the interest outcomes. This finding suggests that this general population, which was unselected for personal or family history of disease, may distinguish to a greater extent between genetic information and other types of health information. This hypothesis is also supported by the lack of relationship between health information seeking and interest in genetic testing, suggesting that genetic testing may not be seen as a way to learn more about one's health and manage health risks, as has been suggested by prior studies conducted in cancer genetic counseling (Rauscher, 2017; Campbell-Salome et al., 2021). In supporting informed decisions about genetic testing as part of routine care, therefore, educational approaches should clearly state what the testing would—and would not—provide in terms of genetic and health risk information.

Neither social influences nor intolerance for uncertainty was predictive of interest in genetic testing for cancer predisposition or carrier status in this population. Our prior research conducted with primary care patients offered genetic susceptibility testing for multiple health conditions had found that social influence from family and friends impacted interest in seeking information about genes (Hay et al., 2012). To explore the importance of social influences further, future research may want to examine different social influences separately. For example, it is possible that interest in genetic testing for carrier status may be more influenced by the normative beliefs of a reproductive partner while interest in testing for cancer predisposition may be more influenced by biological relatives' beliefs or healthcare providers' recommendations. Future research may also want to examine whether a measure of how individuals cope with uncertainty about genetic risks specifically is predictive of interest in genetic testing (Biesecker et al., 2017), given the importance of worry about genetic risks observed among our respondents.

Our findings also add to what is known about interest in genetic testing among young Latina women. We generally found similar interest between Latina and non-Latina women in receiving different types of genetic testing in the next year, although a higher proportion of Latina women reported being interested receiving cancer predisposition testing in the next year and being very interested in this type of testing. However, ethnicity was not a significant predictor of interest in multivariable models, suggesting that younger Latina women are just as interested in testing as non-Latina women. We also found many similarities in predictors of interest, such as the importance of worry about genetic risks and genetic knowledge in both strata. These findings suggest the importance of addressing provider- and system-level barriers that may be driving lack of access to and uptake of genetic testing among interested Latina women (Kaphingst et al., 2015; Hay et al., 2019; Turbitt et al., 2019). We also found that perceived importance of different types of genetic information varied by ethnicity. These findings highlight that culturally appropriate approaches to offering genetic services and supporting informed decisions are strongly needed (Gutierrez et al., 2017; French et al., 2018; Shaibi et al., 2018; Srinivasan et al., 2021), particularly if genetic testing were offered to a broad population.

These findings from this study should be considered in light of its limitations. Because population-based genetic testing is not being offered to this population, we asked about interest in hypothetical testing and actual testing uptake is likely to be lower (Persky et al., 2007; Kaphingst et al., 2019). However, predictors of interest are important to developing educational and decision support efforts. We did not specify the cost of testing in the survey items, which could affect responses. The item wording was based on "genetic testing," but using other terms such as "sequencing" or "screening" could affect level of interest. In addition, we examined interest among potential patients but not providers' attitudes toward offering genetic testing as part of routine healthcare, and this is an important area for future research. Prior research has indicated that provider support for population-based genetic testing may be more limited (Hann et al., 2017). The sample was a convenience sample and a nationally representative sample would be useful in extrapolating interest to the US population. In addition, the survey was only offered in English, and it will be critical for future studies to examine differences among Spanish-speaking Latina women. Examining the importance of variables such as subethnicity and acculturation will also be important for a fuller understanding of the influence of ethnicity on interest and acceptance of genetic testing (Chavez-Yenter et al., 2021a; Chavez-Yenter et al., 2021b).

5 CONCLUSION

Our findings show substantial interest in both cancer predisposition testing and carrier screening among young women if offered as part of routine healthcare. We found similar interest between Latina and non-Latina women in receiving genetic testing, and worry about genetic risks and genetic knowledge were predictors of interest in both of these groups. The findings showed that women who were more concerned about their genetic risks, had higher knowledge about genetics, and perceived genetic information to be more important were more likely to be interested in both types of genetic testing. These findings therefore indicate support from the survey respondents for offering genetic testing for multiple, clinically indicated genetic tests as part of routine health visits. Such efforts will be important in improving access to genetic information among a broader population of patients than has been reached by many genetic testing initiatives to date. However, it will be critical to develop strategies to standardize outreach to all patients, to develop tools to help healthcare providers offer and communicate about genetic testing, and to address the needs of those who have less prior knowledge about genetics and lower health literacy in order to support informed decision making about genetic testing.

DATA AVAILABILITY STATEMENT

The data generated for this study is available upon request from the Corresponding Author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Utah Institutional Review Board. Written informed consent for participation was not required for this study in accordance with the National Legislation and the Institutional requirements.

AUTHOR CONTRIBUTIONS

KAK and WKK designed the study. JRB performed statistical analysis. KAK drafted the manuscript. JRB, BMD, DC-Y, and AV helped to draft the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.866062/full#supplementary-material

REFERENCES

Abul-Husn, N. S., Manickam, K., Jones, L. K., Wright, E. A., Hartzel, D. N., Gonzaga-Jauregui, C., et al. (2016). Genetic Identification of Familial Hypercholesterolemia within a Single U.S. Health Care System. *Science* 354, aaf7000. doi:10.1126/science.aaf7000

Alford, S. H., McBride, C. M., Reid, R. J., Larson, E. B., Baxevanis, A. D., and Brody, L. C. (2011). Participation in Genetic Testing Research Varies by Social Group. *Public Health Genomics* 14, 85–93. doi:10.1159/000294277

American College of Obstetrics and Gynecology (2019a). ACOG Committee Opinion No. 762: Prepregnancy Counseling. *Obstet. Gynecol.* 133, e78–e89. doi:10.1097/AOG.0000000000003013

American College of Obstetrics and Gynecology (2017a). Committee Opinion No. 690 Summary: Carrier Screening in the Age of Genomic Medicine. *Obstet. Gynecol.* 129, 595–596. doi:10.1097/AOG.0000000000001947

American College of Obstetrics and Gynecology (2017b). Committee Opinion No. 691 Summary: Carrier Screening for Genetic Conditions. *Obstet. Gynecol.* 129, 597–599. doi:10.1097/AOG.0000000000001948

American College of Obstetrics and Gynecology (2017c). *Hereditary Breast and Ovarian Cancer Syndrome, Practice Bulletin No. 182*. Washington, DC: American College of Obstetricians and Gynecologists.

American College of Obstetrics and Gynecology (2019b). Hereditary Cancer Syndromes and Risk Assessment: ACOG COMMITTEE OPINION, Number 793. *Obstet. Gynecol.* 134, e143–e149. doi:10.1097/AOG.0000000000003562

Barker, M., Baird, J., Lawrence, W., Vogel, C., Stömmer, S., Rose, T., et al. (2017). Preconception and Pregnancy: Opportunities to Intervene to Improve Women's Diets and Lifestyles. *J. Dev. Orig Health Dis.* 7, 330–333. doi:10.1017/S2040174416000064

Bartley, N., Best, M., Jacobs, C., Juraskova, I., Newson, A. J., Savard, J., et al. (2020). Cancer Patients' Views and Understanding of Genome Sequencing: a Qualitative Study. *J. Med. Genet.* 57, 671–676. doi:10.1136/jmedgenet-2019-106410

Bean, L. J. H., Scheuner, M. T., Murray, M. F., Biesecker, L. G., Green, R. C., Monaghan, K. G., et al. (2021). DNA-based Screening and Personal Health: a Points to Consider Statement for Individuals and Health-Care Providers from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23, 979–988. doi:10.1038/s41436-020-01083-9

Biesecker, B. B., Woolford, S. W., Klein, W. M. P., Brothers, K. B., Umstead, K. L., Lewis, K. L., et al. (2017). PUGS: a Novel Scale to Assess Perceptions of Uncertainties in Genome Sequencing. *Clin. Genet.* 92, 172–179. doi:10.1111/cge.12949

Biesecker, L. G., Mullikin, J. C., Facio, F. M., Turner, C., Cherukuri, P. F., Blakesley, R. W., et al. (2009). The ClinSeq Project: Piloting Large-Scale Genome Sequencing for Research in Genomic Medicine. *Genome Res.* 19, 1665–1674. doi:10.1101/gr.092841.109

Bijlsma, R., Wouters, R., Wessels, H., Sleijfer, S., Beerepoot, L., Ten Bokkel Huinink, D., et al. (2020). Preferences to Receive Unsolicited Findings of Germline Genome Sequencing in a Large Population of Patients with Cancer. *ESMO Open* 5, e000619. doi:10.1136/esmoopen-2019-000619

Bloss, C. S., Stoler, J., Schairer, C. E., Rosenthal, S. B., Cheung, C., Rus, H. M., et al. (2018). Characteristics of Likely Precision Medicine Initiative Participants Drawn from a Large Blood Donor Population. *Health Aff.* 37, 786–792. doi:10.1377/hlthaff.2017.1591

Bollinger, J. M., Scott, J., Dvoskin, R., and Kaufman, D. (2012). Public Preferences Regarding the Return of Individual Genetic Research Results: Findings from a Qualitative Focus Group Study. *Genet. Med.* 14, 451–457. doi:10.1038/gim.2011.66

Brashers, D. E. (2001). Communication and Uncertainty Management. *J. Commun.* 51, 477–497. doi:10.1111/j.1460-2466.2001.tb02892.x

Campbell-Salome, G., Buchanan, A. H., Hallquist, M. L. G., Rahm, A. K., Rocha, H., and Sturm, A. C. (2021). Uncertainty Management for Individuals with Lynch Syndrome: Identifying and Responding to Healthcare Barriers. *Patient Education Couns.* 104, 403–412. doi:10.1016/j.pec.2020.07.017

Canedo, J. R., Miller, S. T., Myers, H. F., and Sanderson, M. (2019). Racial and Ethnic Differences in Knowledge and Attitudes about Genetic Testing in the US: Systematic Review. *J. Genet. Couns.* 28, 587–601. doi:10.1002/jgc4.1078

Canedo, J. R., Wilkins, C. H., Senft, N., Romero, A., Bonnet, K., and Schlundt, D. (2020). Barriers and Facilitators to Dissemination and Adoption of Precision Medicine Among Hispanics/Latinos. *BMC Public Health* 20, 603. doi:10.1186/s12889-020-08718-1

Capalbo, A., Fabiani, M., Caroselli, S., Poli, M., Girardi, L., Patassini, C., et al. (2021). Clinical Validity and Utility of Preconception Expanded Carrier Screening for the Management of Reproductive Genetic Risk in IVF and General Population. *Hum. Reprod.* 36, 2050–2061. doi:10.1093/humrep/deab087

Carleton, R. N., Norton, M. A. P. J., and Asmundson, G. J. G. (2007). Fearing the Unknown: a Short Version of the Intolerance of Uncertainty Scale. *J. Anxiety Disord.* 21, 105–117. doi:10.1016/j.janxdis.2006.03.014

Chavez-Yenter, D., Chou, W. S., and Kaphingst, K. A. (2021a). State of Recent Literature on Communication about Cancer Genetic Testing Among Latinx Populations. *J. Genet. Couns.* 30, 911–918. doi:10.1002/jgc4.1351

Chavez-Yenter, D., Vagher, J., Clayton, M. F., Rindler, M., Shukovich, M., and Kaphingst, K. A. (2021b). "Being Proactive, Not Reactive": Exploring Perceptions of Genetic Testing Among White, Latinx, and Pacific Islander

Populations. *J. Community Genet.* 12, 617–630. doi:10.1007/s12687-021-00542-3

Chew, L. D., Griffin, J. M., Partin, M. R., Noorbaloochi, S., Grill, J. P., Snyder, A., et al. (2008). Validation of Screening Questions for Limited Health Literacy in a Large VA Outpatient Population. *J. Gen. Intern. Med.* 23, 561–566. doi:10.1007/s11606-008-0520-5

Delanne, J., Nambot, S., Chassagne, A., Putois, O., Pelissier, A., Peyron, C., et al. (2019). Secondary Findings from Whole-Exome/genome Sequencing Evaluating Stakeholder Perspectives. A Review of the Literature. *Eur. J. Med. Genet.* 62, 103529. doi:10.1016/j.ejmg.2018.08.010

Dutta-Bergman, M. (2003). Trusted Online Sources of Health Information: Differences in Demographics, Health Beliefs, and Health-Information Orientation. *J. Med. Internet Res.* 5, e21. doi:10.2196/jmir.5.3.e21

Edwards, J. G., Feldman, G., Goldberg, J., Gregg, A. R., Norton, M. E., Rose, N. C., et al. (2015). Expanded Carrier Screening in Reproductive Medicine-Points to Consider. *Obstet. Gynecol.* 125, 653–662. doi:10.1097/aog.0000000000000666

Fagerlin, A., Zikmund-Fisher, B. J., Ubel, P. A., Jankovic, A., Derry, H. A., and Smith, D. M. (2007). Measuring Numeracy without a Math Test: Development of the Subjective Numeracy Scale. *Med. Decis. Making* 27, 672–680. doi:10.1177/0272989x07304449

Fisher, E., Pratt, R., Esch, R., Kocher, M., Wilson, K. R., Lee, W., et al. (2019). The Role of Race and Ethnicity in Views toward and Participation in Genetic Studies and Precision Medicine Research in the United States: a Systematic Review of Qualitative and Quantitative Studies. *Mol. Genet. Genomic Med.*, e1099. doi:10.1002/mgg3.1099

Fitzgerald-Butt, S. M., Bodine, A., Fry, K. M., Ash, J., Zaidi, A. N., Garg, V., et al. (2016). Measuring Genetic Knowledge: a Brief Survey Instrument for Adolescents and Adults. *Clin. Genet.* 89, 235–243. doi:10.1111/cge.12618

French, D. P., Howell, A., and Evans, D. G. (2018). Psychosocial Issues of a Population Approach to High Genetic Risk Identification: Behavioural, Emotional and Informed Choice Issues. *The Breast* 37, 148–153. doi:10.1016/j.breast.2017.11.008

Gavin, L., Moskosky, S., Carter, M., Curtis, K., Glass, E., Godfrey, E., et al. (2014). Providing Quality Family Planning Services: Recommendations of CDC and the U.S. Office of Population Affairs. *MMWR Recomm Rep.* 63, 1–54.

Gilmore, M. J., Schneider, J., Davis, J. V., Kauffman, T. L., Leo, M. C., Bergen, K., et al. (2017). Reasons for Declining Preconception Expanded Carrier Screening Using Genome Sequencing. *J. Genet. Counsel* 26, 971–979. doi:10.1007/s10897-017-0074-y

Goranitis, I., Best, S., Christodoulou, J., Stark, Z., and Boughtwood, T. (2020). The Personal Utility and Uptake of Genomic Sequencing in Pediatric and Adult Conditions: Eliciting Societal Preferences with Three Discrete Choice Experiments. *Genet. Med.* 22, 1311–1319. doi:10.1038/s41436-020-0809-2

Griffin, R. J., Dunwoody, S., and Neuwirth, K. (1999). Proposed Model of the Relationship of Risk Information Seeking and Processing to the Development of Preventive Behaviors. *Environ. Res.* 80, S230–S245. doi:10.1006/enrs.1998.3940

Grody, W. W. (2016). Where to Draw the Boundaries for Prenatal Carrier Screening. *JAMA* 316, 717–719. doi:10.1001/jama.2016.10888

Guo, S., Goodman, M., and Kaphingst, K. (2020). Comparing Preferences for Return of Genome Sequencing Results Assessed with Rating and Ranking Items. *Jrnl of Gene Coun* 29, 131–134. doi:10.1002/jgc4.1186

Gutierrez, A. M., Robinson, J. O., Statham, E. E., Scollon, S., Bergstrom, K. L., Slashinski, M. J., et al. (2017). Portero versus Portador: Spanish Interpretation of Genomic Terminology during Whole Exome Sequencing Results Disclosure. *Personalized Med.* 14, 503–514. doi:10.2217/pme-2017-0040

Halbert, C. H., and Harrison, B. W. (2018). Genetic Counseling Among Minority Populations in the Era of Precision Medicine. *Am. J. Med. Genet.* 178, 68–74. doi:10.1002/ajmg.c.31604

Hall, M. J., and Olopade, O. I. (2006). Disparities in Genetic Testing: Thinking outside the BRCA Box. *JCO* 24, 2197–2203. doi:10.1200/jco.2006.05.5889

Hall, M., and Olopade, O. I. (2005). Confronting Genetic Testing Disparities. *JAMA* 293, 1783–1785. doi:10.1001/jama.293.14.1783

Hann, K. E. J., Fraser, L., Fraser, L., Side, L., Gessler, S., Waller, J., et al. (2017). Health Care Professionals' Attitudes towards Population-Based Genetic Testing and Risk-Stratification for Ovarian Cancer: a Cross-Sectional Survey. *BMC Women's Health* 17, 132. doi:10.1186/s12905-017-0488-6

Hay, J., Kaphingst, K. A., Baser, R., Li, Y., Hensley-Alford, S., and McBride, C. M. (2012). Skin Cancer Concerns and Genetic Risk Information-Seeking in Primary Care. *Public Health Genomics* 15, 57–72. doi:10.1159/000330403

Hay, J. L., Meyer White, K., Sussman, A., Kaphingst, K., Guest, D., Schofield, E., et al. (2019). Psychosocial and Cultural Determinants of Interest and Uptake of Skin Cancer Genetic Testing in Diverse Primary Care. *Public Health Genomics* 22, 58–68. doi:10.1159/000501985

Hildalgo, B., and Goodman, M. (2013). Multivariate or Multivariable Regression? *Am. J. Public Health* 103, 39–40.

Hill, B., Hall, J., Skouteris, H., and Currie, S. (2020). Defining Preconception: Exploring the Concept of a Preconception Population. *BMC Pregnancy Childbirth* 20, 280. doi:10.1186/s12884-020-02973-1

Hillen, M. A., Gutheil, C. M., Strout, T. D., Smets, E. M. A., and Han, P. K. J. (2017). Tolerance of Uncertainty: Conceptual Analysis, Integrative Model, and Implications for Healthcare. *Soc. Sci. Med.* 180, 62–75. doi:10.1016/j.socscimed.2017.03.024

Hoell, C., Wynn, J., Rasmussen, L. V., Marsolo, K., Aufox, S. A., Chung, W. K., et al. (2020). Participant Choices for Return of Genomic Results in the eMERGE Network. *Genet. Med.* 22, 1821–1829. doi:10.1038/s41436-020-0905-3

Horowitz, C. R., Orlando, L. A., Slavotinek, A. M., Peterson, J., Angelo, F., Biesecker, B., et al. (2019). The Genomic Medicine Integrative Research Framework: a Conceptual Framework for Conducting Genomic Medicine Research. *Am. J. Hum. Genet.* 104, 1088–1096. doi:10.1016/j.ajhg.2019.04.006

Institute of medicine (2002). *Unequal Treatment: Understanding Racial and Ethnic Disparities in Health Care*. Washington, DC: National Academy Press.

Jagsi, R., Griffith, K. A., Kurian, A. W., Morrow, M., Hamilton, A. S., Graff, J. J., et al. (2015). Concerns about Cancer Risk and Experiences with Genetic Testing in a Diverse Population of Patients with Breast Cancer. *JCO* 33, 1584–1591. doi:10.1200/jco.2014.58.5885

Johnson, K., Posner, S., Biermann, J., Cordero, J. F., Atrash, H. K., Parker, C. S., et al. (2006). Recommendations to Improve Preconception Health and Health Care - United States: A Report of the CDC/ATSDR Preconception Care Work Group and the Select Panel on Preconception Care. *Morbidity Mortality Weekly Rep.* 55, 1–23. doi:10.1037/e506902006-001

Kaphingst, K. A., Blanchard, M., Milam, L., Pokharel, M., Elrick, A., and Goodman, M. S. (2016b). Relationships between Health Literacy and Genomics-Related Knowledge, Self-Efficacy, Perceived Importance, and Communication in a Medically Underserved Population. *J. Health Commun.* 21, 58–68. doi:10.1080/10810730.2016.1144661

Kaphingst, K. A., Goodman, M., Pandya, C., Garg, P., Stafford, J., and Lachance, C. (2012). Factors Affecting Frequency of Communication about Family Health History with Family Members and Doctors in a Medically Underserved Population. *Patient Education Couns.* 88, 291–297. doi:10.1016/j.pec.2011.11.013

Kaphingst, K. A., Ivanovich, J., Biesecker, B. B., Dresser, R., Seo, J., Dressler, L. G., et al. (2016a). Preferences for Return of Incidental Findings from Genome Sequencing Among Women Diagnosed with Breast Cancer at a Young Age. *Clin. Genet.* 89, 378–384. doi:10.1111/cge.12597

Kaphingst, K. A., Ivanovich, J., Lyons, S., Biesecker, B., Dresser, R., Elrick, A., et al. (2018). Preferences for Learning Different Types of Genome Sequencing Results Among Young Breast Cancer Patients: Role of Psychological and Clinical Factors. *Translational Behav. Med.* 8, 71–79. doi:10.1093/tbm/ibx042

Kaphingst, K. A., Peterson, E., Zhao, J., Gaysynsky, A., Elrick, A., Hong, S. J., et al. (2019). Cancer Communication Research in the Era of Genomics and Precision Medicine: a Scoping Review. *Genet. Med.* 21, 1691–1698. doi:10.1038/s41436-018-0402-0

Kaphingst, K. A., Stafford, J. D., Mcgowan, L. D. A., Seo, J., Lachance, C. R., and Goodman, M. S. (2015). Effects of Racial and Ethnic Group and Health Literacy on Responses to Genomic Risk Information in a Medically Underserved Population. *Health Psychol.* 34, 101–110. doi:10.1037/hea0000177

Kaphingst, K., and Goodman, M. (2016). Importance of Race and Ethnicity in Individuals' Use of and Responses to Genomic Information. *Personalized Med.* 13. doi:10.2217/pme.15.39

Kauffman, T. L., Irving, S. A., Leo, M. C., Gilmore, M. J., Himes, P., McMullen, C. K., et al. (2017a). The NextGen Study: Patient Motivation for Participation in Genome Sequencing for Carrier Status. *Mol. Genet. Genomic Med.* 5, 508–515. doi:10.1002/mgg3.306

Kauffman, T. L., Wilfond, B. S., Jarvik, G. P., Leo, M. C., Lynch, F. L., Reiss, J. A., et al. (2017b). Design of a Randomized Controlled Trial for Genomic Carrier

Screening in Healthy Patients Seeking Preconception Genetic Testing. *Contemp. Clin. Trials* 53, 100–105. doi:10.1016/j.cct.2016.12.007

Khoury, M. J., and Dotson, W. D. (2021). From Genes to Public Health: Are We Ready for DNA-Based Population Screening? *Genet. Med.* 23, 996–998. doi:10.1038/s41436-021-01141-w

Khoury, M. J., Feero, W. G., Chambers, D. A., Brody, L. E., Aziz, N., Green, R. C., et al. (2018). A Collaborative Translational Research Framework for Evaluating and Implementing the Appropriate Use of Human Genome Sequencing to Improve Health. *PLOs Med.* 15, e1002631. doi:10.1371/journal.pmed.1002631

Kinney, A. Y., Gammon, A., Coxworth, J., Simonsen, S. E., and Arce-Laretta, M. (2010). Exploring Attitudes, Beliefs, and Communication Preferences of Latino Community Members Regarding BRCA1/2 Mutation Testing and Preventive Strategies. *Genet. Med.* 12, 105–115. doi:10.1097/gim.0b013e3181c9af2d

Larsen, D., Ma, J., Strassberg, M., Ramakrishnan, R., and Van Den Veyver, I. B. (2019). The Uptake of Pan-Ethnic Expanded Carrier Screening Is Higher when Offered during Preconception or Early Prenatal Genetic Counseling. *Prenatal Diagn.* 39, 319–323. doi:10.1002/pd.5434

Lindor, N. M., Thibodeau, S. N., and Burke, W. (2017). Whole-genome Sequencing in Healthy People. *Mayo Clinic Proc.* 92, 159–172. doi:10.1016/j.mayocp.2016.10.019

Lipkus, I. M., Kuchibhatla, M., McBride, C. M., Bosworth, H. B., Pollak, K. I., Siegler, I. C., et al. (2000). Relationships Among Breast Cancer Perceived Absolute Risk, Comparative Risk, and Worries. *Cancer Epidemiol. Biomarkers Prev.* 9, 973–975.

Machini, K., Ceyhan-Birsoy, O., Azzariti, D. R., Sharma, H., Rossetti, P., Mahanta, L., et al. (2019). Analyzing and Reanalyzing the Genome: Findings from the MedSeq Project. *Am. J. Hum. Genet.* 105, 177–188. doi:10.1016/j.ajhg.2019.05.017

Manchanda, R., Burnell, M., Gaba, F., Desai, R., Wardle, J., Gessler, S., et al. (2020a). Randomised Trial of Population-based BRCA Testing in Ashkenazi Jews: Long-term Outcomes. *BJOG: Int. J. Obstet. Gy* 127, 364–375. doi:10.1111/1471-0528.15905

Manchanda, R., Lieberman, S., Gaba, F., Lahad, A., and Levy-Lahad, E. (2020b). Population Screening for Inherited Predisposition to Breast and Ovarian Cancer. *Annu. Rev. Genom. Hum. Genet.* 21, 373–412. doi:10.1146/annurev-genom-083118-015253

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome Sequencing-Based Screening for BRCA1/2 Expected Pathogenic Variants Among Adult Biobank Participants. *JAMA Netw. Open* 1, e182140. doi:10.1001/jamanetworkopen.2018.2140

McBride, C. M., Alford, S. H., Reid, R. J., Larson, E. B., Baxevanis, A. D., and Brody, L. C. (2009). Characteristics of Users of Online Personalized Genomic Risk Assessments: Implications for Physician-Patient Interactions. *Genet. Med.* 11, 582–587. doi:10.1097/gim.0b013e3181b22c3a

Mighton, C., Carlsson, L., Carlsson, L., Clausen, M., Casalino, S., Shickh, S., et al. (2019). Development of Patient "Profiles" to Tailor Counseling for Incidental Genomic Sequencing Results. *Eur. J. Hum. Genet.* 27, 1008–1017. doi:10.1038/s41431-019-0352-2

Mighton, C., Carlsson, L., Carlsson, L., Clausen, M., Casalino, S., Shickh, S., et al. (2020). Quality of Life Drives Patients' Preferences for Secondary Findings from Genomic Sequencing. *Eur. J. Hum. Genet.* 28, 1178–1186. doi:10.1038/s41431-020-0640-x

Moholdt, T., and Hawley, J. A. (2020). Maternal Lifestyle Interventions: Targeting Preconception Health. *Trends Endocrinol. Metab.* 31, 561–569. doi:10.1016/j.tem.2020.03.002

Murray, M. F., Evans, J. P., and Khoury, M. J. (2019). DNA-based Population Screening: Potential Suitability and Important Knowledge Gaps. *J. Am. Med. Assocation* 323, 307–308.

Murray, M. F., Giovanni, M. A., Doyle, D. L., Harrison, S. M., Lyon, E., Manickam, K., et al. (2021). DNA-based Screening and Population Health: a Points to Consider Statement for Programs and Sponsoring Organizations from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23, 989–995. doi:10.1038/s41436-020-01082-w

National Cancer Institute (2015). Health Information National Trends Survey [Online]. Available: http://hints.cancer.gov/questions/index.jsp.

Nijmeijer, S. C. M., Conijn, T., Lakeman, P., Henneman, L., Wijburg, F. A., and Haverman, L. (2019). Attitudes of the General Population towards Preconception Expanded Carrier Screening for Autosomal Recessive Disorders Including Inborn Errors of Metabolism. *Mol. Genet. Metab.* 126, 14–22. doi:10.1016/j.ymgme.2018.12.004

Ong, R., Howting, D., Rea, A., Christian, H., Charman, P., Molster, C., et al. (2018). Measuring the Impact of Genetic Knowledge on Intentions and Attitudes of the Community towards Expanded Preconception Carrier Screening. *J. Med. Genet.* 55, 744–752. doi:10.1136/jmedgenet-2018-105362

Pagán, J. A., Su, D., Li, L., Armstrong, K., and Asch, D. A. (2009). Racial and Ethnic Disparities in Awareness of Genetic Testing for Cancer Risk. *Am. J. Prev. Med.* 37, 524–530. doi:10.1016/j.amepre.2009.07.021

Parrott, R., Silk, K., Raup Krieger, J., Harris, T., and Condit, C. (2004). Behavioral Health Outcomes Associated with Religious Faith and Media Exposure about Human Genetics. *Health Commun.* 16, 29–45. doi:10.1207/s15327027hc1601_3

Persky, S., Kaphingst, K. A., Condit, C. M., and McBride, C. M. (2007). Assessing Hypothetical Scenario Methodology in Genetic Susceptibility Testing Analog Studies: a Quantitative Review. *Genet. Med.* 9, 727–738. doi:10.1097/gim.0b013e318159a344

Peters, N., Rose, A., and Armstrong, K. (2004). The Association between Race and Attitudes about Predictive Genetic Testing. *Cancer Epidemiol. Biomarkers Prev.* 13, 361–365.

Phillips, K. A., Douglas, M. P., and Marshall, D. A. (2020). Expanding Use of Clinical Genome Sequencing and the Need for More Data on Implementation. *JAMA* 324, 2029–2030. doi:10.1001/jama.2020.19933

Pierle, J. M., and Mahon, S. M. (2019). Genetic Service Delivery Models: Exploring Approaches to Care for Families with Hereditary Cancer Risk. *Clin. J. Oncol. Nurs.* 23, 60–67. doi:10.1188/19.CJON.60-67

Plantinga, M., Birnie, E., Abbott, K. M., Sinke, R. J., Lucassen, A. M., Schuurmans, J., et al. (2016). Population-based Preconception Carrier Screening: How Potential Users from the General Population View a Test for 50 Serious Diseases. *Eur. J. Hum. Genet.* 24, 1417–1423. doi:10.1038/ejhg.2016.43

Porter, K. M., Kauffman, T. L., Koenig, B. A., Lewis, K. L., Rehm, H. L., Richards, C. S., et al. (2018). Approaches to Carrier Testing and Results Disclosure in Translational Genomics Research: the Clinical Sequencing Exploratory Research Consortium Experience. *Mol. Genet. Genomic Med.* 6, 898–909. doi:10.1002/mgg3.453

R Core Team (2019). A Language and Environment for Statistical Computing *[Online]*. Vienna, Austria: R Foundation for Statistical Computing. Available: https://www.R-project.org/.

Rabkina, L., Swanson, A., Aufox, S., Propst, L., Fiddler, M., Wagner, A., et al. (2021). What Women Want: General Population Perspectives and Access to Preconception Expanded Carrier Screening. *Prenatal Diagn.* 41, 1057–1065. doi:10.1002/pd.5995

Rauscher, E. A. (2017). Investigating Uncertainty in Genetic Counseling Encounters: Managing Information about Genetic Cancer Risk. *J. Health Commun.* 22, 896–904. doi:10.1080/10810730.2017.1373875

Roberts, M. C., Mensah, G. A., and Khoury, M. J. (2019). Leveraging Implementation Science to Address Health Disparities in Genomic Medicine: Examples from the Field. *Ethn. Dis.* 29, 187–192. doi:10.18865/ed.29.s1.187

Sanderson, S. C., Linderman, M. D., Suckiel, S. A., Diaz, G. A., Zinberg, R. E., Ferryman, K., et al. (2016). Motivations, Concerns and Preferences of Personal Genome Sequencing Research Participants: Baseline Findings from the HealthSeq Project. *Eur. J. Hum. Genet.* 24, 14–20. doi:10.1038/ejhg.2015.118

Sapp, J. C., Johnston, J. J., Driscoll, K., Heidlebaugh, A. R., Miren Sagardia, A., Dogbe, D. N., et al. (2018). Evaluation of Recipients of Positive and Negative Secondary Findings Evaluations in a Hybrid CLIA-Research Sequencing Pilot. *Am. J. Hum. Genet.* 103, 358–366. doi:10.1016/j.ajhg.2018.07.018

Shaibi, G. Q., Kullo, I. J., Singh, D. P., Sharp, R. R., De Filippis, E., Cuellar, I., et al. (2018). Developing a Process for Returning Medically Actionable Genomic Variants to Latino Patients in a Federally Qualified Health center. *Public Health Genomics* 21, 77–84. doi:10.1159/000494488

Singer, E., Antonucci, T., and Van Hoewyk, J. (2004). Racial and Ethnic Variations in Knowledge and Attitudes about Genetic Testing. *Genet. Test.* 8, 31–43. doi:10.1089/109065704323016012

Smit, A. K., Reyes-Marcelino, G., Keogh, L., Dunlop, K., Newson, A. J., and Cust, A. E. (2020). Implementation Considerations for Offering Personal Genomic Risk Information to the Public: a Qualitative Study. *BMC Public Health* 20, 1028. doi:10.1186/s12889-020-09143-0

Southwick, S. V., Esch, R., Gasser, R., Cragun, D., Redlinger-Grosse, K., Marsalis, S., et al. (2020). Racial and Ethnic Differences in Genetic Counseling Experiences and Outcomes in the United States: a Systematic Review. *Jrnl of Gene Coun* 29, 147–165. doi:10.1002/jgc4.1230

Srinivasan, T., Sutton, E. J., Beck, A. T., Cuellar, I., Hernandez, V., Pacyna, J. E., et al. (2021). Integrating Genomic Screening into Primary Care: Provider Experiences Caring for Latino Patients at a Community-Based Health center. *J. Prim. Care Community Health* 12, 1–10. doi:10.1177/21501327211000242

Turbitt, E., Roberts, M. C., Hollister, B. M., Lewis, K. L., Biesecker, L. G., and Klein, W. M. P. (2019). Ethnic Identity and Engagement with Genome Sequencing Research. *Genet. Med.* 21, 1735–1743. doi:10.1038/s41436-018-0410-0

Van Elten, T. M., Geelen, A., Gemke, R. J. B. J., Groen, H., Hoek, A., van Poppel, M. N. M., et al. (2019). Preconception Lifestyle Intervention Reduces Long Term Energy Intake in Women with Obesity and Infertility: a Randomised Controlled Trial. *Int. J. Behav. Nutr. Phys. Act* 16, 3. doi:10.1186/s12966-018-0761-6

Van Steijvoort, E., Chokoshvili, D., W Cannon, J., Peeters, H., Peeraer, K., Matthijs, G., et al. (2020). Interest in Expanded Carrier Screening Among Individuals and Couples in the General Population: Systematic Review of the Literature. *Hum. Reprod. Update* 26, 335–355. doi:10.1093/humupd/dmaa001

Wertz, D. C., Sorenson, J. R., and Heeren, T. C. (1986). Clients' Interpretation of Risks provided in Genetic Counseling. *Am. J. Hum. Genet.* 39, 253–264.

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Primary Care Implementation of Genomic Population Health Screening Using a Large Gene Sequencing Panel

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To realize the promise of genomic medicine, harness the power of genomic technologies, and capitalize on the extraordinary pace of research linking genomic variation to disease risks, healthcare systems must embrace and integrate genomics into routine healthcare. We have implemented an innovative pilot program for genomic population health screening for any-health-status adults within the largest health system in Vermont, United States. This program draws on key research and technological advances to safely extract clinical value for genomics in routine health care. The program offers no-cost, non-research DNA sequencing to patients by their primary care providers as a preventive health tool. We partnered with a commercial clinical testing company for two next generation sequencing gene panels comprising 431 genes related to both high and low-penetrance common health risks and carrier status for recessive disorders. Only pathogenic or likely pathogenic variants are reported. Routine written clinical consultation is provided with a concise, clinical "action plan" that presents core messages for primary care provider and patient use and supports clinical management and health education beyond the testing laboratory's reports. Access to genetic counseling is free in most cases. Predefined care pathways and access to genetics experts facilitates the appropriate use of results. This pilot tests the feasibility of routine, ethical, and scalable use of population genomic screening in healthcare despite generally imperfect genomic competency among both the public and health care providers. This article describes the program design, implementation process, guiding philosophies, and insights from 2 years of experience offering testing and returning results in primary care settings. To aid others planning similar programs, we review our barriers, solutions, and perceived gaps in the context of an implementation research framework.

Keywords: genomic medicine, population health, primary care, pilot implementation, screening, implementation research framework, real-world, clinical pilot

1 INTRODUCTION

We exist at the intersection of advances in genomics technology and quality, rapidly growing knowledge of the genetic underpinnings of human disease and susceptibilities, systems to support quality, and trending emphasis on maximizing preventive care opportunities. This frames an opportunity to realize a research-enlightened model of genomics-informed preventive healthcare.

Efforts to implement healthcare innovations often fail in the real world, even when research data supports their widespread use (Damschroder et al., 2009). Demonstrating feasibility of implementing genomic population health screening in a healthcare setting is a core challenge (Murray et al., 2018; Murray et al., 2021). Failures may occur for many reasons. Since many implementation barriers may be anticipated, frameworks for planning and evaluating implementations have been developed to facilitate informed planning and stimulate more implementation successes (Ginsburg et al., 2019; King et al., 2020). Implementation frameworks may be used during planning and executing implementations and when evaluating outcomes. Different frameworks have unique strengths (Roberts et al., 2019; King et al., 2020).

The Consolidated Framework for Implementation Research (CFIR) is a flexible option, whose creators derived five major domains from earlier healthcare implementation frameworks and theories: inner and outer settings, the individuals involved, the process, and the intervention (Damschroder et al., 2009). It defines within each domain distinct theoretical constructs that correspond to key success ingredients for each domain. CFIR's inner and outer settings and the individuals involved domains constitute the implementation context. Constructs probing the motivations and rationale reside in the outer setting, while the characteristics of an organization, like culture, structure, readiness, and priority, comprise the constructs of the inner setting. CFIR refinements for implementing genomic medicine have been proposed (Orlando et al., 2018).

We report here the successful implementation of clinical genomic population health screening in primary care outpatient settings affiliated with a regional academic medical center in a rural US state. Key goals of the pilot intervention are listed in **Table 1**. To assist others considering similar efforts, our implementation is described here using a CFIR-based implementation science framework.

2 CONTEXT

The context of an implementation has great bearing on its likelihood of success. This report describes our implementation using CFIR domains. We are guided by each domain's CFIR constructs (Damschroder et al., 2009; Orlando et al., 2018; King et al., 2020) without explicitly decomposing to them.

TABLE 1 | Key goals of the genomic population health pilot implementation program.

Demonstrate the Feasibility of a Real-world genomic population health program with primary care at the center and genomics expertise in the background
Provide adult primary care patients of any health status and their providers with information about and access to a novel healthcare intervention built on prior genomics and genomic medicine research
Formulate and put into practice an accessible, one-page clinical informed consent form for genomic population health screening
Mimic conditions of recommended population health screening programs including no cost to patients for testing
Reduce or eliminate cost barriers for related genetic counseling (in-person or telemedicine), family member "cascade" testing for the health risks, and for reproductive partners of those with identified recessive carrier status
Incorporate scalability and existing workflows into the design, where possible, and identify opportunities and strategies for future improvements
Primary testing occurs in a Clinical Laboratory Improvement Amendments (CLIA) regulated laboratory using validated gene sequencing and confirmation methods
Define recommended responses to positive results in advance in the form of evidence-based Care Pathways designed by clinical specialists, communicated by written action plans, and activated by primary care providers
Provide patients and their providers with likely pathogenic and pathogenic germline variants in the context of information and suggested actions to address health and reproductive risks, using appropriate language
Clinical genomic population health test reports are treated like any other health information, placed in the patient's secure electronic health record, and provided to patients
Patients and their primary care providers can work together to incorporate personal, social, and other health context into a responsive care plan
Provide updated reports and clinical updates whenever variant pathogenicity is reclassified

2.1 CFIR Outer Setting

The screening pilot occurs in Vermont, United States. Vermont is among the few states making strides toward healthcare reform with emphasis on value-based care (Grembowski and Marcus-Smith, 2018; Kissam et al., 2019). The focus signals openness to investment in innovative health prevention activities. Vermont's accountable care organization (ACO), OneCare Vermont, is facilitating the transition to value-based care models. Federal, state, and private health insurers contract with the ACO and enrolled providers for a risk-adjusted, quality-focused, single annual payment for healthcare services. Alignment with the ACO allows better visibility into the real-world health impacts of innovations in population health screening.

Research involving return of actionable genomic sequencing results to patients for clinical use (Duow and Marjanovic, 2016; Linderman et al., 2016; Sanderson et al., 2016; Suckiel et al., 2016; Ryan et al., 2017; Murray et al., 2018; Rego et al., 2018; Reuter et al., 2018; Sapp et al., 2018; Schwartz et al., 2018; David et al., 2019; Nussbaum et al., 2019; Williams, 2019; Zoltick et al., 2019; Walton et al., 2020; David et al., 2021; Kelly et al., 2021; Khoury and Dotson, 2021; Lemke et al., 2021; Miller et al., 2021), potential harms of proactive testing, quality of next generation sequencing technology, and implementation of genomic medicine (Weitzel

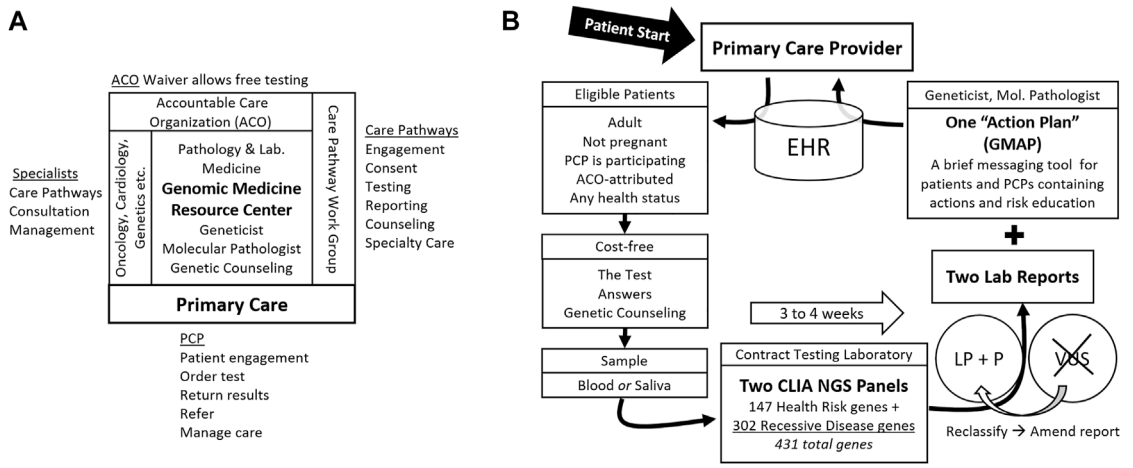

FIGURE 1 | Genomic Population Health Pilot Program: Organization and Testing Process. **(A)** The multi-disciplinary team, its interfaces, and team member activities. The Genomic Medicine Resource Center provides support for primary care providers (PCP) and patients and coordinates the team. **(B)** The testing process and test details. Patients engage first with their primary care provider (PCP). Arrows indicate steps in the process. Abbreviations: Electronic health record (EHR), accountable care organization (ACO), Clinical Laboratory Improvement Amendments (CLIA), next generation sequencing (NGS), likely pathogenic (LP), pathogenic (P), variant of uncertain significance (VUS), and Genomic Medicine Action Plan (GMAP).

et al., 2016; Ginsburg et al., 2019; Williams, 2019) strongly informed our design.

Primary care is not a traditional setting for genetic testing or screening. Primary care providers do order pre-conception and prenatal screens and sample for newborn screening. Genomic literacy and competency among primary care providers is limited outside those areas. Upon receiving a positive genetic screening result, primary care providers' responsive actions may be limited to patient notification and referral to a relevant specialist, or to following scripts, such as those provided by newborn screening laboratories. In general, time is the most limited resource for primary care providers and their staff. At the same time, risk assessment and directing and managing preventive care, the main objectives of genomic population health, occurs principally in the primary care setting.

Professional guidelines and resources for actionability of results, including the ACMG secondary findings guidance (American College of Medical Genetics and Genomics, 2019; Directors of the American College of Medical Genetics and Genomics, 2019; Nussbaum et al., 2019), ClinGen expert assessments (Rivera-Muñoz et al., 2018), and locally sourced specialty specific guidance, served as anchors for the design. However, updated non-genetics specialty practice guidelines are scarce for many of the health risk genes or are based on data from patients screened because of affected family members, often after an affected member had a positive indication-based test result. Current breast cancer genetic testing guidelines fail to identify almost half of individuals with a breast cancer risk gene pathogenic or likely pathogenic variant (Beitsch et al., 2019).

Clinical genetics laboratories now have extensive experience classifying the pathogenicity of gene sequence variations according to standardized systems (Richards et al., 2015; Nykamp et al., 2017) and linking variants to peer-reviewed literature supporting clinical validity. New variant and clinical validity/utility information evolves and justifies re-classification of variants with a necessity to update clinical reports. Nonetheless, evidence is lacking to accurately classify much of the human genomic sequence variation as pathogenic, benign, or likely so. For these variants of unknown/uncertain clinical significance (VUSs), it is not currently known whether they impact health.

Anecdotal reports describe missed, inappropriate, and or unnecessary medical responses after genetic or health-risk testing. These have been used to warn against broad-based genomic screening at population scale (Murray et al., 2018). Restricted genetic competency among non-geneticists tasked with interpreting genetic test results may facilitate insufficient responses even when preventive opportunities exist. Genetic disease expertise clearly has a role in population genomic screening (Lemke et al., 2021).

The popularity of consumer-oriented genomic testing and concerted efforts to increase the genomic literacy of Americans has fostered growing public awareness of links between heritable genetic variation and disease. Programs that performed health-related genomic screening tests for physicians and health administrators have helped them personally identify with the potential for routine genomic risk screening and raised awareness and interest among non-genetic specialists and primary care leaders (Briggs, 2016; Masterson, 2016).

At the same time, widespread testing has raised concern regarding the privacy of genetic information, genetic discrimination, as well as the commoditization of genetic data. Many people are unaware that a genetic result obtained outside of a healthcare setting is not subject to HIPAA privacy law protections nor CLIA laboratory quality certification, and many lack clarity about the extent of protections against genetic discrimination provided by federal and state laws.

Information relevant to a patient's health is recorded in the health record. Yet electronic health records (EHRs) generally lack

robust, expansible, accessible, and readily implementable functions to store, annotate, retrieve, and update germline genetic information and annotations that may remain clinically relevant for many decades (Walton et al., 2020).

While large cohorts of research participants have received exome or genome sequencing results, fully clinical programs screening large numbers of health risk genes have until recently been offered only in clinics catering to self-pay clients. Research screening programs are being adapted to a clinical model.

2.2 CFIR Inner Setting

The University of Vermont Medical Center (UVMMC) is a regional academic tertiary care center serving a largely rural population in Vermont and northern New York, where Northern-European ancestry and white race are claimed by most of the population. UVMMC is the academic teaching hospital of the UVM Health Network that includes five other rural hospitals, home health and hospice, a physician organization, and collaboration with a Federally Qualified Health Center. By the end of 2022, all will operate on UVMMC's Epic Systems EHR instance. UVMMC and Network partner Porter Hospital have multiple community primary care clinics in Chittenden and Addison counties, VT.

Traditional models of genetic disease detection and prevention are practiced, including mandated newborn screening, variable documentation of family health history, genetic specialist evaluation, genetic counseling, and genetic testing of individuals and families at risk or manifesting genetic conditions. No DNA-based primary screening of people without risk factors occurs. Individuals at higher risk of genetic predisposition due to a diagnosis of colon or endometrial cancer are screened for Lynch Syndrome using immunohistochemistry. Individuals with a family history suggesting predisposition to cancer may be referred to the Familial Cancer Program of genetic oncologists and genetic counselors.

An on-site Genomic Medicine Laboratory, directed by molecular pathologists, two Ph.D. molecular biologists, and a clinical and laboratory geneticist, performs NGS sequencing of tumor DNA and RNA for precision oncology therapy. All clinical germline testing is sent to referral laboratories.

UVMMC has a robust Patient and Family Advisors (PFA) program (Celenza et al., 2017; Wahlberg et al., 2021). PFAs are volunteers invited to provide patient- and family-centered perspectives to implementation teams during project planning.

UVMMC health information technology (HIT) resources are extensive yet principally focused on business operations and dissemination of Epic Systems products throughout the health system.

2.3 CFIR Characteristics of Individuals and Implementation Roles

The pilot was envisioned, designed and supported by the Chair of the Department of Pathology and Laboratory Medicine (DGBL), a molecular pathologist who founded the Genomic Medicine Program. The Genomic Population Screening Program implementation was led by an ABMG Clinical Geneticist (RSW) with both laboratory and patient care expertise. Both (DGBL and RSW) have been involved in national efforts to promote realization of the genomic medicine potential in health care. The geneticist has broad experience in genetic and genomic medicine, including solo genetics practice in rural and suburban areas, academic and non-academic settings, workforce training, education, policy, clinical molecular genetics, and rare disease research. The Chair of Family Medicine (TCP) and the Family Medicine champion provider (AWR) both had professional experiences arising from the Illumina "Understanding Your Genome" (UYG) program performed locally in 2017 that informed their participation and commitment (Briggs, 2016; Masterson, 2016). Both Chairs are leaders at the UVMMC and the UVM Health Network with access to health system leaders.

An experienced clinical and laboratory certified genetic counselor (CAG) helped plan and execute the pilot, she provided the genetic counselor's perspective and performed genetic counseling. A second genetic counselor provided temporary, part-time support.

Three retired non-medical professionals from the community who volunteer as PFAs provide input during both planning and execution phases. Ten PFA volunteers contributed as a group to develop a new written clinical consent form, as well as a brief animated video providing a patient-oriented overview of the program.

Participating PCPs largely belong to two multi-site family medicine practice groups of the UVM Health Network Medical Group. Most were recruited informally by the PCP champion and other participating PCPs, while a few were approached by knowledgeable patients. Most are physicians, but nurse practitioners and physician assistants also participate. None received participation incentives.

Patients offered the test must meet these eligibility criteria: at least 18 years old, they and their partner are not pregnant, their PCP participates in the pilot and received program training, and the patient is attributed to Vermont's ACO. There are no restrictions based on health status, family history, or other health risk factors.

2.4 CFIR Implementation Process

2.4.1 Planning for Implementation

An approximately 1 year long planning process occurred prior to offering the first test. Test information, engagement materials, and a mandatory consent form were developed, implementation partners were engaged and contracted, and care pathways were designed for those conditions having the highest expected follow-up need after a positive test. For most providers and staff contributing to the planning and early implementation phases, a portion of usual salary was paid.

Planning culminated in a business plan approved by UVMMC leaders. It communicated the project's scope, model, justifications, and expected or potential impacts on the

institution's operations and employees as well as patients. No UVMMC funding was requested.

2.4.2 Legal, Compliance, and Ethics

Legal and compliance considerations arise from making this an extension of clinical care. Using a CLIA-certified laboratory and working within HIPAA and other health statutes and regulations is essential. The protections and limitations of the Genetic Information Nondiscrimination Act and Vermont's additional non-discrimination statutes are emphasized when educating patients about potential testing risks. An M.D. medical ethicist and the health system's legal counsel guided our decisions regarding ethically and legally important issues. ACOs are permitted to issue waivers for innovative care programs. We obtained such a waiver to permit us to legally offer the screening test and associated genetic counseling at no cost.

2.5 CFIR Intervention Characteristics

2.5.1 Guiding Principles

We developed a set of principles that guided us as we designed and modified the program. These included implementation as a clinical pilot program, taking pains to avoid mischaracterization as a research study. The need for simplicity and practicality in a contemporary clinical environment was essential. Like other preventive health testing, patient participation is voluntary and with clinical informed consent and results are placed in the EHR. Health condition and risk information need to be available to providers. Genetic test reports convert genetic testing results into health preserving actions. Patients and providers have varying capacities and tolerances for information complexity and benefit from ready access to experts.

We placed primary care at the center of the patient activity because that is where most preventive health screening and day-to-day health risk management occurs. In addition, patients generally have a trusting relationship with their primary care provider. Specialists are included in the program for referral of patients with actionable results best managed by the most expert healthcare available. Because we envision the program as a pilot for widespread genomic population health screening, we strive for scalability in the program's elements, communications, and workflows.

We support testing and general genetic counseling at no cost so that lack of financial resources does not prohibit access. We wish to demonstrate the feasibility and character of population-based screening that will eventually be included in value-based insurance benefits, and include Vermonters who are not necessarily healthy, wealthy, or employed. Lack of need for billing also simplified implementation.

2.5.2 Genetics Practice, Laboratory Experience, and Administrative Location

The participation of a clinical geneticist and genetic counselor, both with molecular laboratory experience, and a molecular pathologist and laboratory founder, provided perspective on how the design interfaced with traditional medicine, medical genetics, and external partners. Locating the program administration in the clinical Genomic Medicine Laboratory leveraged the broad multi-specialty and primary-care connections of the hospital laboratory as well as infrastructure for contracting with reference laboratories.

2.5.3 Care Pathways

To address concerns about inappropriate use and shortage of definitive guidelines for genes in our panel, we worked with physician specialists in cardiology and hereditary cancer to design evidence-informed care pathways. A Care Pathway Work Group chaired by the geneticist was established for this purpose. As the testing workflows and care provided after positive test results impacts patients, PCPs, and staff, each contributed representatives to the Care Pathway Work Group in addition to specialty members. Three PFAs joined this group and were instrumental in the development of pre-test Care Pathways for introducing the test to patients and to inform and educate them prior to deciding whether to test, as well as discussing the post-test results disclosure pathways.

Other members of the work group include the PCP champion, a nurse-administrator champion, and the genetic counselor. During the planning phase, a family medicine practice director, a cardiologist specializing in electrophysiology, a genetic oncologist, and an M.D. medical ethicist participated.

Specialty Care Pathways describe specific steps for responding to positive test results in certain genes, including which clinical correlation tests the PCP may order, the specialty referral criteria, and anticipated tests that may be done for staging and screening during evaluation by a specialist. Evidence-informed Care Pathways for genes in other specialty areas are designed by the clinical geneticist in consultation with published literature and local specialists as relevant test results occur.

2.5.4 Use of Existing Systems

Implementation is easier when existing systems can be incorporated in the design. We leveraged primary care's models of annual wellness visits and continuity of care to place novel testing in an existing practice framework. A well-established laboratory send-out workflow facilitated partnering with a commercial laboratory instead of onsite testing and germline variant interpretation. Patients with results suggesting cancer predisposition are referred to the existing Familial Cancer Program. Our model for providing free, test-related general genetic counseling evolved. The pragmatic solution was contracting with our Clinical Genetics service for patient- and provider-driven genetic counseling requests. We did not leverage any potential EHR functionality that required customization or a "build," as we lacked access to the necessary HIT resources during the reported-on period.

2.5.5 Avoiding Confusion With Traditional Genetic Screening and Evaluation Paradigms

We characterize this program as genomic population health screening. Pains are taken to emphasize that this new test should not replace existing indication-based genetic evaluation

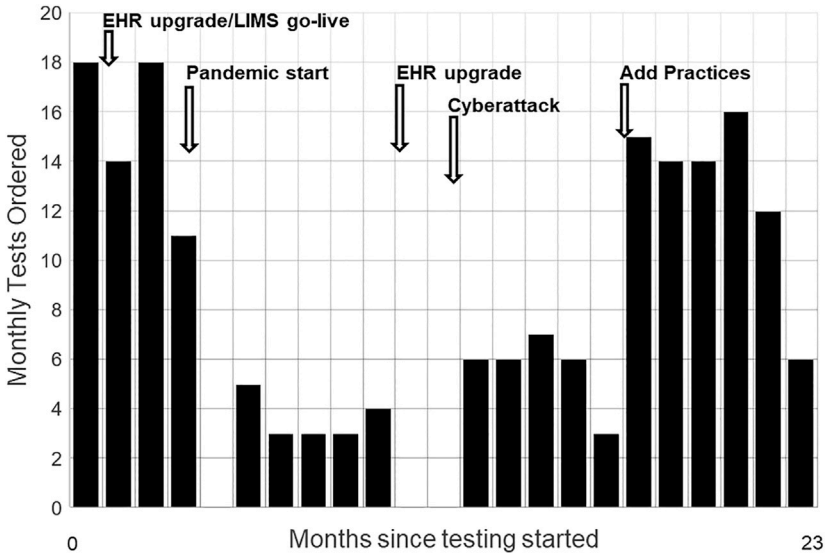

FIGURE 2 | Monthly Test Volumes and Key Events. Monthly test volumes during the first 23 months of testing, starting November 2019. Disruptive events included major upgrades to the electronic health record (EHR), replacement of the hospital's laboratory information system (LIMS), the onset of the COVID-19 pandemic, an EHR upgrade requiring widespread staff training, and a cyberattack that took all information systems offline for weeks. Adding a second practice group with its own physician champion increased volumes.

and testing. Nor should it replace existing genetic disease or risks screenings, like newborn screening and pre-conception/pre-natal carrier testing. Patients with personal or family history indications for medical genetic evaluation are asked to utilize existing specialty care services for those needs. However, because this screening test has the potential to identify *unrelated* hidden health risks, patients are not excluded for having a genetic testing indication, an existing genetic diagnosis, nor any other diagnosis.

An important distinction from indication-based genetic testing is that variants of unknown significance (VUSs) are not reported in the program's screening test. This is because the prior probability of many screened-for conditions is assumed to be zero in the tested population because they are not selected for any phenotype (Murray et al., 2018). This is an important educational topic for PCPs.

3 DETAIL

3.1 The Testing Process (The Intervention)

3.1.1 Test Information and Offering the Test

During pre-visit planning meetings, PCPs, and staff identify eligible patients. Testing is offered to those by their primary care provider during usual care. This may occur at an annual wellness visit, or at any other visit where discussing the test does not interfere with the visit's primary focus. Non-physician staff may inform patients that a new screening test is available. They may play the 1-min and 46-second-long animated overview video. PCPs develop brief scripts which they feel help introduce the test to patients.

A folder given to the patient contains written information about the test at multiple levels of depth as well as key forms. This "patient packet" contains a tri-fold brochure, a 6-page "Frequently asked Questions (FAQ)" document, a list of genes covered by the test, the hospital-approved one-page clinical consent form, and "next-steps" instructions describing sample collection options and logistics. Each of these contains contact information for the Genomic Medicine Resource Center (GMRC) (**Figure 1A**), where questions are answered by a geneticist or genetic counselor for free, and where formal pre-test genetic counseling is arranged on request. For the PCP's convenience, the required send-out test order forms, customized for the test, are also included in the patient packet. The public web page offers the video and downloadable patient packet materials (**Supplementary Materials**).

Patients review the information and ask questions of the PCP. PCPs refer patients with genetic or logistical questions, or those taking more time, to the GMRC. Patients may decide to proceed with the test immediately or take time to review and decide. Those deciding to test must sign the consent form which is scanned into the EHR before an order can be entered. A blood or saliva sample is obtained and shipped to the testing laboratory by the UVMMC clinical laboratory along with the testing laboratory's requisition completed by the PCP.

3.1.2 Performing the Test

The testing laboratory accessions requisitions and samples. Orders are tracked locally by the GMRC staff using the testing laboratory's secure online portal account dedicated to the program. We portray to patients a single test that may detect potential health risks for themselves and their family members. At the testing laboratory, this consists of two standard NGS gene panels. The first 147 gene panel is a "Pro-active" health screen for monogenic cancer and cardiovascular risks as well as some

TABLE 2 | Notable Events. Ongoing quality surveillance identified refinement opportunities.

Event	Count	Response
The test was ordered in error. Quality surveillance identified lack of a signed consent. Testing was halted, the order was cancelled, and results were neither recorded nor released	1	PCPs were instructed not to "pend" orders while a patient considers whether to test
A patient complained because they received a bill for indicated professional services for an identified health risk	1	Although the limits of cost-free test-related services are delineated in the pre-test patient information, the importance of timely reminders during the patient journey is now emphasized
A patient with an anxiety disorder complained to their PCP of increased symptoms during testing and immediately after result delivery. The PCP successfully managed the transient exacerbation	1	Onboarding education cautions about timing of testing for patients with active mental health concerns are further emphasized
Report made to the health system's risk reporting system	None	None
Signature or manual data entry errors involving paper test requisitions or paper consent forms	~5%	Communications to correct each. Provider and staff re-education, and continued pressure for EHR integration resources

relatively common recessive risks (Haverfield et al., 2021). The second, 302-gene panel is a "Comprehensive Carrier" screen for monogenic recessive disorders. The panels overlap, so the union of genes sequenced is 431 (Wildin, 2019). Turnaround time is three to 4 weeks.

3.1.3 Preparing and Augmenting the Results for Action

The testing laboratory's results are reported in multipage PDF documents, one for each gene panel. GMRC staff download reports from the secure portal. The reports contain information about the variants found, the diseases they are linked to, inheritance patterns, and, in some cases, notations regarding reduced penetrance. The basis for variant classification as Likely Pathogenic (LP) or Pathogenic (P) using the testing laboratory's variant classification system (Nykamp et al., 2017) is included. Variants of uncertain significance (VUSs) are not reported. If VUSs are subsequently reclassified as LP or P, the testing laboratory issues an amended report with the new or classification-altered variants.

The GMRC staff reviews the testing laboratory's reports and produces a templated "Genomic Medicine Action Plan" (GMAP) messaging document (manuscript in preparation). Briefly, the one-to three-page GMAP is designed to focus provider and patient attention on the actionability of the results. Another function is to limit inappropriate responses to the results. The GMAP suggests PCP and patient actions and education and notes appropriate care pathways. The GMAP is pre-pended to the two report PDFs and the three documents merged. This augmented report is placed in the EHR as the original test order is finalized and PCPs are notified.

3.1.4 Returning Results to Patients and Genetic Counseling

PCPs receive guidance from the GMRC on how to return results and discuss them with patients; however, they develop their own protocols for how this is done in their practice. PCPs may perform clinical correlations to refine the risk for any positive results guided by the GMAP, such as reviewing personal and family health histories and ordering additional testing, procedures, and or referrals.

Post-test general genetic counseling is offered at no cost and is encouraged to discuss any results, especially in complex scenarios. Patients referred to the Familial Cancer Program receive genetic counseling during that billed specialty visit. For referral to other specialties lacking their own genetic counselors, a no-cost genetic counseling visit is strongly encouraged before the specialty visit. Genetic counseling is available in person or via tele video.

3.1.5 Family Member and Partner Testing

The information resulting from individual screening is useful to family members and to couples who may become pregnant. The GMAP messaging urges patients to review the full test reports that contain information about recessive disease risk, inheritance patterns, family member testing, and partner testing. It encourages patients to share the results with family members and briefly summarizes inheritance risks. The testing laboratory offers no-cost testing of blood relatives within 90 days of the report for any positive result on the "Pro-active" panel. The GMAP also suggests reproductive partner testing where appropriate and highlights low-cost partner testing offered by the testing laboratory. Genetic counseling is recommended in conjunction with both family member and partner testing. However, this pilot program does not manage family member or partner testing.

3.2 Summary of Testing Experience

Testing began 1 November 2019, in one Family Medicine practice with one PCP champion. Additional PCPs and practices joined as roll-out issues were resolved and as clinic workloads permitted. By March 2020, four additional PCPs and one additional clinic site were offering testing. Nearly all patients were tested by a Family Medicine PCP. The remainder were Internal Medicine patients who heard about and requested the test. Since patients are offered testing in the context of primary care visits, they reflect the demographics and health status of individuals frequenting primary care offices.

Two years after testing began, twenty different PCPs had ordered at least one test. One quarter of the providers ordered

three quarters of the tests. 186 patients between 18 and 92 years old had been tested. Median age was 58. Thirteen percent of tests had no reportable variants. The rest reported one or more dominant or recessive likely pathogenic or pathogenic variants.

3.3 Adapting to Changes in Outer Setting

Figure 2 shows monthly tests and the sources and timing of unanticipated inner setting demands on primary care and Genomic Medicine. Operational disruptions from the COVID-19 pandemic interrupted testing for about 2 months. Staffing issues quieted hoped-for expansion of the perceived optional activity to more primary care providers. We built a public web page where patients engaged through telemedicine visits can view the animated educational video, and download test information, educational resource documents, and the consent form, including contact information for the GMRC (Wildin, 2020). A home saliva sampling kit option was also added.

In response to laboratory wide needs, an HIT systems architect was engaged. This experienced professional performs a critical adaptor function to the HIT operations and prevailing culture of our setting.

3.4 Quality Assessment

To assess early patients' perceptions of the program's implementation effectiveness and to focus quality improvement efforts, in June 2020 we mailed a two-page survey to the first 61 patients tested along with a postage-paid return envelope. After two reminder letters, 19 surveys were returned. One was blank and excluded from tabulation. The **Supplementary Material** shows 18 tabulated responses in the survey instrument format. Aside from logistical challenges like receiving printed results in the mail, which we worked to improve, the survey indicated general satisfaction or enthusiasm about the testing design and process, and for the value proposition. Of note, patients strongly endorsed that the PCP's office is the right place to offer this testing.

Table 2 describes events captured by our quality surveillance processes and how we responded. Most resemble those occasionally encountered in health care and none affected patient health. While data about the rate of patients choosing to test when offered testing, and why patients declined testing, are potentially informative, their collection was not practical during this pilot implementation.

4 DISCUSSION

4.1 Conclusion

The key goals of this pilot implementation of clinical genomic population health screening of any-health-status adults were accomplished (**Table 1**). This demonstrates the feasibility of translating lessons from prior population sequencing and return of results research into clinical practice, which was the primary goal. Key differentiators of our implementation include placing primary care at the center, using a large, pre-defined clinically relevant target gene panel performed in a clinical laboratory, offering testing as part of usual preventive care at no cost, providing a written action plan with the test reports, and not being a research protocol.

The implementation we describe here leveraged all the opportunities and overcame most of the challenges cited for "non-traditional genetic testing" in the American College of Medical Genetics and Genomics' "Points to Consider" analyses, including the important roles primary care providers contribute (Bean et al., 2021; Murray et al., 2021). Strengths included leadership engagement with tools like a personal genomics test that occurred years prior to beginning the pilot, getting formal buy in from medical center administration with a non-financial business plan, involving diverse stakeholders in the design and implementation process and making it worth their time, and leveraging existing workflows wherever possible.

We contracted for existing validated tests and primary reporting with a commercial laboratory. This allowed us to move forward sooner and with less expense than if we had to implement germline testing, variant interpretation, and reporting ourselves.

Indirect measures of success include that new PCPs continue volunteering, most PCPs involved have continued to offer the test, and patients continue to get tested. Notably, no participation incentives are provided to the PCPs. Recruiting new PCPs was actively limited due to unrelated staff shortages and suspended during the COVID-19 public health crisis, redemonstrating the susceptibility of new prevention-oriented programs to externally imposed prioritization.

Patient complaints are few, are related to process and communication, and are easily addressed. Unanticipated resource demands have not surfaced, and no critical element of the complex multi-disciplinary design has failed or had to be withdrawn. Our patient quality survey is a direct measure addressing some of the same data types as the survey by Orlando et al. (2018). The results are generally positive and support the assertion that the process is sufficiently patient-centric.

Barriers to scaling up are common in new interventions. We underestimated the need for leadership engagement in HIT and the relative priority for planned system-wide HIT transformation, where tension for change was far higher. HIT resources were unavailable to build consent, order, and resulting experiences familiar to the PCPs. The EHR-plus-paper order process we used instead burdens clinic staff and dissuaded some PCPs from participating. This adaptation is also the principal source of tracked process errors. EHR-based improvements will be prioritized once the system-wide Epic implementation is completed in April 2022. A separate, secure data system was built internally to track the multiple process steps. The solution allows oversight but is neither interfaced nor scalable. The criterion that tested patients are attributable in Vermont's ACO was similarly challenging because ACO status is not reliably reflected in our EHR. It requires a manual inter-institutional lookup process.

The strong knowledge and experience of the principal implementers and of the primary care and other key partners, and the continued involvement of the PFAs, all contributed to resilience in the face of disruptive shifts in the setting that eluded anticipation, such as the COVID-19 pandemic and a UVMMC cyberattack.

4.2 Generalizability

The implementation of genomic population health screening in primary care at our institution benefited from elements in

the outer setting, like the ACO, and in the inner setting, like engaged leaders who embrace innovation, champion providers, a highly collaborative team with broad expertise and capabilities, and availability of non-research funding of the pilot. While not unique, these advantages are not universal. Our guiding design principles may not be shared in every instance, and situations calling for pragmatism may also diverge. Presenting our implementation openly and in a recognized framework may help others identify their unique paths to success.

4.3 Future Directions

While not a goal of the pilot, we recognize that the patients' clinical results combined with their personal and family health histories represent data types underlying a key phase of learning healthcare systems (LHS) (Schwartz et al., 2018; Williams et al., 2018). Having met our goal of demonstrating feasibility, we anticipate building a real-world LHS with related implementation, outcomes, return on investment, personal, educational, and health system research that can be combined or compared with similar data from other genomic population health screening programs.

We wish to increase testing for younger and healthy adults, who visit their PCP less often, by engaging them through EHR patient portal messages (Christensen et al., 2021) and by expanding testing to women's health clinics. To accomplish enhanced risk assessment for genetic disease risks, family health history and genomic population health risk information should be co-analyzed (Wildin et al., 2021). This adds complexity but could propel family member ("cascade") testing, an important added value for genomic population health screening.

Finally, since our pilot's funding is finite, there is a need for both stable and scalable investment in this and similar programs that support the enhanced prevention focus of value-based care. We envision genomic population screening as a future benefit in value-based care payment contracts, supporting the preservation of a healthy state in both individuals and populations.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RW authored this manuscript and created figures and tables; the remaining authors provided valuable input for the final version. RW lead the implementation, created novel program elements including the action plan format and survey, established the reporting workflow, chairs the care pathway work group, and creates action plans for clinical results. AR leads the primary care contingent of the care pathway work group and is the Family Medicine champion physician testing patients and helping other family medicine providers onboard. CG supported program development and care pathway work group activities, provided a genetic counsellor perspective, and has drafted preliminary action plans. She provides genetic counselling to engaged and tested patients. TP helped with pilot design, provides leadership to participating family medicine providers, and monitors program impact on operations. DL envisioned and designed the genomic population health pilot, established partnerships and contracts, led development of the engagement video and consent form, interfaces with health system leaders, creates action plans for clinical results, and contributed to the manuscript revisions.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.867334/full#supplementary-material

REFERENCES

American College of Medical Genetics and Genomics (2019). ACMG Response to Nussbaum et al. Letter on ACMG Policy Statement: The Use of Secondary Findings Recommendations for General Population Screening: a policy statement of the ACMG. *Genet. Med.* 21 (12), 2838–2839. doi:10.1038/s41436-019-0573-3

Bean, L. J. H., Scheuner, M. T., Murray, M. F., Biesecker, L. G., Green, R. C., Monaghan, K. G., et al. (2021). DNA-Based Screening and Personal Health: A Points to Consider Statement for Individuals and Health-Care Providers from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (6), 979–988. doi:10.1038/s41436-020-01083-9

Beitsch, P. D., Whitworth, P. W., Hughes, K., Patel, R., Rosen, B., Compagnoni, G., et al. (2019). Underdiagnosis of Hereditary Breast Cancer: Are Genetic Testing Guidelines a Tool or an Obstacle? *Jco* 37 (6), 453–460. doi:10.1200/jco.18.01631

Briggs, J. (2016). *Individualized Medicine Blog*. FL, USA: Mayo Clinic Center for Individualized Medicine. [Internet]. [cited 2022]. Available from: https://individualizedmedicineblog.mayoclinic.org/2016/06/07/understanding-your-genome-personalizing-your-medicine/.

Celenza, J. F., Zayack, D., Buus-Frank, M. E., and Horbar, J. D. (2017). Family Involvement in Quality Improvement. *Clin. Perinatology* 44 (3), 553–566. doi:10.1016/j.clp.2017.05.008

Christensen, K. D., Bell, M., Zawatsky, C. L. B., Galbraith, L. N., Green, R. C., Hutchinson, A. M., et al. (2021). Precision Population Medicine in Primary Care: The Sanford Chip Experience. *Front. Genet.* 12, 626845. doi:10.3389/fgene.2021.626845

Damschroder, L. J., Aron, D. C., Keith, R. E., Kirsh, S. R., Alexander, J. A., and Lowery, J. C. (2009). Fostering Implementation of Health Services Research Findings into Practice: A Consolidated Framework for Advancing Implementation Science. *Implementation Sci.* 4, 50. doi:10.1186/1748-5908-4-50

David, K. L., Best, R. G., Brenman, L. M., Bush, L., Deignan, J. L., Flannery, D., et al. (2019). Patient Re-contact after Revision of Genomic Test Results: Points to Consider-A Statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 21 (4), 769–771. doi:10.1038/s41436-018-0391-z

David, S. P., Dunnenberger, H. M., Ali, R., Matsil, A., Lemke, A. A., Singh, L., et al. (2021). Implementing Primary Care Mediated Population Genetic Screening within an Integrated Health System. *J. Am. Board Fam. Med.* 34 (4), 861–865. doi:10.3122/jabfm.2021.04.200381

Directors of the American College of Medical Genetics and Genomics (2019). The Use of ACMG Secondary Findings Recommendations for General Population Screening: A Policy Statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 21 (7), 1467

Duow, T., and Marjanovic, S. (2016). Population-scale Sequencing and the Future of Genomic Medicine: Learning from Past and Future Efforts. *RAND Health Q.* 6 (2), 1–29. doi:10.7249/RR1520

Ginsburg, G. S., Horowitz, C. R., and Orlando, L. A. (2019). What Will it Take to Implement Genomics in Practice? Lessons from the IGNITE Network. *Personalized Med.* 16 (4), 259–261. doi:10.2217/pme-2019-0021

Grembowski, D., and Marcus-Smith, M. (2018). The 10 Conditions that Increased Vermont's Readiness to Implement Statewide Health System Transformation. *Popul. Health Manag.* 21 (3), 180–187. doi:10.1089/pop.2017.0061

Haverfield, E. V., Esplin, E. D., Aguilar, S. J., Hatchell, K. E., Ormond, K. E., Hanson-Kahn, A., et al. (2021). Physician-directed Genetic Screening to Evaluate Personal Risk for Medically Actionable Disorders: A Large Multi-center Cohort Study. *BMC Med.* 19 (1), 199. doi:10.1186/s12916-021-01999-2

Kelly, M. A., Leader, J. B., Wain, K. E., Bodian, D., Oetjens, M. T., Ledbetter, D. H., et al. (2021). Leveraging Population-based Exome Screening to Impact Clinical Care: The Evolution of Variant Assessment in the Geisinger MyCode Research Project. *Am. J. Med. Genet.* 187 (1), 83–94. doi:10.1002/ajmg.c.31887

Khoury, M. J., and Dotson, W. D. (2021). From Genes to Public Health: Are We Ready for DNA-Based Population Screening? *Genet. Med.* 23 (6), 996–998. doi:10.1038/s41436-021-01141-w

King, D. K., Shoup, J. A., Raebel, M. A., Anderson, C. B., Wagner, N. M., Ritzwoller, D. P., et al. (2020). Planning for Implementation Success Using RE-AIM and CFIR Frameworks: A Qualitative Study. *Front. Public Health* 8, 59. doi:10.3389/fpubh.2020.00059

Kissam, S. M., Beil, H., Cousart, C., Greenwald, L. M., and Lloyd, J. T. (2019). States Encouraging Value-Based Payment: Lessons from CMS's State Innovation Models Initiative. *Milbank Q.* 97 (2), 506–542. doi:10.1111/1468-0009.12380

Lemke, A. A., Amendola, L. M., Thompson, J., Dunnenberger, H. M., Kuchta, K., Wang, C., et al. (2021). Patient-Reported Outcomes and Experiences with Population Genetic Testing Offered through a Primary Care Network. *Genet. Test. Mol. Biomarkers* 25 (2), 152–160. doi:10.1089/gtmb.2020.0275

Linderman, M. D., Nielsen, D. E., and Green, R. C. (2016). Personal Genome Sequencing in Ostensibly Healthy Individuals and the PeopleSeq Consortium. *J. Pers Med.* 6 (2). doi:10.3390/jpm6020014

Masterson, K. (2016). *For One Vermont Man, Sequencing His Whole Genome Solved a Life of Pain*, 6. USA: VPR NewsVermont Public Radio, 22.

Miller, D. T., Lee, K., Gordon, A. S., Amendola, L. M., Adelman, K., Bale, S. J., et al. (2021). Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2021 Update: a Policy Statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (8), 1391–1398. doi:10.1038/s41436-021-01171-4

Murray, M. F., Evans, J. P., Angrist, M., Chan, K., Uhlmann, W. R., Doyle, D. L., et al. (2018). *A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults*. Washington, DC: NAM Perspectives: National Academy of Medicine.

Murray, M. F., Giovanni, M. A., Doyle, D. L., Harrison, S. M., Lyon, E., Manickam, K., et al. (2021). DNA-based Screening and Population Health: A Points to Consider Statement for Programs and Sponsoring Organizations from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (6), 989–995. doi:10.1038/s41436-020-01082-w

Nussbaum, R. L., Haverfield, E., Esplin, E. D., and Aradhya, S. (2019). Response to "The Use of ACMG Secondary Findings Recommendations for General Population Screening: A Policy Statement of the American College of Medical Genetics and Genomics (ACMG)". *Genet. Med.* 21 (12), 2836–2837. doi:10.1038/s41436-019-0572-4

Nykamp, K., Anderson, M., Powers, M., Garcia, J., Herrera, B., Ho, Y.-Y., et al. (2017). Sherloc: A Comprehensive Refinement of the ACMG-AMP Variant Classification Criteria. *Genet. Med.* 19 (10), 1105–1117. doi:10.1038/gim.2017.37

Orlando, L. A., Sperber, N. R., Voils, C., Nichols, M., Myers, R. A., Wu, R. R., et al. (2018). Developing a Common Framework for Evaluating the Implementation of Genomic Medicine Interventions in Clinical Care: The IGNITE Network's Common Measures Working Group. *Genet. Med.* 20 (6), 655–663. doi:10.1038/gim.2017.144

Rego, S., Dagan-Rosenfeld, O., Zhou, W., Sailani, M. R., Limcaoco, P., Colbert, E., et al. (2018). High-frequency Actionable Pathogenic Exome Variants in an Average-Risk Cohort. *Cold Spring Harb Mol. Case Stud.* 4 (6), 3178. doi:10.1101/mcs.a003178

Reuter, M. S., Walker, S., Thiruvahindrapuram, B., Whitney, J., Cohn, I., Sondheimer, N., et al. (2018). The Personal Genome Project Canada: Findings from Whole Genome Sequences of the Inaugural 56 Participants. *CMAJ* 190 (5), E126–E136. doi:10.1503/cmaj.171151

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al. (2015). Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 17 (5), 405–424. doi:10.1038/gim.2015.30

Rivera-Muñoz, E. A., Milko, L. V., Harrison, S. M., Azzariti, D. R., Kurtz, C. L., Lee, K., et al. (2018). ClinGen Variant Curation Expert Panel Experiences and Standardized Processes for Disease and Gene-Level Specification of the ACMG/AMP Guidelines for Sequence Variant Interpretation. *Hum. Mutat.* 39 (11), 1614–1622. doi:10.1002/humu.23645

Roberts, M. C., Mensah, G. A., and Khoury, M. J. (2019). Leveraging Implementation Science to Address Health Disparities in Genomic Medicine: Examples from the Field. *Ethn. Dis.* 29 (Suppl. 1), 187–192. doi:10.18865/ed.29.S1.187

Ryan, K. A., De Vries, R. G., Uhlmann, W. R., Roberts, J. S., and Gornick, M. C. (2017). Public's Views Toward Return of Secondary Results in Genomic Sequencing: It's (Almost) All about the Choice. *J. Genet. Counsel* 26 (6), 1197–1212. doi:10.1007/s10897-017-0095-6

Sanderson, S. C., Linderman, M. D., Suckiel, S. A., Diaz, G. A., Zinberg, R. E., Ferryman, K., et al. (2016). Erratum: Motivations, Concerns and Preferences of Personal Genome Sequencing Research Participants: Baseline Findings from the HealthSeq Project. *Eur. J. Hum. Genet.* 24 (1), 153. doi:10.1038/ejhg.2015.179

Sapp, J. C., Johnston, J. J., Driscoll, K., Heidlebaugh, A. R., Miren Sagardia, A., Dogbe, D. N., et al. (2018). Evaluation of Recipients of Positive and Negative Secondary Findings Evaluations in a Hybrid CLIA-Research Sequencing Pilot. *Am. J. Hum. Genet.* 103 (3), 358–366. doi:10.1016/j.ajhg.2018.07.018

Schwartz, M. L. B., McCormick, C. Z., Lazzeri, A. L., Lindbuchler, D. A. M., Hallquist, M. L. G., Manickam, K., et al. (2018). A Model for Genome-First Care: Returning Secondary Genomic Findings to Participants and Their Healthcare Providers in a Large Research Cohort. *Am. J. Hum. Genet.* 103 (3), 328–337. doi:10.1016/j.ajhg.2018.07.009

Suckiel, S. A., Linderman, M. D., Sanderson, S. C., Diaz, G. A., Wasserstein, M., Kasarskis, A., et al. (2016). Impact of Genomic Counseling on Informed Decision-Making Among Ostensibly Healthy Individuals Seeking Personal Genome Sequencing: The HealthSeq Project. *J. Genet. Counsel* 25 (5), 1044–1053. doi:10.1007/s10897-016-9935-z

Wahlberg, K. J., Burnett, M., Muthukrishnan, P., Purcell, K., Repp, A. B., van Eeghen, C., et al. (2021). Partnering with Patients in a Quality Improvement Curriculum for Internal Medicine Residents. *J. Patient Exp.* 8, 2374373521999604. doi:10.1177/2374373521999604

Walton, N. A., Johnson, D. K., Person, T. N., Reynolds, J. C., and Williams, M. S. (2020). Pilot Implementation of Clinical Genomic Data into the Native

Electronic Health Record: Challenges of Scalability. *ACI Open* 04, e162–e166. doi:10.1055/s-0040-1721490

Weitzel, K. W., Alexander, M., Alexander, M., Bernhardt, B. A., Calman, N., Carey, D. J., et al. (2016). The IGNITE Network: A Model for Genomic Medicine Implementation and Research. *BMC Med. Genomics* 9, 1. doi:10.1186/s12920-015-0162-5

Wildin, R. S. (2019). *Genomic DNA Test Information (Gene List) USA: UVM Health Network*. [Gene List for the Pilot Genomic Population Health Program] Available from: https://www.uvmhealth.org/assets/2020-08/genomic-dna-test-information101419.pdf.

Wildin, R. S. (2020). *Genomic Population Health and the Genomic DNA Test USA and Your Health Care Providers Use Your Genes to Inform Your Health Care*. Burlington: University of Vermont Medical Center. [UVM Medical Center Offers the Genomic DNA Test to Help You Available from: https://uvmhealth.org/GenomicDNAtest.

Wildin, R. S., Messersmith, D. J., and Houwink, E. J. F. (2021). Modernizing Family Health History: Achievable Strategies to Reduce Implementation Gaps. *J. Community Genet.* 12 (3), 493–496. doi:10.1007/s12687-021-00531-6

Williams, M. S., Buchanan, A. H., Davis, F. D., Faucett, W. A., Hallquist, M. L. G., Leader, J. B., et al. (2018). Patient-Centered Precision Health in a Learning Health Care System: Geisinger's Genomic Medicine Experience. *Health Aff.* 37 (5), 757–764. doi:10.1377/hlthaff.2017.1557

Williams, M. S. (2019). Early Lessons from the Implementation of Genomic Medicine Programs. *Annu. Rev. Genom. Hum. Genet.* 20, 389–411. doi:10.1146/annurev-genom-083118-014924

Zoltick, E. S., Linderman, M. D., Linderman, M. D., McGinniss, M. A., Ramos, E., Ball, M. P., et al. (2019). Predispositional Genome Sequencing in Healthy Adults: Design, Participant Characteristics, and Early Outcomes of the PeopleSeq Consortium. *Genome Med.* 11 (1), 10. doi:10.1186/s13073-019-0619-9

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A Polygenic Score for Type 2 Diabetes Improves Risk Stratification Beyond Current Clinical Screening Factors in an Ancestrally Diverse Sample

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A substantial proportion of the adult United States population with type 2 diabetes (T2D) are undiagnosed, calling into question the comprehensiveness of current screening practices, which primarily rely on age, family history, and body mass index (BMI). We hypothesized that a polygenic score (PGS) may serve as a complementary tool to identify high-risk individuals. The T2D polygenic score maintained predictive utility after adjusting for family history and combining genetics with family history led to even more improved disease risk prediction. We observed that the PGS was meaningfully related to age of onset with implications for screening practices: there was a linear and statistically significant relationship between the PGS and T2D onset (−1.3 years per standard deviation of the PGS). Evaluation of U.S. Preventive Task Force and a simplified version of American Diabetes Association screening guidelines showed that addition of a screening criterion for those above the 90th percentile of the PGS provided a small increase the sensitivity of the screening algorithm. Among T2D-negative individuals, the T2D PGS was associated with prediabetes, where each standard deviation increase of the PGS was associated with a 23% increase in the odds of prediabetes diagnosis. Additionally, each standard deviation increase in the PGS corresponded to a 43% increase in the odds of incident T2D at one-year follow-up. Using complications and forms of clinical intervention (i.e., lifestyle modification, metformin treatment, or insulin treatment) as proxies for advanced illness we also found statistically significant associations between the T2D PGS and insulin treatment and diabetic neuropathy. Importantly, we were able to replicate many findings in a Hispanic/Latino cohort from our database, highlighting the value of the T2D PGS as a clinical tool for individuals with ancestry other than European. In this group, the T2D PGS provided additional disease risk information beyond that offered by traditional screening methodologies. The T2D PGS also had predictive value for the age of onset and for prediabetes among T2D-negative Hispanic/Latino participants. These findings strengthen the notion that a T2D PGS could play a role in the clinical setting across multiple ancestries, potentially improving T2D screening practices, risk stratification, and disease management.

Keywords: polygenic score, type 2 diabees, consumer genomics, genetic risk, diabetes screening

1 INTRODUCTION

The United States and other Western countries face an epidemic of type 2 diabetes mellitus (T2D). Population-wide screening is critical for identifying T2D-positive and prediabetic individuals in order to prevent severe pathology associated with more severe or protracted disease. Despite detailed screening guidelines developed by The U.S. Preventive Services Task Force and the American Diabetes Association (ADA), diagnostic delay in prediabetes and T2D continues to hamper timely and effective treatment (Samuels et al., 2006). In 2020, the Centers for Disease Control (CDC) estimated that over 7 million undiagnosed T2D cases exist among current U.S. residents, and a diagnostic rate of only 15.3% for the 80 + million individuals living with prediabetes (Centers for Disease Control and Prevention, 2020). By 2050, the number of undiagnosed cases could be over 13 million, as T2D prevalence is projected to increase to 25–28% of the U.S. population (Boyle et al., 2010).

This high rate of progression can be mitigated with improved screening and risk stratification methods. The T2D epidemic described above is not only a case identification problem but a resource allocation problem. Novel methods are needed to improve screening and risk stratification in order to most effectively allocate resources to healthcare providers managing the prevention and treatment of the disease.

The heritability of T2D has been estimated at 25–72% (Almgren et al., 2011; Florez et al., 2018), and genome-wide association studies (GWAS) have shown a highly polygenic architecture to be associated with risk for the disease (Xue et al., 2018). Thus, predictive genetic models that produce a polygenic score (PGS) containing many thousands of genetic variants have been increasingly investigated (Reisberg et al., 2017; Khera et al., 2018). Indeed, systematic reviews and an online depository of PGS together provide information about dozens of published distinct PGS for T2D, comprised of only three variants, to nearly 7 million variants (Padilla-Martínez et al., 2020; Lambert et al., 2021).

We hypothesized that a T2D PGS developed from a large-scale database and consisting of over 11,000 T2D-associated genetic variants would complement existing screening methods and improve individuals' stratification across the T2D risk spectrum. First, we developed a novel PGS derived from a very large multi-ancestry sample in the 23andMe database; the PGS under study in this manuscript is not the one included in the 23andMe Personal Genome Service as of March 2022. Next, we hypothesized that the PGS would add unique predictive value over and above traditional factors that inform T2D screening decisions in the clinic: family history, age, and body mass index (BMI; Pippitt et al., 2016; American Diabetes Association, 2018; USPSTF, 2021). We also hypothesized that the T2D PGS would be associated with earlier age of onset of T2D, prevalence of prediabetes among those without a T2D diagnosis, T2D incidence after one year, and manifestations of severity including differences in T2D treatments and complications of T2D. Finally, given that PGS derived from samples of primarily European descent have exhibited limited transferability when assessed in other populations (Martin et al., 2019), we evaluated the T2D PGS in a second 23andMe cohort consisting of individuals with Hispanic/Latino ancestry to underscore the value of the T2D PGS as a clinical tool applied to those with ancestry other than European.

2 MATERIALS AND METHODS

2.1 Study Participants and Survey Methodology

We recruited study participants from all genotyped 23andMe customers who opted to participate in research with 23andMe. All participants provided informed consent under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services. Individual-level data from this study are not publicly available per the IRB-approved study protocol. Participants were included in the analysis on the basis of consent status as checked at the time data analyses were initiated.

A series of questions asked if a participant had ever been diagnosed with T2D by a physician. Those who answered affirmatively were considered cases, whereas those who indicated no personal history of T2D were considered controls. Participants who reported latent autoimmune diabetes in adults (LADA), maturity onset diabetes of the young (MODY), or only history of gestational diabetes were not counted as T2D cases. Participants without history of T2D diagnosis who reported any history of diagnosis of "high blood sugar or prediabetes" were counted as cases of prediabetes.

Those who reported a history of T2D diagnosis were asked follow-up questions about history of prescription treatment (metformin, insulin) and physician-directed lifestyle modifications. These participants were also asked about history of diagnosis of diabetes microvascular complications: neuropathy, nephropathy, and retinopathy.

Follow up surveys were made available one year later to ascertain if any participants had received a new diagnosis of T2D in the past 12 months. Incident cases were defined as those who had no existing diagnosis of type 2 diabetes at the baseline measurement at the time of enrollment, but who indicated a new diagnosis that occurred at least one but no more than two years after the initial question was answered. Additional questions asked about age of diagnosis of T2D, height and weight, and birth year. Ancestry category (European, Hispanic/Latino) was self-reported. Participants were required to have a minimum age of 20 and maximum age of 79 years old. Additional exclusions were: providing conceptually inconsistent responses like an age of T2D onset older than a currently reported age, reporting age of onset younger than age 20, reporting underweight or extreme obese BMI (BMI <18.5 or >69), or reporting a duration of time between initial diagnosis and current age greater than three standard deviations from the mean of this metric (>40 years). Individuals who were in the sample used for the GWAS or to train the PGS were excluded from the study.

Because a question from a separate survey was used to assess family history of T2D among first degree relatives, there were fewer available responses to this question relative to others,

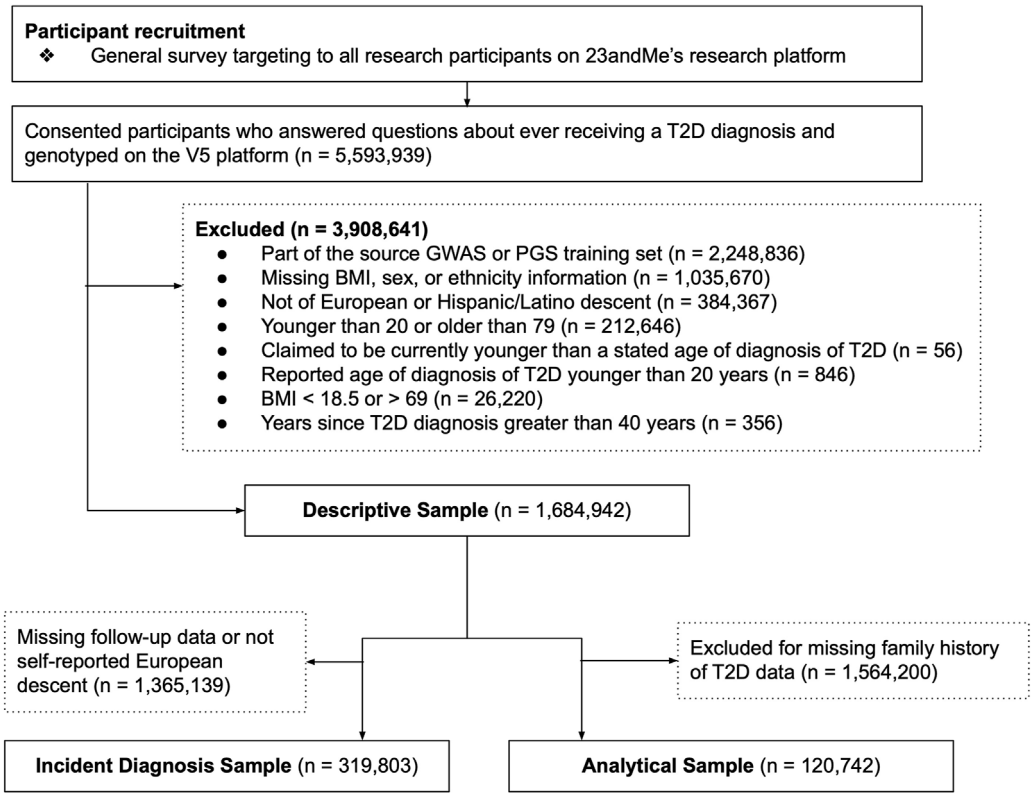

FIGURE 1 | Participant recruitment and analysis flow diagram. Three data sets were used for components of this analysis. The Descriptive Sample was used to generate plots, to estimate raw prevalences, or to estimate unadjusted odds ratios. The Incident Diagnosis Sample was used to assess the association between the polygenic score (PGS) and incident diagnosis over time. The Analytical Sample was used for regression models that included family history as a predictor. Sub-sampling was required due to missing data in key survey questions required for analysis, and participant attrition over time.

reflected in the participant flow diagram (**Figure 1**). To maximize sample size, descriptive analyses of the data (i.e., prevalence of T2D along the spectrum of the PGS) and unadjusted odds ratios between factors like the PGS and T2D prevalence include all available data (the Descriptive Sample), whereas regression analysis involving family history were performed in a subset of the full data set with family history data (Analytical Sample). Lastly, due to loss of participation with time, the sample used to assess incidence of T2D (Incidence Sample) also represents a subset of the full data, and there was only sufficient data to perform the analysis among those of self-reported European descent (**Figure 1**).

2.2 Genotyping and Polygenic Score Development

DNA extracted from saliva samples was assayed on the Illumina Infinium Global Screening Array (Illumina, San Diego, CA), consisting of approximately 640,000 common variants supplemented with ~50,000 custom probes. This platform is referred to as 23andMe platform V5, and underwent quality controls as described previously (Nakka et al., 2019). Only participants genotyped on this platform are included in this analysis. A polygenic score associated with the likelihood of having T2D was developed using the methods described in 23andMe White Paper 23–21 (Ashenhurst et al., 2020). In brief, single nucleotide polymorphisms (SNPs) were selected from a meta-analysis of three GWAS conducted in individuals of European, Black/African American, and Hispanic/Latino descent. Candidate models based on nine variant sets determined by varying *p*-value and window distances were evaluated in tuning sets that were not included in the GWAS. Finally, based on best performance in the tuning cohorts, one variant set was chosen for final assessment in the European and Hispanic/Latino test cohorts, which were not included in the GWAS or model training.

The final model containing 11,999 SNPs showed a significant association with the likelihood of having T2D among participants of European descent [area under the receiver operator curve, AUC = 0.656, CI (0.654,0.659), **Supplementary Table S2**] as well as Hispanic/Latino individuals [AUC = 0.635, CI (0.628,0.642)]. Age and sex variables provided more information than the PGS alone in both the European descent [AUC = 0.774, CI (0.773,0.776)] and Hispanic/Latino [AUC = 0.811, CI (0.806,0.816)] subsamples. The combined model with demographic features and the PGS were the most predictive [European AUC = 0.814, CI (0.812,0.816), Hispanic/Latino AUC = 0.841, CI (0.837,0.845)]. The discriminative

TABLE 1 | Sample descriptives.

Self-reported Ancestry	N	Age mean (SD)	Sex (%) (Female)	T2D Prevalence (%)
European	1,528,668	47.6 (15.8)	60.4	3.2
Hispanic/Latino	156,274	41.0 (14.2)	60.6	2.6
European sub-sample with family history data	113,126	53.3 (15.8)	66.5	4.6
Hispanic/Latino subsample with family history data	7,616	45.2 (14.9)	64.2	3.7
European sub-sample with one-year incidence data	319,803	50.5 (16.0)	68.3	0.9

The incidence sub-sample was composed of those who were T2D-negative at baseline and provided one year follow-up data.

performance of this model ranks it among the leading models cited in the PGS Catalog as of March 2022 (Lambert et al., 2021). For complete detail about the PGS, see information in **Supplemental Materials**.

2.3 Statistical Analyses

Statistical analyses were conducted in statsmodels (v0.12.1) in Python (Seabold and Perktold, 2010). A study-wise significance threshold was defined as $p < 0.0018$ based on 28 independent comparisons and a Bonferroni correction. Reported odds ratios and linear model betas are adjusted for age, BMI (log transformed and standardized), sex, and first-degree relative family history of T2D unless otherwise described. All confidence intervals (CIs) provided are 95% CIs. To maintain participant privacy, counts or statistics that could uniquely identify fewer than five people are not provided in this manuscript.

3 RESULTS

3.1 Participant Characteristics

The final Descriptive Analysis sample consisted of N = 1,528,668 individuals of European descent and N = 156,4274 of Hispanic/Latino descent. The subsample with available family history data (the European Analytical Sample, N = 113,126, Hispanic/Latino N = 7,616) was smaller, as was the sample with available repeated measures (European Incidence Sample, N = 319,803). Full sample descriptives are provided in **Table 1**, and participant exclusions are shown with a flowchart in **Figure 1**. The prevalence of self-reported T2D within each sex and decade of age in the multi-ancestry sample used to train the PGS are shown in **Supplementary Figure S1**. The median age of T2D diagnosis was 50 (mean = 48.3, SD = 11.2), and 43 (mean = 42.9, SD = 11.4) in the European-descent and Latino sub-samples, respectively.

3.2 The Polygenic Score Provides Information Not Captured by Family History

Current clinical practices rely heavily on family history of disease (FH) to identify patients at increased risk of developing conditions. But the full scope of heritability cannot be captured by FH alone, and not all individuals know their family history (e.g., those who were adopted), leaving open the possibility of under-identifying disease risk. We hypothesized that the T2D PGS combined with FH would improve the prediction of disease development more than either factor alone. This analysis was performed in the Analytical Sample (**Figure 1**).

Among those in the lowest genetic risk ventile, 20.8% of controls and 65.2% of cases reported positive FH. Among those in the highest risk ventile, positive FH prevalence was 42.9% for controls and 73.1% for cases (**Figure 2A**). There was a significant relationship between family history status and the PGS across the Analytical Sample as estimated in a logistic regression model; each standard deviation in the PGS was associated with 32% greater odds of reporting family history of the condition [$\beta = 0.27$, $p < 0.0018$, OR = 1.32, CI (1.30,1.33)]

We next assessed several logistic regression models of T2D diagnosis as a function of the T2D PGS, positive FH, and the common T2D screening factors of age and BMI (Pippitt et al., 2016; Zheng et al., 2018) in a training sample, comprised of 75% of the analytic sample; a test set of 25% was reserved for model evaluation. Both FH and the PGS were statistically significant as predictors in separate models (**Table 2**) as well as in a model including both FH and PGS as predictors. The combined model had the best predictive performance [as assessed by Cox-Snell's pseudo R2 statistic = 0.21, and by AUC in the out-of-sample test set, AUC = 0.85 (0.85,0.86)], compared to models with only FH [R2 = 0.19, AUC = 0.83 (0.83,0.84)] or only the PGS [R2 = 0.17, AUC = 0.83 (0.82,0.84)], showing that FH and PGS contribute unique information as predictors in each other's presence.

3.3 Potential Contribution of the Polygenic Score to Screening Practices

Although individual health care systems may use their own criteria, current screening guidelines often use two main sources: The U.S. Preventive Services Task Force (USPSTF, 2021) and the American Diabetes Association (ADA, 2018). The USPSTF currently recommends screening for abnormal blood glucose and T2D in adults 35–70 years of age who are overweight or obese and repeating blood glucose testing every 3 years if results are typical. Individuals from populations with higher prevalence of diabetes (American Indian/Alaska Native, Black, Hawaiian/Pacific Islander, Hispanic/Latino) should be considered for earlier screening (USPSTF). The ADA proposes screening for T2D beginning at age 45 for all people. Screening for prediabetes and onset of future T2D in asymptomatic people should be considered in adults of any age who are overweight and have one or more additional risk factors for diabetes (ADA). These risk factors include overweight and obesity, physical inactivity, abnormal lipid levels, high blood pressure, and

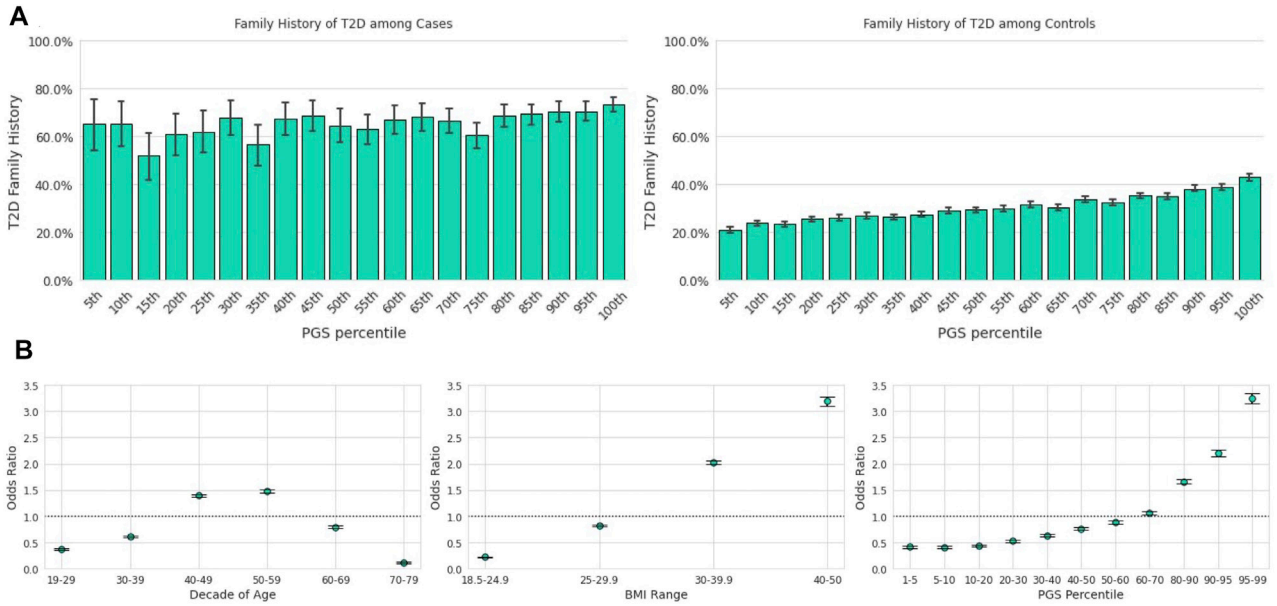

FIGURE 2 | The T2D PGS is a predictor on par with traditional risk factors. Error bars here represent empirically derived 95% confidence intervals. **(A)**: Research participants who self-reported their family history were binarized into two groups: those with a first-degree relative with T2D and those without. The fraction of participants with a positive family history of T2D (y-axis) is plotted as a function of PGS ventile (x-axis) among T2D cases (left panel) and T2D controls (right panel). **(B)**: Unadjusted odds ratios (y-axis) of having T2D relative to the entire study population were calculated for each decade of age (left panel), BMI category (center panel), and PGS percentile (right panel). Error bars represent analytically computed 95% confidence intervals.

TABLE 2 | Logistic regression between prevalent T2D, family history, and the PGS among those of European descent.

Model	Base model	Family history only	Polygenic score only	Combined model
Intercept	−6.34	−6.82	−6.7	−7.13
Family History	-	1.34	-	1.23
Standardized Polygenic Score	-	-	0.48	0.43
Female Sex	−0.46	−0.57	−0.50	−0.60
Decade of Age	0.06	0.05	0.07	0.06
Standardized Log Body Mass Index	0.72	0.66	0.68	0.64
Cox-Snell's Pseudo R2	0.14	0.18	0.18	0.21
Test Set AUC (95% CIs)	0.80 (0.79, 0.80)	0.83 (0.83, 0.84)	0.83 (0.82, 0.84)	0.85 (0.85, 0.86)

All coefficients derived from logistic regression were significant p *<0.0018 in all models. N = 84,844 for all models. The model that included both family history and the PGS was the most predictive in terms of both pseudo R2 and out-of-sample AUC.*

smoking. Despite both screening recommendations, many at-risk individuals, as well as prediabetic and T2D cases, are being missed annually. We hypothesized that the T2D PGS could identify individuals who would benefit from earlier screening for T2D solely based on their genetic risk.

3.3.1 Univariate and Multivariate Associations Between T2D Prevalence and Screening Factors

Using the T2D PGS in the Descriptive Sample, we calculated the unadjusted odds ratio (OR) of having T2D for a given PGS percentile range relative to the total population. We compared this outcome to the OR of the risk factors highlighted in both guidelines, age and BMI (**Figure 2B**), which were also calculated relative to the total study population. Age was scored as age of diagnosis for cases, and current age for controls. We observed substantial overlap in the unadjusted OR magnitudes associated with the three variables: The range of risk associated with the PGS, OR = 0.41 [CI (0.38,0.44)] at the 1st-5th percentile to OR = 3.25 [CI (3.16,3.35)] at the 95th-99th percentile, was comparable to the range associated with BMI, OR = 0.22 [CI (0.21,0.23)] at BMI 18.5–24.9 to OR = 3.19 [CI (3.11,3.28)] at BMI 40–50. Risk of prevalent T2D was highest for ages 50–59 [OR = 1.49, CI (1.45,1.52)] and lowest for ages 70–79 [OR = 0.11, CI (0.10,0.12)].

Age, BMI, and the PGS were statistically significant and independent predictors of T2D prevalence in a multivariate logistic regression model described in the prior section comparing competing models (**Table 2**). The jointly estimated odds were as follows: decade of age [OR = 1.07, CI (1.06,1.07)], log-transformed standardized BMI [OR = 1.90, CI (1.84,1.96)], and the standardized PGS [OR = 1.54, CI (1.50,1.58)], all ps <0.0018.

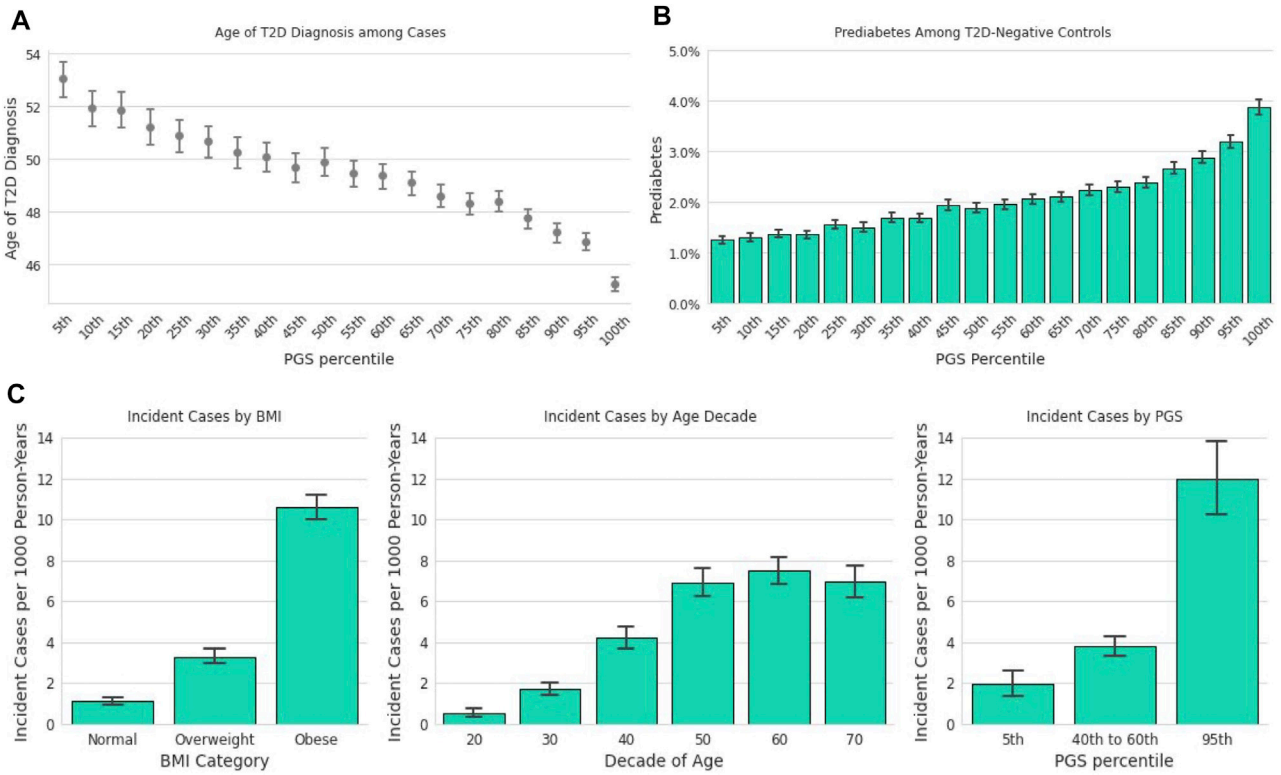

FIGURE 3 | The T2D PGS is associated with diagnosis and incidence. **(A)**: Mean age at T2D diagnosis (y-axis) is plotted against PGS ventiles (x-axis) among participants who self-reported their age at T2D diagnosis. **(B)**: Prevalence of prediabetes (y-axis) is plotted for T2D-negative participants against ventiles of the PGS. **(C)**: A one-year incidence ratio was calculated among participants who were T2D negative at an initial time point and filled out a 1-year follow-up survey. T2D incidence (y-axis) was found to increase with increasing BMI (x-axis, left panel), with age up to the 60s (x-axis, middle panel), and PGS percentile (x-axis, right panel).

3.3.2 Adding the Polygenic Score to Screening Guidelines

Another way to understand the utility of the application of specific screening guidelines is to estimate the sensitivity and specificity of those decision trees. We evaluated the application of USPSTF and ADA guidelines in our data with and without including the PGS in screening decisions. For these analyses, age of diagnosis was used for cases, and current age for controls. Hypothetical updated guidelines divide the PGS at those at or above the 90th percentile, versus those below.

The USPSTF criteria focus primarily on age and BMI. In our sample, the sensitivity of those criteria was 0.79, and the specificity was 0.58. To the USPSTF we added an additional criterion to screen individuals who are 35 or older, have normal BMI, but have a PGS at or greater than the 90th percentile. This resulted in an incremental increase in sensitivity (0.81) as well as a small decrease is specificity (0.56).

The ADA criteria include risk factors beyond the scope of this analysis (e.g., physical inactivity, history of cardiovascular disease, women with polycystic ovary syndrome, etc. (ADA, 2018). We chose to evaluate a simpler model that includes only age, BMI, and family history of T2D. Here, given the liberal criterion of screening all individuals 45 or older, the sensitivity was high (0.96) and the specificity was low (0.30). We added the additional criterion to screen adults (age 18 or older) with normal range BMI who have a PGS at or greater than the 90th percentile. This addition provided a small increase to sensitivity (0.97) and a slight decrease in specificity (0.28).

3.4 The Polygenic Score is Associated With Age of Diagnosis

Earlier age of disease onset has been correlated with genetic risk for various conditions (Seibert et al., 2018; Mars et al., 2020). We examined the relationship between the T2D PGS and self-reported T2D age of diagnosis (AOD) to assess how well the model predicts disease development timing. In the Descriptive Sample, individuals in the lowest ventile of the PGS reported a mean AOD of 53.0 years compared to 45.2 years for those in the highest ventile, a difference of 7.8 years (**Figure 3A**). Furthermore, the T2D PGS was a statistically significant predictor for T2D AOD in a linear regression model that included BMI and family history of T2D in a subset of Analytic Sample who were T2D-positive and reported age of diagnosis (N = 4,663). Each standard deviation increase in the PGS was associated with a 1.37-year decrease in AOD [CI (−1.60, −1.16), p <0.0018], a relationship similar to that of standardized log of BMI [β = −1.73, CI (−2.04, −1.43), p < 0.0018]. Positive

family history of T2D was not a significant predictor of AOD [β = −1.06, CI (−1.71, −0.41), p = 0.001, total model R2 = 0.07].

3.5 Prediabetes in Type 2 Diabetes-Negative Individuals

We hypothesized that the PGS model could also be used to predict the risk of prediabetes among those who were T2D-negative. Stratified by the T2D PGS, the prevalence of prediabetes in the highest PGS ventile in the Descriptive Sample was over 3-times the prevalence in the lowest PGS ventile, 1.3 vs. 3.9%, respectively (**Figure 3B**). We evaluated a logistic regression model of prediabetes diagnosis using age, BMI, T2D family history, and the T2D PGS as predictors among T2D-negative individuals in the Analytic Sample (n = 107,923). Each standard deviation increase of the PGS was associated with a 23% increase in the odds of prediabetes diagnosis [OR = 1.23, CI (1.19, 1.26), p <0.0018]. Prediabetes was also strongly associated with standardized log of BMI, [OR = 1.60, CI (1.55, 1.65), p < 0.0018] and family history of T2D, [OR = 2.03, CI (1.89,2.18), p < 0.0018], but not with female sex [OR = 1.05, CI (0.97,1.13), p = 0.2].

3.6 Incident Cases

In the subset of data with responses to annual follow-up surveys (**Figure 1**; Incident Diagnosis Sample), the mean time difference between the baseline response and the follow-up response was 446 days (SD = 102 days). The overall one-year incidence proportion, 4.86 per 1,000 person-years, is lower than but comparable to the 6.9 per 1,000 person-years statistic reported by the CDC for 2018 (Centers for Disease Control and Prevention, 2020). The incidence in the 23andMe database increased with decade of age, BMI, and PGS (**Figure 3C**). Stratified by PGS, the one-year incidence of T2D in the highest genetic risk ventile was over six times that of individuals in the lowest ventile (1.97 vs. 11.97 cases per 1,000), and roughly three times of individuals in the 40th-60th percentile (3.80 vs. 11.97 cases per 1,000). This rate of incidence among those with the greatest genetic risk was higher than those with obese BMI (10.64 cases per 1,000 person-years).

We evaluated a logistic regression model with incident case status as the outcome and age, standardized log BMI, T2D family history, and the PGS as predictors. The PGS proved to be a statistically significant predictor, where each standard deviation increase in PGS corresponded to a 43% increase in the odds of T2D incidence [OR = 1.43, CI (1.33,1.53), p < 0.0018], which was about half the incident risk associated with family history [OR = 3.02, CI (2.41,3.78), p < 0.0018], but was comparable to BMI [OR = 1.82, CI (1.67,1.99), p < 0.0018].

3.7 The Polygenic Score Informs Disease Progression

We hypothesized that genetic risk for developing T2D as determined by the T2D PRS would also be associated with the risk of a more severe disease phenotype, as measured by the escalation of treatment strategy and by the rate of the development of T2D microvascular complications in a cohort of T2D-positive individuals in the Analytic Sample (**Figure 1**). We found that individuals with higher PGS values were more likely to be prescribed insulin (**Figure 4A**). We evaluated logistic regression models with the PGS, age, sex, and BMI to predict prevalence of prescribed treatment. Each standard deviation increase in the PGS was associated with 14% higher odds of being prescribed insulin [OR = 1.14, CI (1.09,1.19), p < 0.0018]. The PGS was not a statistically significant predictor of metformin treatment [OR = 1.05, CI (0.99,1.11), p = 0.09], or following only lifestyle modifications [OR = 0.89, CI (0.82,0.96), p = 0.004], Family history was significantly associated with metformin treatment [OR = 1.33, CI (1.14,1.55), p < 0.0018], but not insulin [OR = 1.21, CI (1.03,1.36), p = 0.02] or only lifestyle modifications [OR = 1.22, CI (1.00,1.48), p = 0.11].

We next assessed the utility of the PGS for predicting the rate of development of diabetes microvascular complications (**Figure 4B**). For this analysis, both current reported age and years since initial T2D diagnosis were entered into the logistic model in addition to the PGS, age, BMI, and sex. Each standard deviation increase in the PGS was associated with 10% higher odds of diabetic neuropathy [OR = 1.10, CI (1.04,1.16), p < 0.0018]. However, the PGS was not significantly associated with higher odds of diabetic nephropathy [OR = 1.05, CI (0.96,1.16), p = 0.25] or with diabetic retinopathy [OR = 1.07, CI (0.98,1.18), p = 0.12]. Family history was not associated with any of these three outcomes. Together, these data show the T2D PGS is associated with some but not all forms of disease severity as measured by prescribed treatment and prevalence of complications over time.

3.8 Polygenic Score Associations are Transferable to Hispanic/Latino Individuals

We hypothesized that the findings showing the relevance of the T2D PGS would replicate in other ethnicities. We were able to repeat many, but not all, of the specific analyses in the self-reported 23andMe Hispanic/Latino cohort (N = 156,410, see Methods and Materials and **Figure 1** for participant recruitment flowchart).

Among those who were T2D-negative at the time of the survey, family history of T2D was more common among those with higher genetic risk as indexed by the PGS than lower (**Figure 5A**; data for T2D-positive cases not shown due to smaller sample size and privacy requirements). As in the European-descent sample, family history was associated but not redundant with the PGS in a logistic model [OR = 1.42, CI (1.35,1.49), p <0.0018]. We examined the PGS performance as a predictor of T2D while controlling for T2D family history. This analysis showed the PGS to be a statistically significant predictor of T2D that provides unique information in a model containing age, BMI, family history, and the PGS [OR = 1.51, CI (1.37,1.67), p <0.0018; **Table 3**]. As in the sample of European descent, the model containing both the PGS and family history had the highest AUC in the Hispanic/Latino test set [AUC = 0.87, CI (0.85,0.91)].

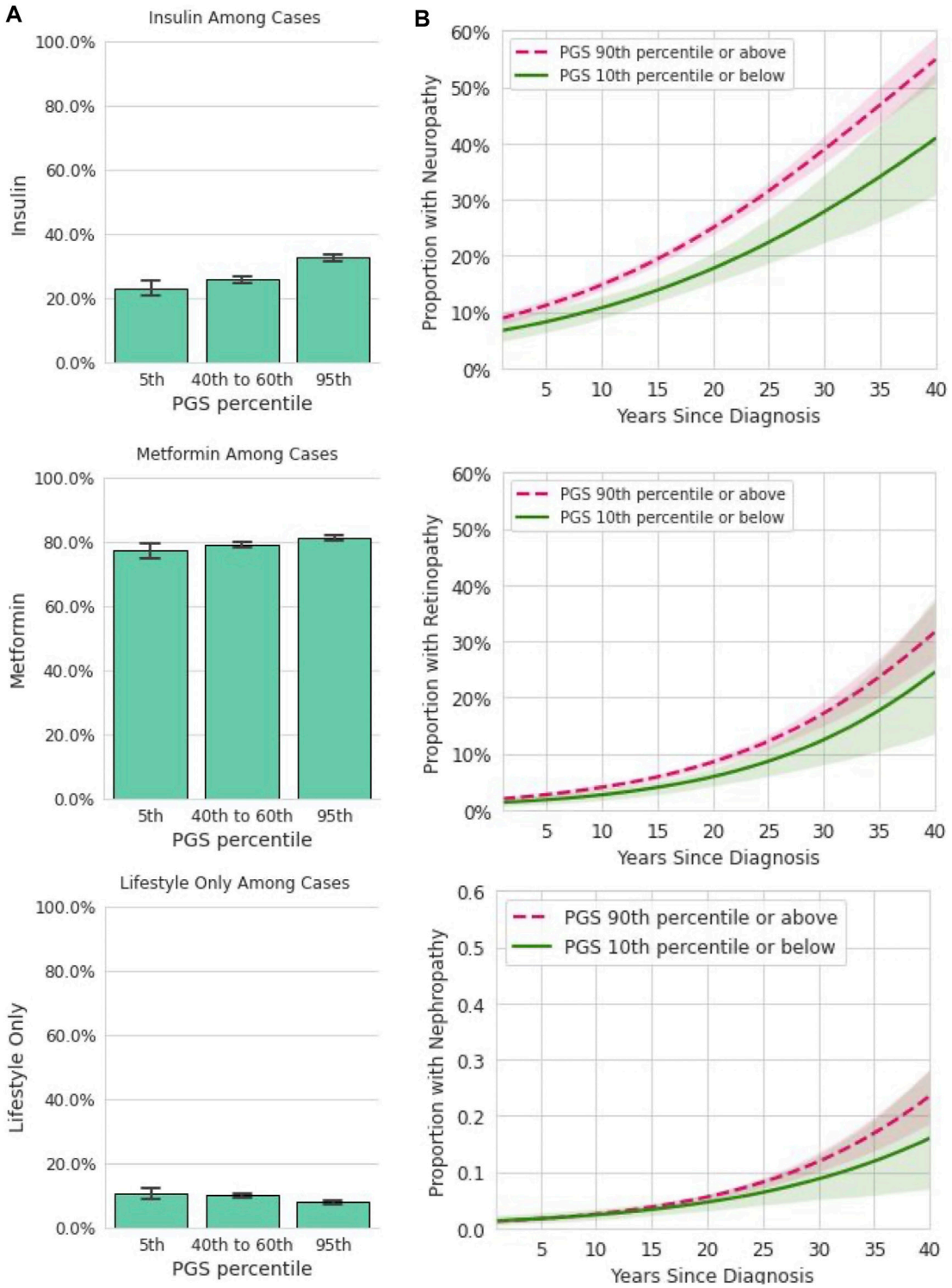

FIGURE 4 | Among participants with T2D, the PGS is associated with some forms of treatment and disease complications. **(A)**: In a dataset restricted to participants who reported a T2D diagnosis and provided information on prescribed treatments, insulin, metformin, and lifestyle only are plotted (y-axis) for participants in the 5th, 40–60th, and 95th percentiles of the PGS (x-axis). Error bars represent empirically derived 95% confidence intervals. Insulin prescriptions were significantly associated with the PGS in multivariate models controlling for age, sex, BMI, and family history of T2D. **(B)**: Data shown are the relationship between years since T2D diagnosis and microvascular complications, stratified by PGS percentile in a logistic model. Shaded areas represent 95% confidence intervals. Neuropathy was significantly associated with the PGS in multivariate models controlling for age, sex, BMI, and family history of T2D.

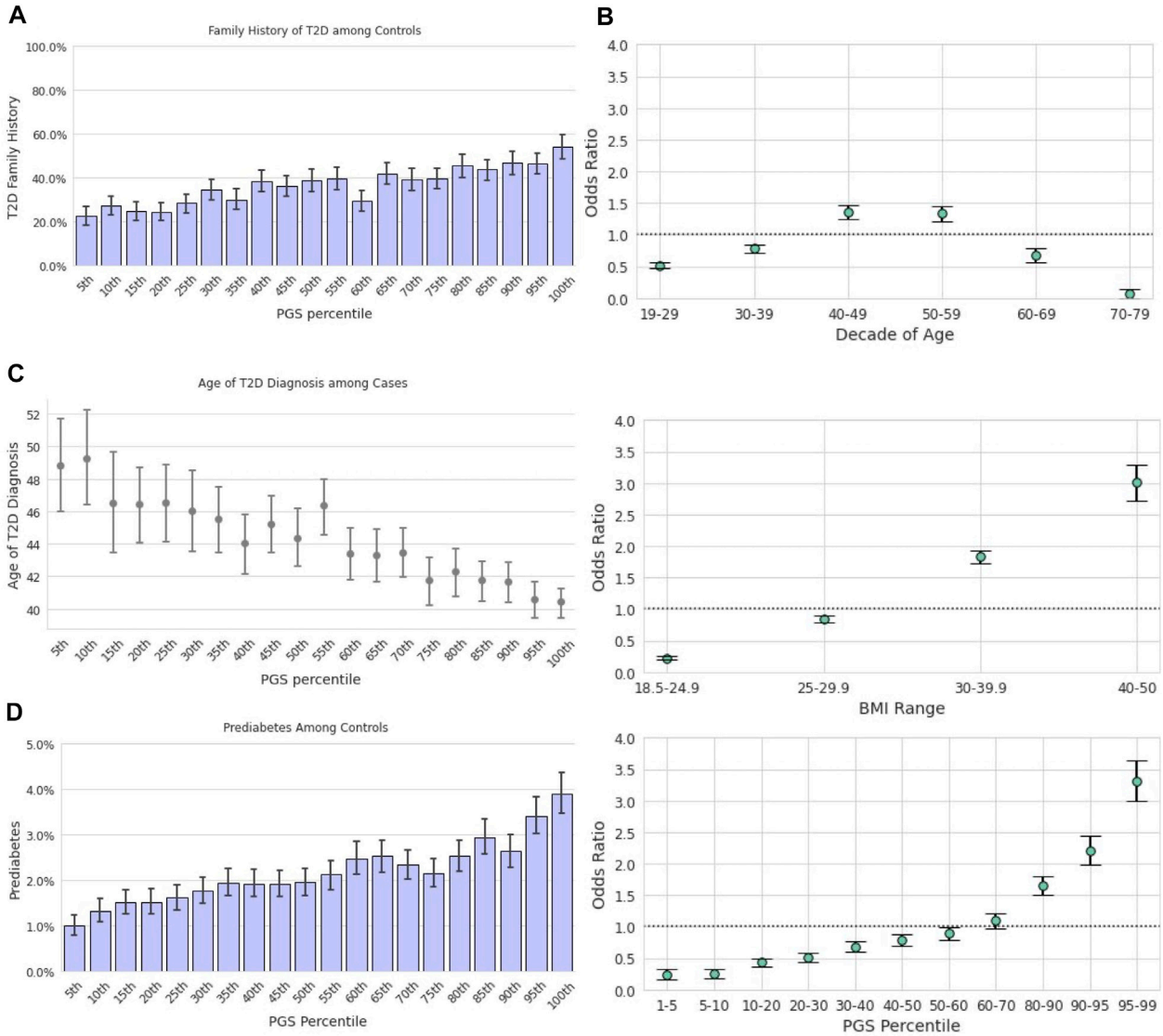

FIGURE 5 | Repeated analysis in the Hispanic/Latino sample. **(A)**: The prevalence of family history of T2D among T2D-negative participants. Data among T2D-positive participants are not provided due to privacy practices. **(B)**: Odds ratios (y-axis) of having T2D relative to the Hispanic/Latino study population were calculated for each decade of age, BMI category, and Latino-specific PGS percentile. Error bars represent analytically computed 95% confidence intervals. **(C)**: Mean age at T2D diagnosis among cases (y-axis) is plotted against Hispanic/Latino-specific PGS ventiles (x-axis) among participants who self-reported their age at T2D diagnosis. Error bars represent empirically derived 95% confidence intervals. **(D)**: The prevalence of prediabetes among T2D-negative participants was significantly associated with the PGS, as shown with increasing ventiles of the PGS distribution. Data among T2D-positive participants are not provided due to privacy practices.

We also examined the PGS's ability to stratify Hispanic/Latino individuals by an unadjusted odds ratio of having T2D as compared to age and BMI (**Figure 5B**). Similar trends were observed as reported in the European cohort; the range of risk associated with the PGS, OR = 0.24 [CI (0.18,0.33)] at the 1st-5th percentile to OR = 3.32 [CI (3.02,3.64)] at the 95th-99th percentile, was comparable to the range associated with BMI, OR = 0.23 [CI (0.20,0.25)] at BMI 18.5 to 24.9 to OR = 3.01 [CI (2.75,3.29)] at BMI 40–50. Risk of prevalent T2D was highest for ages 40–49 [OR = 1.36, CI (1.26,1.47)] and lowest for ages 70–79 [OR = 0.07, CI (0.04,0.14)].

Addition of a hypothetical screening criterion at the 90th percentile of the PGS (as described in **Section 3.3.2**) to both the USPSTF and ADA criteria slightly increased sensitivity and reduced sensitivity. Our estimation of the sensitivity of USPSTF increased from 0.69 to 0.70 and reduced the specificity from 0.61 to 0.60. The addition to the simplified ADA criteria increased the sensitivity from 0.93 to 0.95, and decreased the specificity from 0.43 to 0.40.

We observed a correlation between increasing PGS and younger age of T2D diagnosis in the Hispanic/Latino cohort **Figure 5C**). Mean AOD ranged from 48.8 to 40.4 years from lowest to highest PGS ventile, a difference of 8.4 years. However, this relationship was not statistically significant [$\beta = -0.61$, CI

TABLE 3 | Logistic regression between prevalent T2D, family history, and the PGS in the Hispanic/Latino replication sample.

Model	Base model	Family history only	Polygenic score only	Combined model
Intercept	–5.82	–6.58	–6.15	–6.83
Family History	-	1.72	-	1.58
Standardized Polygenic Score	-	-	0.48	0.42
Female Sex	–0.46	–0.55	–0.48	–0.55
Decade of Age	0.06	0.05	0.06	0.05
Standardized Log Body Mass Index	0.74	0.69	0.70	0.67
Cox-Snell's Pseudo R2	0.14	0.20	0.18	0.23
Test Set AUC (95% CIs)	0.83 (0.80, 0.87)	0.86 (0.83, 0.90)	0.86 (0.82, 0.90)	0.88 (0.85, 0.91)

All coefficients derived from logistic regression were significant p *<0.0018 in all models. N = 5,712 for all models. The model that included both family history and the PGS, was the most predictive in terms of pseudo R2 and out-of-sample AUC.*

(−1.62,0.40), $p = 0.24$] in a linear model trained to predict AOD from BMI, family history of T2D, and genetics in a small subset of the Hispanic/Latino cohort with complete data (N = 248).

Prediabetes in Hispanic/Latino T2D-negative participants was nearly four times more prevalent in those in the highest PGS ventile (3.9%) compared to the lowest ventile (1.0%; **Figure 5D**). We evaluated a logistic regression model of prediabetes diagnosis among T2D-negative individuals using age, BMI, T2D family history, and the T2D PGS as predictors. One standard deviation in the PGS was associated with a 36% increase in the odds of prediabetes among those without T2D [OR = 1.36, CI (1.22,1.51), p <0.0018], which was comparable to that of standardized log-BMI [OR = 1.64, CI (1.46,1.86), p <0.0018] and family history of T2D [OR = 1.60, CI (1.22,2.11), $p < 0.0018$].

Insufficient data were available in the Hispanic/Latino cohort to evaluate the association between the T2D PGS and incident diagnosis, treatment prevalences, or microvascular disease complications.

4 DISCUSSION

Type 2 diabetes is a disease of metabolic dysregulation that begins years before symptoms are evident and complications arise. An estimated 1 in 3 American adults have prediabetes and 5–10% of these individuals will receive a T2D diagnosis within one year (Tabák et al., 2012). Lifestyle can be extremely successful in reversing the course of the disease, mostly when initiated early (Glechner et al., 2018). Thus, there is potential for polygenic scores to identify additional people who may be overlooked by traditional screening methods and who could benefit from earlier lifestyle modifications and medical intervention. Although the real-world impact of incorporating a T2D PGS in clinical practice remains to be thoroughly studied, we demonstrate its utility in identifying individuals with increased risk for prediabetes among the T2D-negative population. Furthermore, the PGS is also highly correlated with earlier age of T2D onset and can be used to predict incident T2D cases from a population of susceptible individuals. We also found the risk profile conferred by increasing PGS to be comparable to risk associated with increasing age and BMI. Taken together, these findings argue strongly for including a T2D PGS in a clinical assessment of T2D risk and prophylactic decision-making if available.

4.1 Incorporating Genetic Risk Into Screening Tools

Studies are beginning to hint at the clinical utility of PGS. Still, the combination of FH and PGS as a more robust method of predicting the individual likelihood of developing a complex disease has yet to be fully explored. Clinicians recognize that at-risk individuals may be missed when relying on FH alone for disease prediction and that gathering a FH is time-consuming and often neglected. Furthermore, not all individuals have knowledge of family history. A clinical tool encompassing FH and PGS may improve disease prediction.

Previous publications have employed several methods to assess whether polygenic scores add predictive utility when used jointly with family history, including examining predictive model performance (Sun et al., 2013; Helfand, 2016; Hughes et al., 2021) and determining whether risk estimates for PGS remained significant after adjustment for family history (Tada et al., 2016). In the present study, we observed an increasing relationship between both T2D genetic risk and positive family history among European-descent and Hispanic/Latino-descent T2D-negative individuals. We also found, however, that family history is associated with but not equivalent to genetic risk. Factors other than genetics, such as common environment, may also contribute to the risk conferred by family history, and polygenic inheritance results in more generational variability than monogenic patterns (i.e., Mendelian inheritance). Ultimately, a model including both family history and the PGS proved better at predicting T2D than each factor separately in terms of pseudo R2, out-of-sample AUC, and sensitivity when added to both USPSTF and ADA guidelines in both the European-descent and Hispanic/Latino cohorts. These results indicate that information captured in the PGS is not completely redundant with family history, and that disease risk is most comprehensively assessed when genetic analysis is combined with standard clinical risk factors.

Screening for prediabetes and T2D is often based on a set of guidelines that determine eligibility based on well-documented risk factors such as age, BMI, positive family history, membership in a high-risk race or ethnic group, and environmental or behavioral factors (Pippitt et al., 2016). In the present study, we have demonstrated the validity of the T2D PGS as a risk factor that contributes information over and above family history.

Addition of the PGS to the USPSTF screening guidelines incrementally improved sensitivity, with a corresponding small decrease in specificity. We note that ADA guidelines, however, have very high sensitivity with or without the PGS.

Optimization of the sensitivity and specificity of these guidelines within medical systems could include the PGS as a risk factor, considering that it does provide some information that is independent of family history. It is beyond the scope of the present study, but medical economic analysis could find that screening younger people who may not have traditional risk factors but do have a higher PGS, and perhaps delaying screening for older people with no risk factors and a low PGS could balance sensitivity, specificity, and screening costs. This optimization is even more plausible as costs for genome-wide genotyping continue to decrease. Indeed, a single genomic assay could be used for multiple purposes beyond T2D screening throughout a person's life.

4.2 Genetic Risk and Disease Severity

In addition to identifying more cases of T2D, several studies have suggested that genetic screening could be useful for predicting disease severity (Paul et al., 2018; Oetjens et al., 2019; Chen et al., 2020). T2D impacts individuals differently; some experience mild symptoms, controlled relatively easily by lifestyle intervention and minimal therapeutic intervention, while others experience severe complications and have a difficult time with disease management. Many patients progress from nonmedical, lifestyle-only treatment to medications like metformin, and some require insulin as their condition shifts from impaired glucose tolerance to insulin insufficiency. T2D severity is also closely associated with diabetic microvascular complications, the most common of which are diabetic retinopathy, nephropathy, and neuropathy.

In the present study, we found the T2D PGS to correlate with treatment options where those at higher PGS were more likely to be treated with insulin. Metformin treatment or lifestyle-only interventions were not significantly associated with the PGS. Yet for complications of T2D, the PGS was markedly related to the rate of neuropathy diagnosis, but not to nephropathy and retinopathy. Further work may identify sub-scales within a T2D PGS that associate with specific biological pathways or systems, illuminating specific causes of genetic risk and complications (Udler et al., 2018; Tremblay et al., 2021). Together, these findings are only an initial indication that the T2D PGS may be indicative of specific forms of disease progress, but further studies are needed to explore this thoroughly.

4.3 Assessing Genetic Risk in People of all Ancestral Backgrounds

Type 2 diabetes is on the rise across the world and in the United States its burden is disproportionately felt by Black/African Americans and Hispanic/Latino individuals (Centers for Disease Control and Prevention, 2020). Thus, the clinical utility of the T2D PGS is especially relevant for non-European individuals. Taken in the context of the massive Euro-centric bias in the field of polygenic risk prediction (Martin et al., 2019), we considered it important to evaluate the application of the PGS in a non-European population with a sufficient sample size for most of this analysis. It is critical that individuals from all backgrounds be provided the opportunity to participate in genomic research, and that all efforts are made to assess and calibrate PGS in diverse samples.

We selected the 23andMe Hispanic/Latino cohort because this T2D PGS has roughly comparable performance in this group as in European-descent individuals, as evidenced by the AUROC (0.656 in European-descent and 0.635 in Hispanic/Latino-descent individuals) and other risk stratification statistics, and because we had sufficient family history data in this cohort for a sufficiently powered study. Our analyses show that, as in the European cohort, the PGS provides valuable information for identifying at-risk Hispanic/Latino individuals, on par with risk factors already used for clinical decision-making. These findings serve as an important proof of principle for the application of polygenic prediction to assessing risk in underserved populations. 23andMe's efforts to recruit a more diverse pool of study participants (23andMe, 2019) will enable additional follow-up studies with population-specific versions of the T2D PGS in order to deliver better value to our customers and provide more accurate tools for clinicians and their patients.

4.4 Limitations and Conclusions

The present study has several limitations that should be considered when interpreting the results. All phenotypes were obtained through participant self-report, although 23andMe's previous work has shown the accuracy and robustness of this form of data collection at scale (Eriksson et al., 2010; Tung et al., 2011). We expect the additional granularity into treatments, disease complications, and biomarker/fasting glucose data obtained through clinical health records would likely improve the ability of the PGS to predict these phenotypes in T2D-positive individuals, as well as more precision in the definition of a participant with "prediabetes." Missing data across survey instruments resulted in smaller subsamples used for regression modeling compared to the larger sample with T2D diagnostic and demographic information. Models assumed linear relationships between the outcomes and age or BMI, whereas non-linear relationships may better explain the data. Additionally, due to limited family history and incident data, we were unable to expand our analyses beyond those of European and Hispanic/Latino descent.

Typically, PGS (including this one) do not include rare variants with large effects, which, if present, would contribute far more risk than the polygenic background of common variants; nonetheless, being rare, most people do not carry these variants, and a PGS based on common variants would be relevant for most of the population. To maintain the scope of the present study, our evaluation of the sensitivity and specificity of the ADA guidelines did not include all risk factors included in the guidelines, and we did not attempt optimization of screening decision thresholds, including economic analyses. The analysis of microvascular complications of diabetes did not account for individual differences in treatment history, which would also affect the rate of development of these complications. We did not have data representing the age of onset of these complications, precluding survival analysis.

In this paper we present the possible clinical relevance of a T2D PGS as a predictor of disease risk and severity that provides some information that is independent of family history. Given this, the PGS could be considered as an additional risk factor in screening guidelines and could be used to help inform clinical decision making. The replication of many findings in a Hispanic/Latino cohort indicates the transferability across other populations when datasets of sufficient size exist and PGS with sufficient performance can be developed.

DATA AVAILABILITY STATEMENT

Individual-level data from this study are not publicly available per the IRB-approved study protocol.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical & Independent Review Services. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JA, BK, RK and OSa: Study design, analysis and manuscript writing. SA, PF, RK and SS: Study design, analysis assistance. LB and MM: Study design, data collection. OSv, SD and JP: Manuscript writing, study design.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.871260/full#supplementary-material

REFERENCES

23andMe (2019). 23andMe's Populations Collaborations Program Supports Research in Understudied Groups. 23andMe Blog. Available at: https://blog.23andme.com/23andme-research/23andmes-population-collaboration-program-supports-research-in-understudied-groups/(Accessed July 24, 2020).

Almgren, P., Lehtovirta, M., Lehtovirta, M., Isomaa, B., Sarelin, L., Taskinen, M. R., et al. (2011). Heritability and Familiality of Type 2 Diabetes and Related Quantitative Traits in the Botnia Study. *Diabetologia* 54, 2811–2819. doi:10.1007/s00125-011-2267-5

American Diabetes Association (2018). 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 41, S13–S27. doi:10.2337/dc18-S002

Ashenhurst, J. R., Zhan, J., Multhaup, M. L., Kita, R., Sazonova, O. V., Krock, B., et al. (2020). A Generalized Method for the Creation and Evaluation of Polygenic Scores. 23andMe, Inc. Available at: https://permalinks.23andme.com/pdf/23_21-PRSMethodology_May2020.pdf (Accessed January 3, 2022).

Boyle, J. P., Thompson, T. J., Gregg, E. W., Barker, L. E., and Williamson, D. F. (2010). Projection of the Year 2050 burden of Diabetes in the US Adult Population: Dynamic Modeling of Incidence, Mortality, and Prediabetes Prevalence. *Popul. Health Metrics* 8, 29. doi:10.1186/1478-7954-8-29

Centers for Disease Control and Prevention (2020). National Diabetes Statistics Report. Atlanta (GA): U.S. Dept of Health and Human Services. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf.

Chen, L., Wang, Y.-F., Liu, L., Bielowka, A., Ahmed, R., Zhang, H., et al. (2020). Genome-wide Assessment of Genetic Risk for Systemic Lupus Erythematosus and Disease Severity. *Hum. Mol. Genet.* 29, 1745–1756. doi:10.1093/hmg/ddaa030

Eriksson, N., Macpherson, J. M., Tung, J. Y., Hon, L. S., Naughton, B., Saxonov, S., et al. (2010). Web-based, Participant-Driven Studies Yield Novel Genetic Associations for Common Traits. *Plos Genet.* 6, e1000993. doi:10.1371/journal.pgen.1000993

Florez, J. C., Udler, M. S., and Hanson, R. L. (2018). "Genetics of Type 2 Diabetes," in *Diabetes in America*. Editors C. C. Cowie, S. S. Casagrande, A. Menke, M. A. Cissell, M. S. Eberhardt, J. B. Meigs, et al. (Bethesda (MD)(US): National Institute of Diabetes and Digestive and Kidney Diseases). Available at: http://www.ncbi.nlm.nih.gov/books/NBK567998/(Accessed January 28, 2022).

Glechner, A., Keuchel, L., Affengruber, L., Titscher, V., Sommer, I., Matyas, N., et al. (2018). Effects of Lifestyle Changes on Adults with Prediabetes: A

Systematic Review and Meta-Analysis. *Prim. Care Diabetes* 12, 393–408. doi:10.1016/j.pcd.2018.07.003

Helfand, B. (2016). A Comparison of Genetic Risk Score with Family History for Estimating Prostate Cancer Risk. *Asian J. Androl.* 18, 515–519. doi:10.4103/1008-682X.177122

Hughes, E., Tshiaba, P., Wagner, S., Judkins, T., Rosenthal, E., Roa, B., et al. (2021). Integrating Clinical and Polygenic Factors to Predict Breast Cancer Risk in Women Undergoing Genetic Testing. *JCO Precision Oncol.* 5, PO.20.00246. doi:10.1200/PO.20.00246

Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., et al. (2018). Genome-wide Polygenic Scores for Common Diseases Identify Individuals with Risk Equivalent to Monogenic Mutations. *Nat. Genet.* 50, 1219–1224. doi:10.1038/s41588-018-0183-z

Lambert, S. A., Gil, L., Jupp, S., Ritchie, S. C., Xu, Y., Buniello, A., et al. (2021). The Polygenic Score Catalog as an Open Database for Reproducibility and Systematic Evaluation. *Nat. Genet.* 53, 420–425. doi:10.1038/s41588-021-00783-5

Mars, N., Koskela, J. T., Ripatti, P., Kiiskinen, T. T. J., Havulinna, A. S., et al. (2020). Polygenic and Clinical Risk Scores and Their Impact on Age at Onset and Prediction of Cardiometabolic Diseases and Common Cancers. *Nat. Med.* 26, 549–557. doi:10.1038/s41591-020-0800-0

Martin, A. R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B. M., and Daly, M. J. (2019). Clinical Use of Current Polygenic Risk Scores May Exacerbate Health Disparities. *Nat. Genet.* 51, 584–591. doi:10.1038/s41588-019-0379-x

Nakka, P., Pattillo Smith, S., O'Donnell-Luria, A. H., McManus, K. F., Mountain, J. L., Ramachandran, S., et al. (2019). Characterization of Prevalence and Health Consequences of Uniparental Disomy in Four Million Individuals from the General Population. *Am. J. Hum. Genet.* 105, 921–932. doi:10.1016/j.ajhg.2019.09.016

Oetjens, M. T., Kelly, M. A., Sturm, A. C., Martin, C. L., and Ledbetter, D. H. (2019). Quantifying the Polygenic Contribution to Variable Expressivity in Eleven Rare Genetic Disorders. *Nat. Commun.* 10, 4897. doi:10.1038/s41467-019-12869-0

Padilla-Martínez, F., Collin, F., Kwasniewski, M., and Kretowski, A. (2020). Systematic Review of Polygenic Risk Scores for Type 1 and Type 2 Diabetes. *Ijms* 21, 1703. doi:10.3390/ijms21051703

Paul, K. C., Schulz, J., Bronstein, J. M., Lill, C. M., and Ritz, B. R. (2018). Association of Polygenic Risk Score with Cognitive Decline and Motor Progression in Parkinson Disease. *JAMA Neurol.* 75, 360. doi:10.1001/jamaneurol.2017.4206

Pippitt, K., Li, M., and Gurgle, H. E. (2016). Diabetes Mellitus: Screening and Diagnosis. *Am. Fam. Physician* 93, 103–109.

Reisberg, S., Iljasenko, T., Läll, K., Fischer, K., and Vilo, J. (2017). Comparing Distributions of Polygenic Risk Scores of Type 2 Diabetes and Coronary Heart Disease within Different Populations. *PloS one* 12, e0179238. doi:10.1371/journal.pone.0179238

Samuels, T. A., Cohen, D., Brancati, F. L., Coresh, J., and Kao, W. H. (2006). Delayed Diagnosis of Incident Type 2 Diabetes Mellitus in the ARIC Study. *Am. J. Manag. Care* 12, 717–724.

Seabold, S., and Perktold, J. (2010). "Statsmodels: Economic and Statistical Modeling with python," in Proceedings of the 9th Python in Science Conference, Austin, Texas, June 28 to July 3, 2010.

Seibert, T. M., Fan, C. C., Wang, Y., Zuber, V., Karunamuni, R., Parsons, J. K., et al. (2018). Polygenic hazard Score to Guide Screening for Aggressive Prostate Cancer: Development and Validation in Large Scale Cohorts. *BMJ* 360, j5757. doi:10.1136/bmj.j5757

Sun, J., Na, R., Hsu, F.-C., Zheng, S. L., Wiklund, F., Condreay, L. D., et al. (2013). Genetic Score Is an Objective and Better Measurement of Inherited Risk of Prostate Cancer Than Family History. *Eur. Urol.* 63, 585–587. doi:10.1016/j.eururo.2012.11.047

Tabák, A. G., Herder, C., Rathmann, W., Brunner, E. J., and Kivimäki, M. (2012). Prediabetes: a High-Risk State for Diabetes Development. *Lancet* 379, 2279–2290. doi:10.1016/S0140-6736(12)60283-9

Tada, H., Melander, O., Louie, J. Z., Catanese, J. J., Rowland, C. M., Devlin, J. J., et al. (2016). Risk Prediction by Genetic Risk Scores for Coronary Heart Disease Is Independent of Self-Reported Family History. *Eur. Heart J.* 37, 561–567. doi:10.1093/eurheartj/ehv462

Tremblay, J., Haloui, M., Attaoua, R., Tahir, R., Hishmih, C., Harvey, F., et al. (2021). Polygenic Risk Scores Predict Diabetes Complications and Their Response to Intensive Blood Pressure and Glucose Control. *Diabetologia* 64, 2012–2025. doi:10.1007/s00125-021-05491-7

Tung, J. Y., Do, C. B., Hinds, D. A., Kiefer, A. K., Macpherson, J. M., Chowdry, A. B., et al. (2011). Efficient Replication of over 180 Genetic Associations with Self-Reported Medical Data. *PLoS ONE* 6, e23473. doi:10.1371/journal.pone.0023473

Udler, M. S., Kim, J., von Grotthuss, M., Bonàs-Guarch, S., Cole, J. B., Chiou, J., et al. (2018). Type 2 Diabetes Genetic Loci Informed by Multi-Trait Associations point to Disease Mechanisms and Subtypes: A Soft Clustering Analysis. *Plos Med.* 15, e1002654. doi:10.1371/journal.pmed.1002654

USPSTF (2021). Prediabetes and Type 2 Diabetes: Screening. US Preventive Service Task Force. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/screening-for-prediabetes-and-type-2-diabetes (Accessed January 4, 2022).

Xue, A., Wu, Y., Wu, Y., Zhu, Z., Zhang, F., Kemper, K. E., et al. (2018). Genome-wide Association Analyses Identify 143 Risk Variants and Putative Regulatory Mechanisms for Type 2 Diabetes. *Nat. Commun.* 9, 2941. doi:10.1038/s41467-018-04951-w

Zheng, Y., Ley, S. H., and Hu, F. B. (2018). Global Aetiology and Epidemiology of Type 2 Diabetes Mellitus and its Complications. *Nat. Rev. Endocrinol.* 14, 88–98. doi:10.1038/nrendo.2017.151

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Incomplete Penetrance of Population-Based Genetic Screening Results in Electronic Health Record

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The clinical value of population-based genetic screening projects depends on the actions taken on the findings. The Healthy Nevada Project (HNP) is an all-comer genetic screening and research project based in northern Nevada. HNP participants with CDC Tier 1 findings of hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome (LS), or familial hypercholesterolemia (FH) are notified and provided with genetic counseling. However, the HNP subsequently takes a "hands-off" approach: it is the responsibility of notified participants to share their findings with their healthcare providers, and providers are expected to implement the recommended action plans. Thus, the HNP presents an opportunity to evaluate the efficiency of participant and provider responses to notification of important genetic findings, using electronic health records (EHRs) at Renown Health (a large regional hospital in northern Nevada). Out of 520 HNP participants with findings, we identified 250 participants who were notified of their findings and who had an EHR. 107 of these participants responded to a survey, with 76 (71%) indicating that they had shared their findings with their healthcare providers. However, a sufficiently specific genetic diagnosis appeared in the EHRs and problem lists of only 22 and 10%, respectively, of participants without prior knowledge. Furthermore, review of participant EHRs provided evidence of possible relevant changes in clinical care for only a handful of participants. Up to 19% of participants would have benefited from earlier screening due to prior presentation of their condition. These results suggest that continuous support for both participants and their providers is necessary to maximize the benefit of population-based genetic screening. We recommend that genetic screening projects require participants' consent to directly document their genetic findings in their EHRs. Additionally, we recommend that they provide healthcare providers with ongoing training regarding documentation of findings and with clinical decision support regarding subsequent care.

Keywords: CDC Tier 1, HBOC, BRCA, EHR, Lynch, familial hypercholesterolemia, genetic screening, population health

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INTRODUCTION

Population-based genetic screening (PbGS) can be a valuable risk assessment tool for relatively common genetic conditions with high penetrance such as hereditary breast and ovarian cancer (HBOC), Lynch syndrome (LS) and familial hypercholesterolemia (FH) (Tafe, 2015; Lambert et al., 2019; Evans et al., 2020; Manchanda et al., 2020; Patel et al., 2020; Ficarazzi et al., 2021). Many

individuals at-risk for these conditions are not identified by current medical practices (Manickam et al., 2018; Grzymski et al., 2020; Murray et al., 2020; Patel et al., 2020) and their family members may benefit from cascade genetic screening (George et al., 2015; Patel et al., 2020). However, screening the general population can only be effective if genetic findings are successfully disseminated to project participants and if a significant portion of the screened individuals follow recommended actions. However, this may not necessarily be the case as it has been shown that the uptake of genetic testing and their results may be sub-optimal and that primary care providers are still not comfortable with genetic testing (Press et al., 2000; Binetti et al., 2006; Finlay et al., 2008; George et al., 2015; Godino et al., 2016; Bijlsma et al., 2018; Menko et al., 2019; Actkins et al., 2021; David et al., 2021).

Not all PbGS projects are alike, and their underlying design may affect the dissemination and uptake of the genetic findings. The Healthy Nevada Project (HNP) (Grzymski et al., 2020; Read et al., 2021) is an all-comer health determinants PbGS research project based in northern Nevada. The second phase of the HNP provides clinical exome sequencing (Helix, 2017) for all participants, of which there are currently 45,000 (roughly 5 percent of the regional population). HNP participants are asked for three levels of consent: consent to 1) provide a saliva sample, 2) receive notification of positive findings and genetic consultation and 3) participate in further research. Only the first consent is required to participate in the HNP. As previously described (Grzymski et al., 2020), more than 99 percent of participants consented to receive notification of positive findings and consultations by licensed genetic counselors (LGCs) for three CDC Tier 1 conditions (Centers for Disease Control and Prevention, 2021; Miller et al., 2021) (T1pos) with a potential for individual and population health benefit: HBOC, LS and FH. LGCs attempt to contact each T1pos participant up to six times based on the preferred contact method(s) provided at the time of consent. Once T1pos participants have been successfully contacted, the LGCs explain the significance of each participant's finding and outline what the participant should do next. Next steps include obtaining confirmatory testing, notifying the participant's primary care physician (PCP) of the findings, and formulating an appropriate action plan with their PCP. Other than direct contact with the LGCs, no alternative notification methods were employed, and for the results presented in this study, the HNP did not directly update the participant's electronic health record (EHR) with their genetic findings and results were not directly accessible to physicians or other healthcare personnel. The HNP does not notify participants regarding absence of findings. While sequencing was performed by a CLIA-certified lab, interpretations were performed by HNP personnel (Grzymski et al., 2020) during the initial phase of the HNP. Therefore, confirmatory testing was required as part of the project protocol. Later, interpretations were provided by a CLIA-certified lab, but the requirement for confirmatory testing remained as part of the protocol.

The HNP is supported by Renown Health[1] (Renown), the largest healthcare provider in northern Nevada. Since Renown provides nearly 70 percent of the inpatient care and about 50 percent of primary care in the region, its EHR offers an opportunity to examine the effect of returning actionable genetic findings on the diagnoses recorded and the clinical actions subsequently taken by the participants and their healthcare providers.

We report here the effect of returning genetic findings on diagnoses and clinical actions recorded in the Renown EHR for HBOC, LS and FH T1pos participants in the HNP.

METHODS

For details of the HNP and definitions of pathogenic and likely pathogenic T1pos findings please see (Grzymski et al., 2020).

We conducted a comprehensive electronic review of extracted data from T1pos participants' Renown's EHRs (including clinical notes). We also reviewed responses from a survey sent to all T1pos consenting participants regarding delivery of findings and follow-up actions.

EHR Review

EHR data were available from Renown via the Epic[2] Clarity database, a large subset of the data in the Epic EHR application. EHR data were available from 2006 to 23 August 2021, although the EHR wasn't fully implemented until 2011. The patient diagnosis data review was conducted in June 2021 and participants were included for EHR review if at least 3 months passed since the T1pos notification to ensure that participants had time to respond to their findings.

Diagnoses were retrieved using native application diagnosis codes (nDx) found in more than forty clinical and administrative/billing tables. Each nDx was associated with an entry date as well as a native diagnosis description and mapping (if available) to ICD-9-CM[3] and/or ICD-10-CM[4] codes. In general, nDxs map to one or more ICD codes and are often more specific than ICD codes. Because of their greater specificity, we used nDxs for our analysis rather than ICD codes.

All retrieved nDxs were initially reviewed based on their description and only diagnoses deemed relevant to the T1pos finding of an individual were retained (**Supplementary Material S1**). A detailed review of the remaining nDxs was conducted to determine relevance to each specific T1pos condition. All nDxs reviews were conducted by a physician (GE) with an Internal Medicine background. Prior knowledge of T1pos conditions was defined as a genetic diagnosis appearing in the EHR prior to the notification date.

For ancillary procedures, we focused on retrieving representative screenings for each condition: mammograms and other types of screening breast imaging procedures for

[1]Renown Health, Reno, NV, United States https://www.renown.org/about/.

[2]Epic, Verona, WI, United States https://www.epic.com/.

[3]International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).https://www.cdc.gov/nchs/icd/icd9cm.htm.

[4]International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM).https://www.cdc.gov/nchs/icd/icd10cm.htm.

HBOC (Winters et al., 2017; Lee et al., 2020), colonoscopies for LS (Jasperson et al., 2010; Peterse et al., 2020) and LDL tests for FH (Youngblom et al., 2014; Jellinger et al., 2017). LDL laboratory results were retrieved directly from the results table in Clarity based on native component codes, whereas imaging and other procedures were collected based on orders, results, and mentions in the clinical notes. We also retrieved indications that a mastectomy or oophorectomy was performed from diagnosis tables, clinical notes, and surgery log tables.

Clinical notes for all participants with medical records were retrieved based on a comprehensive keyword search using terms related to each individual condition (HBOC, LS, FH); to genetic testing, findings, or consultations; and to the HNP. Several iterations of the keyword search term collection were performed until no missed terms were found in two repetitive random samples of 100 notes from the entire collection of T1pos participants' notes. All selected notes were then manually reviewed by a single reviewer (GE) for any references pertinent to T1pos findings.

To determine whether participants and their physicians possibly enacted changes to clinical care after notification, we visually examined patient timelines. Changes in care were suspected under the following conditions: if there was an increase in the frequency of mammographies or if prophylactic mastectomies or oophorectomies were performed (HBOC), if a new colonoscopy was ordered without prior history of screening colonoscopy or outside of the recommended timeframe of repeat colonoscopy (LS), for FH we used change in LDL levels as an overall indicator of lifestyle changes and outcome of possible prescribing of effective lipid lowering medications.

Explicit referrals for confirmatory genetic testing were not visible from the Renown EHR. However, we examined recorded referrals for LGCs within the Renown EHR as well as available data from the third-party vendor[5] that conducted genetic consultations on behalf of the HNP and was responsible for such recommendations for confirmatory testing.

Survey

Surveys were sent in January 2020 and October 2021 to 462 T1pos participants that had consented to further research participation (not all were included in our study due to a cutoff point of May 2021 for T1pos results). The survey (**Supplementary Material S2**) was electronic, and participants answered up to 24 questions, depending on their responses. Several reminders were sent within 2 weeks to participants who had not yet responded to the survey. Survey responses were then aggregated and analyzed, and the responses of participants who were also Renown patients were matched with their EHR.

Statistical Analysis

Most results reported in this study were descriptive and did not require the use of statistical tests. However, Fisher's Exact Tests were used to test whether the likelihood that a participant was T1pos, was notified, or had an EHR record differed due to sex or race, and Wilcoxon Rank Sum Tests were used to test whether there were differences due to age. Pearson's Chi-squared Tests were used to test whether survey responses differed between T1pos conditions. A Bonferroni correction was used to adjust for multiple testing where appropriate.

RESULTS

Description of Study Participants

On May 2021 there were 520 HNP participants (out of 41,835) that were T1pos for HBOC (268 participants), LS (102 participants) and/or FH (153 participants) (**Figure 1**). There were two participants with both HBOC and FH and one participant with both HBOC and LS. Participants in this study were notified between September 2018 and September 2020. Notification and counseling were completed for 293 (56.3%) of the 520 T1pos participants, and notification success was significantly higher for white participants (**Table 1**).

Out of the 520 T1pos participants, 417 had reviewable EHRs. After filtering out diagnoses clearly unrelated to HBOC, LS or FH, 14,584 nDXs were collected for those 417 participants (corresponding to an average of 35 unique native diagnoses per participant). 250 (60%) of the 417 participants with Renown EHR were successfully notified. Their mean age was 47.5, they were 33.2% male, and they had a total of 9,034 nDXs, or an average of 36 unique nDXs per individual. All notified participants with EHR record met the minimum required 3 months time span between notification and EHR review (mean 2.2 years, minimum 0.9 years, maximum 2.9 years). 41 of these participants had EHR records with 20 or less nDXs, while mean time span for nDXs was 8.6 years (standard deviation: 6.0 years). Therefore, none of these participants were excluded due to lack of follow-up.

Among T1pos participants with reviewable EHRs, there were 72 out of 417 individuals with malignancies typically associated with HBOC or LS. Fifty such malignancies occurred prior to the initiation of the HNP in 2018 and only five individuals were referred to genetic consultation. Three of the five had meaningful related family history documented in the EHR prior or around the time of the diagnosis of malignancy. Sixteen participants were diagnosed with HBOC/LS typical malignancies after 2017 and prior to notification by the HNP of their T1pos findings. Five of them were referred to a LGC, three of them with strong family history documented at the time of or prior to the cancer diagnosis.

Genetic Diagnoses in the EHR

Based on review of genetic diagnoses among the 250 notified participants with EHR, 38 (15%) had EHR evidence that knowledge of their condition preceded notification, while 212 had no evidence of prior knowledge in their EHR (**Figure 1**). 47 (19%) could have benefited from earlier

[5]Genome Medical, South San Francisco, CA, United States https://www.genomemedical.com/.

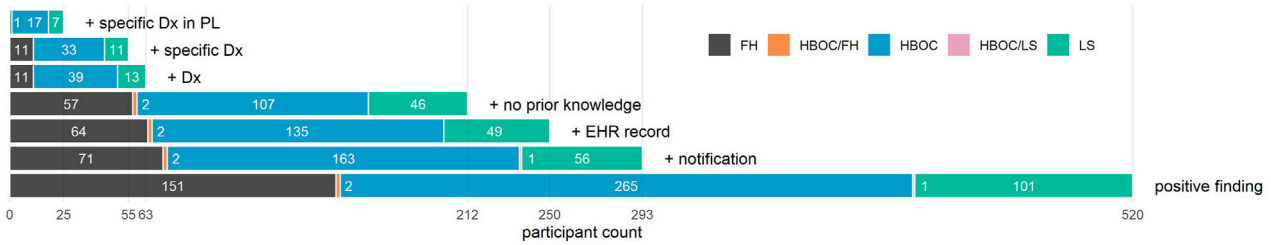

FIGURE 1 | Bar graph depicting counts of participants who meet increasingly restrictive criteria. From bottom to top, participants are limited to (1) those who had a positive finding for HBOC, LS, and/or FH; (2) those who were also notified of their finding and had a genetic consultation; (3) those who also had an EHR record at Renown; (4) those who also had no knowledge of their finding documented in their EHR prior to notification; (5) those who also had a relevant genetic diagnosis documented in their EHR after notification; (6) those whose diagnosis was specific to their condition; and (7) those whose diagnosis appeared in their problem list. Total participant counts for each additional criterion appear on the *x*-axis, while counts for each distinct condition (or set of conditions) are superimposed on each bar.

notification due to prior presentation of disease (27 HBOC, 9 LS, and 11 CVD before the age of 50 years).

Many of the genetic nDxs were non-specific even though specific nDxs, including some mentioning specific variants, exist in the system (**Table 2**). The four most frequent nDxs were non-specific and map directly to correspondingly non-specific ICD-10-CM codes. For HBOC, the nDx often indicated only breast or ovarian cancer susceptibility rather than susceptibility to all cancers associated with HBOC. Of the 212 participants who were notified, had an EHR, and did not have prior knowledge, 63 (30%) had at least a non-specific genetic diagnosis in their EHR, 55 (26%) had a specific genetic diagnosis in their EHR, and 25 (12%) had a specific genetic diagnosis listed in their problem list (PL) (**Figure 1**). We also noted that among more than 35,000 HNP participants with EHR records, 354 have a diagnosis of "Familial Hypercholesterolemia". However, 316 of these participants were not T1pos. Also, only 11 (19%) of the 59 FH-notified participants without prior knowledge had a specific FH diagnosis, and only one of these diagnoses appeared in the PL. Review of the clinical notes of the 354 HNP participants with an FH diagnosis found only a single case where the clinical FH diagnosis was supported by a documented Dutch Lipid Clinic Network Criteria (DLCN). No evidence of use of the Simon Broome or the Making Early Diagnosis Prevents Early Death (MEDPED) clinical criteria was found.

Changes in Care due to Notification

Visually examining patient timelines for the 85 female HBOC patients (**Figure 2A**), we found 10 patients (12%) who appeared to have a change in care. Seventy-five female HBOC patients (88%) exhibited no change in care, of which 40 either had prior cancer or prior knowledge of their HBOC status. Among the 49 LS patients (**Figure 2B**), four (8%) did not have prior colon cancer and appeared to have received a colonoscopy related to their notification. Forty-five LS patients (92%) exhibited no change in care, of which 10 had prior cancer or prior knowledge of their LS status. Among the 66 FH patients (**Figure 2C**), LDL levels improved (at least temporarily) for six (9%) of the patients. Sixty (91%) of the patients positive for FH variants exhibited no change in care, of which 10 had CVD prior to both the notification of their FH status and the age of 50 years.

The survey sent to T1Pos-notified (**Supplementary Material S2**) had an overall response rate of 39.6% and a 42.8% response rate among individuals with an EHR, for a total of 107 respondents with an EHR (**Figure 3**). Among these 107 respondents, 18 (17%) indicated that they did not recall being notified, and 76 (71%) indicated that they reported their findings to their healthcare providers. Of the 76 who reported their findings, 42 indicated that an action plan was formulated for them with 40 of those indicating that they were following their plan. Nine indicated they were not sure whether a plan was formulated for them; however, seven of those indicated they were following their plan. Altogether, 62% indicated that they were following their plan. 26 (34%) indicated that they had prior knowledge of their T1pos status (but only 11 of these had prior EHR documentation), and at least 45 (59%) indicated that they reported their findings to a Renown-affiliated provider. Of these 45, 18 (40%) had a diagnosis in the PL. Of the 59 participants that indicated no prior knowledge of their T1pos status, three (5%) had EHR documentation of their finding that preceded notification and 50 (85%) indicated that they reported their findings; none of the nine participants who did not report their findings (15%) had documentation in their EHRs ($p = 0.02$, Fisher exact, 2-tail). 22 (44%) of the 50 without prior knowledge and who reported their findings had a relevant nDx in their EHR, but only 13 (26%) had a relevant nDx in their PL. 81 (91%) of 89 respondents who recalled being notified indicated that they had shared or planned to share their T1pos results with their family members. Differences in responses to the survey between the three T1pos conditions were not statistically significant.

Additional Results

The review of the clinical notes indicated that one participant notified their provider of their finding but specifically requested for it not to be documented. Their finding subsequently does not appear in their EHR.

According to data from HNP's third-party vendor for 94 of the participants, only 18 participants (19%) sought confirmatory testing while 48 (51.1%) declined

TABLE 1 | Demographic statistics associated with Tier 1 status, notification status, and whether a participant had an EHR record. Comparisons of age, sex, and ethnicity were made for all Tier 1 conditions combined, and for HBOC, LS, and FH participants separately.

	N (%)	Age, Mean (SD)*	Female, n (%)**	White, n (%)**	Missing Demographic Data, n (%)
HNP	41835 (100.0%)	51.7 (17.2)	27836 (66.6%)	33958 (81.3%)	47 (0.1%)
All Tier 1 conditions					
HNP					
Tier 1 positive	520 (1.2%)	50.1 (17.2)	343 (66.1%)	429 (82.7%)	1 (0.2%)
Tier 1 negative	41315 (98.8%)	51.7 (17.2)	27493 (66.6%)	33529 (81.2%)	46 (0.1%)
p-values		0.0458	0.8149	0.4287	
Tier 1 positive					
notified	293 (56.3%)	50.1 (17.7)	194 (66.2%)	261 (89.1%)	0 (0.0%)
not notified	227 (43.7%)	50.1 (16.6)	149 (65.9%)	168 (74.3%)	1 (0.4%)
p-values		0.9025	1.0000	**0.0000**†	
Tier 1 positive + notified					
EHR	250 (85.3%)	50.5 (17.9)	166 (66.4%)	228 (91.2%)	0 (0.0%)
no EHR	43 (14.7%)	47.5 (17.0)	28 (65.1%)	33 (76.7%)	0 (0.0%)
p-values		0.3294	0.863	0.0136	
Hereditary Breast and Ovarian Cancer Syndrome					
HNP					
HBOC positive	268 (0.6%)	49.1 (17.1)	166 (62.2%)	225 (84.3%)	1 (0.4%)
HBOC negative	41567 (99.4%)	51.7 (17.2)	27670 (66.6%)	33733 (81.2%)	46 (0.1%)
p-values		0.0183	0.1342	0.2376	
HBOC positive					
notified	166 (61.7%)	49.0 (17.2)	102 (61.4%)	144 (86.7%)	0 (0.0%)
not notified	102 (37.9%)	49.3 (17.0)	64 (63.4%)	81 (80.2%)	1 (1.0%)
p-values		0.7518	0.7955	0.1681	
HBOC positive + notified					
EHR	137 (82.5%)	50.0 (17.1)	85 (62.0%)	123 (89.8%)	0 (0.0%)
no EHR	29 (17.5%)	44.1 (17.3)	17 (58.6%)	21 (72.4%)	0 (0.0%)
p-values		0.093	0.8341	0.0293	
Lynch Syndrome					
HNP					
LS positive	102 (0.2%)	52.1 (17.9)	72 (70.6%)	85 (83.3%)	0 (0.0%)
LS negative	41733 (99.8%)	51.7 (17.2)	27764 (66.6%)	33873 (81.3%)	47 (0.1%)
p-values		0.8365	0.4619	0.7031	
LS positive					
notified	57 (55.3%)	51.6 (18.7)	41 (71.9%)	52 (91.2%)	0 (0.0%)
not notified	45 (43.7%)	52.7 (17.0)	31 (68.9%)	33 (73.3%)	0 (0.0%)
p-values		0.8031	0.8278	0.0301	
LS positive + notified					
EHR	49 (86.0%)	51.2 (19.1)	36 (73.5%)	45 (91.8%)	0 (0.0%)
no EHR	8 (14.0%)	54.1 (16.6)	5 (62.5%)	7 (87.5%)	0 (0.0%)
p-values		0.8094	0.6735	0.5446	
Familial Hypercholesterolemia					
HNP					
FH positive	153 (0.4%)	50.4 (16.9)	106 (69.3%)	121 (79.1%)	0 (0.0%)
FH negative	41682 (99.6%)	51.7 (17.2)	27730 (66.6%)	33837 (81.3%)	47 (0.1%)
p-values		0.3932	0.5478	0.4686	
FH positive					
notified	73 (47.4%)	51.2 (18.1)	52 (71.2%)	67 (91.8%)	0 (0.0%)
not notified	80 (51.9%)	49.7 (15.8)	54 (67.5%)	54 (67.5%)	0 (0.0%)
p-values		0.6323	0.726	**0.0003**†	
FH positive + notified					
EHR	66 (90.4%)	50.7 (18.6)	46 (69.7%)	61 (92.4%)	0 (0.0%)
no EHR	7 (9.6%)	55.3 (11.5)	6 (85.7%)	6 (85.7%)	0 (0.0%)
p-values		0.4593	0.665	0.4663	

**Test of statistical difference was Wilcoxon Rank Sum Test.*

***Test of statistical difference was Fisher's Exact Test.*

†Statistically significant after Bonferroni correction, $p < 0.0014$.

TABLE 2 | Relative abundance of unique diagnoses appearing in participant EHRs. Shaded diagnoses are considered to be sufficiently specific for clinical purposes.

Diagnoses	N	%	ICD-9-CM	ICD-10-CM
Genetic susceptibility to malignant neoplasm of breast	59	15.3		Z15.01
Genetic susceptibility to other malignant neoplasm	54	14.0		Z15.09
Genetic susceptibility to malignant neoplasm of ovary	39	10.1		Z15.02
Genetic susceptibility to malignant neoplasm of breast	29	7.5	V84.01	Z15.01
BRCA2 gene mutation positive in female	16	4.2	V84.01, V84.02, V84.09	Z15.01, Z15.02, Z15.09
Familial hypercholesterolemia	14	3.6		E78.01
BRCA2 positive	13	3.4	V84.01	Z15.01, Z15.09
Familial hypercholesterolemia	11	2.9	272	E78.01
Lynch syndrome	11	2.9	V84.09	Z15.09
Genetic susceptibility to malignant neoplasm of ovary	10	2.6	V84.02	Z15.02
BRCA1 positive	10	2.6	V84.01	Z15.01, Z15.09
Breast cancer genetic susceptibility	9	2.3	V84.01	Z15.01
BRCA gene mutation positive in female	9	2.3	V84.01, V84.02, V84.09	Z15.01, Z15.02, Z15.09
BRCA gene mutation positive	9	2.3	V84.01, V84.02	Z15.01, Z15.09
BRCA positive	8	2.1	V84.01, V84.02	Z15.01, Z15.09
BRCA2 genetic carrier	8	2.1	V84.01	Z15.01, Z15.09
BRCA2 gene mutation positive	8	2.1	V84.01	Z15.01, Z15.09
BRCA gene positive	7	1.8	V84.01, V84.02	Z15.01, Z15.09
Genetic susceptibility to other malignant neoplasm	6	1.6	V84.09	Z15.09
BRCA1 gene mutation positive	6	1.6	V84.01	Z15.01, Z15.09
Genetic susceptibility to malignant neoplasm of prostate	5	1.3		Z15.03
Genetic susceptibility to breast cancer	4	1.0	V84.01	Z15.01
Genetic carrier of other disease	3	0.8		Z14.8
PMS2-related Lynch syndrome (HNPCC4)	3	0.8	V84.09	Z15.09
BRCA gene mutation positive in male	3	0.8	V84.01, V84.09, V84.03	Z15.01, Z15.03, Z15.09
BRCA1 gene mutation positive in female	3	0.8	V84.01, V84.02, V84.09	Z15.01, Z15.02, Z15.09
BRCA2 gene mutation positive in male	3	0.8	V84.01, V84.03, V84.09	Z15.01, Z15.03, Z15.09
Other genetic carrier status (V83.89)	2	0.5	V83.89	Z14.8
Genetic predisposition to breast cancer	2	0.5	V84.01	Z15.01
Abnormal genetic test	2	0.5	795.2	R89.8
Carrier of gene for Lynch syndrome	2	0.5	V83.89	Z14.8
BRCA1 gene mutation positive in male	2	0.5	V84.01, V84.03, V84.09	Z15.01, Z15.09, Z15.03
Genetic predisposition to malignant neoplasm of breast	1	0.3	V84.01	Z15.01
Genetic susceptibility to ovarian cancer	1	0.3	V84.02	Z15.02
Genetic predisposition to ovarian cancer	1	0.3	V84.02	Z15.02
Genetic predisposition to disease	1	0.3	V84.89	Z15.89
BRCA1 genetic carrier	1	0.3	V84.01	Z15.01, Z15.09
Genetic susceptibility to other disease	1	0.3		Z15.89
Breast cancer, BRCA2 positive, unspecified laterality (HCC)	1	0.3	174.9, V84.01	C50.919, Z15.02, Z15.09
Other genetic carrier status	1	0.3	V83.89	Z14.8
Monoallelic mutation of PMS2 gene	1	0.3	V84.09	Z15.09
PMS2 deficiency	1	0.3	758.5	Q99.8
MSH6-related endometrial cancer (HCC)	1	0.3	182	C54.1
MSH6-related Lynch syndrome (HNPCC5)	1	0.3	V84.09	Z15.09
BRCA gene mutation test positive	1	0.3	V84.01	Z15.01, Z15.09
Familial hypercholesterolemia due to heterozygous low density lipoprotein (LDL) receptor mutation	1	0.3	272	E78.01
Familial hypercholesterolemia due to homozygous low density lipoprotein (LDL) receptor mutation	1	0.3	272	E78.01
Summary				
specific diagnoses (grey highlighted)	93	24.2	NA	NA
non-specific diagnoses	292	75.8	NA	NA

confirmatory testing during the initial counseling session. One confirmatory test resulted in no finding. However, among all notified participants with EHRs, 49 (19.6%) had a referral for a LGC and 32 (15.1% of those without prior knowledge) had a referral after notification.

Since our study period coincided with the COVID-19 pandemic, we also reviewed the frequency of encounters and procedures for the 250 notified participants with EHR to ensure that our findings were not affected by a persistent decline in healthcare services. **Supplementary Figure S1** shows that other than a temporary decline in procedures and encounters at the beginning of the pandemic, healthcare utilization levels for participants in this study rebounded after several months to pre-pandemic levels.

DISCUSSION

The initial HNP model of returning CDC Tier 1 results was to empower the participants with their results. This "hands-off" approach relied on participants to act after notification and

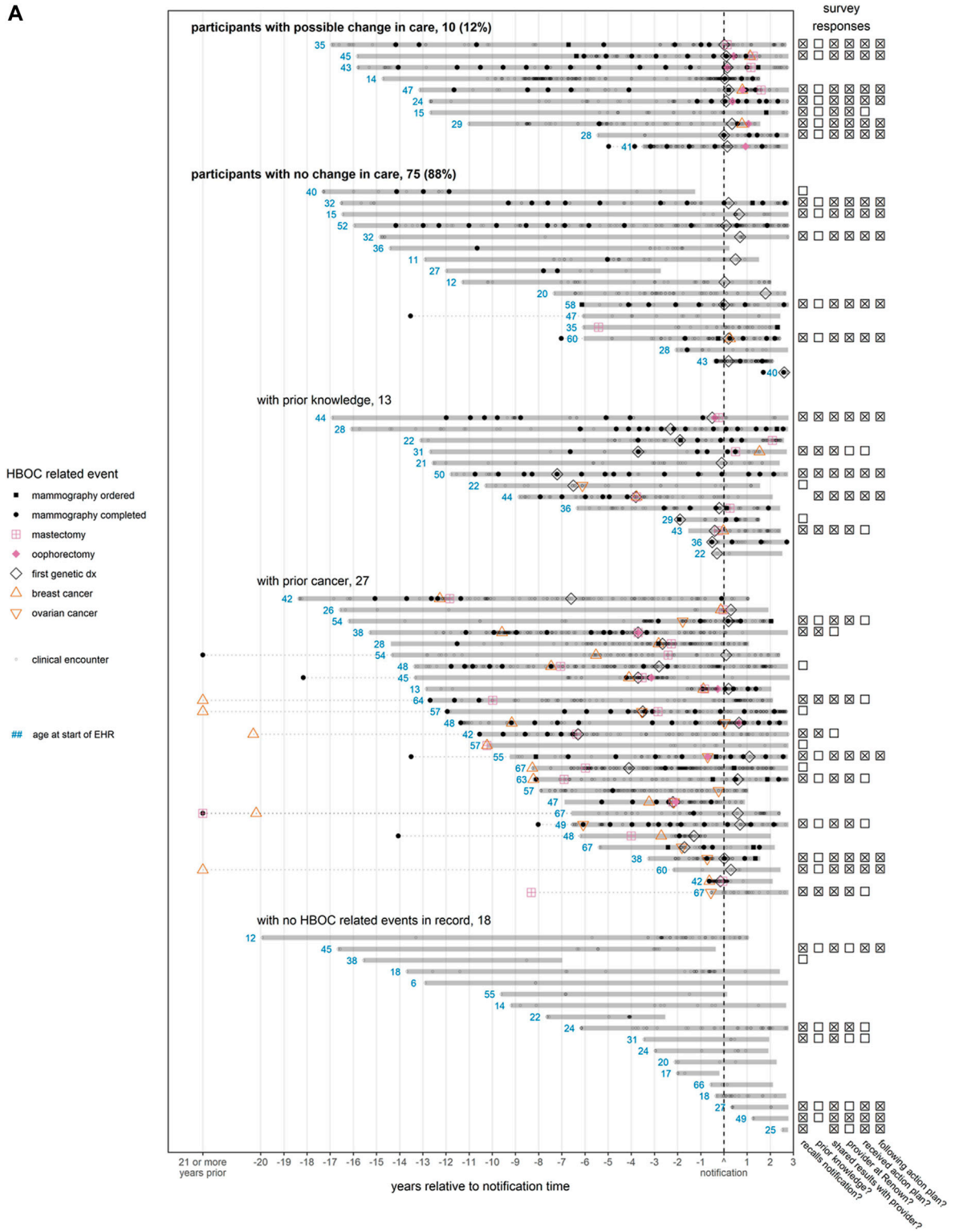

FIGURE 2 | (A) (B) (C)—EHR timelines and survey responses for participants notified of findings. Each solid horizontal line represents a distinct participant medical record, with the duration of the medical record relative to the participant's notification date indicated by the span of the line. A patient's medical record is defined to begin with patient's first record (procedure, diagnosis, or clinical encounter) and to end at the maximum date of the database (8/23/2021) or 1.5 years after the patient's last record, whichever comes first. If an event recorded in the notes occurs outside of this timespan, it is linked to the remainder of the patient record with a dotted line. To preserve space, any event in the notes occurring at least 21 years prior to notification is marked on the *x*-axis as occurring "21 or more years prior". The "first genetic

(*Continued*)

FIGURE 2 | dx" is the first time that a diagnosis indicating a variant associated with a given condition appears in a patient record. Points indicating CVD (ischemic heart events, cerebrovascular events, or peripheral vascular disease) or cancer (breast, ovarian, colorectal, or endometrial) are plotted at the earliest date a diagnosis was recorded. Since some diagnoses indicate a history of CVD or cancer, the disease may have been present earlier in the patient timeline. The red numbers indicate the age in years of a patient at the first event related to a patient's finding, which is defined as a genetic diagnosis (all conditions); mammography, breast or ovarian cancer, or mastectomy (HBOC, panel **(A)**; colonoscopy, or colorectal or endometrial cancer (LS, panel **(B)**; CVD diagnosis or LDL test (FH, panel **(C)**. For FH (panel C), LDL test colors indicate the concentration of LDL in mg/dL. If available, survey responses are displayed to the right of each patient's timeline. Questions answered affirmatively ("Yes") or ambivalently ("Not sure" or "I don't know") are marked with an "x", while survey questions answered negatively ("No") are marked with an empty box. Questions not answered are left blank. From the left column to the right column, the questions are as follows: (1) "Did you receive positive genetic findings from the Healthy Nevada Project?", (2) "Were you aware of your genetic variant prior to participating in the Healthy Nevada Project?", (3) "Have you shared your results with any of your healthcare providers?", (4) "Are any of the providers you shared your results with a Renown/Hometown Health associated provider?", (5) "Did your provider design an action plan for you to follow?", (6) "Are you currently following the action plan suggested by your provider?". Patient records are grouped according to apparent participant responses to notification in their EHR. For HBOC (panel A), records are considered to exhibit a possible change in care after notification if there was an increase in the frequency of mammographies, or if there was a mastectomy/oophorectomy not preceded by cancer. For LS (panel B), records are considered to exhibit a possible change in care if there was an increase in the frequency of colonoscopies. For FH (panel C), records are considered to exhibit a change in care if LDL levels decreased (at least temporarily) to target levels (<100 mg/dl) after notification. For all conditions, participants with no change in care who had both prior presentation of disease (cancer or CVD) and prior knowledge were grouped according to whichever came first.

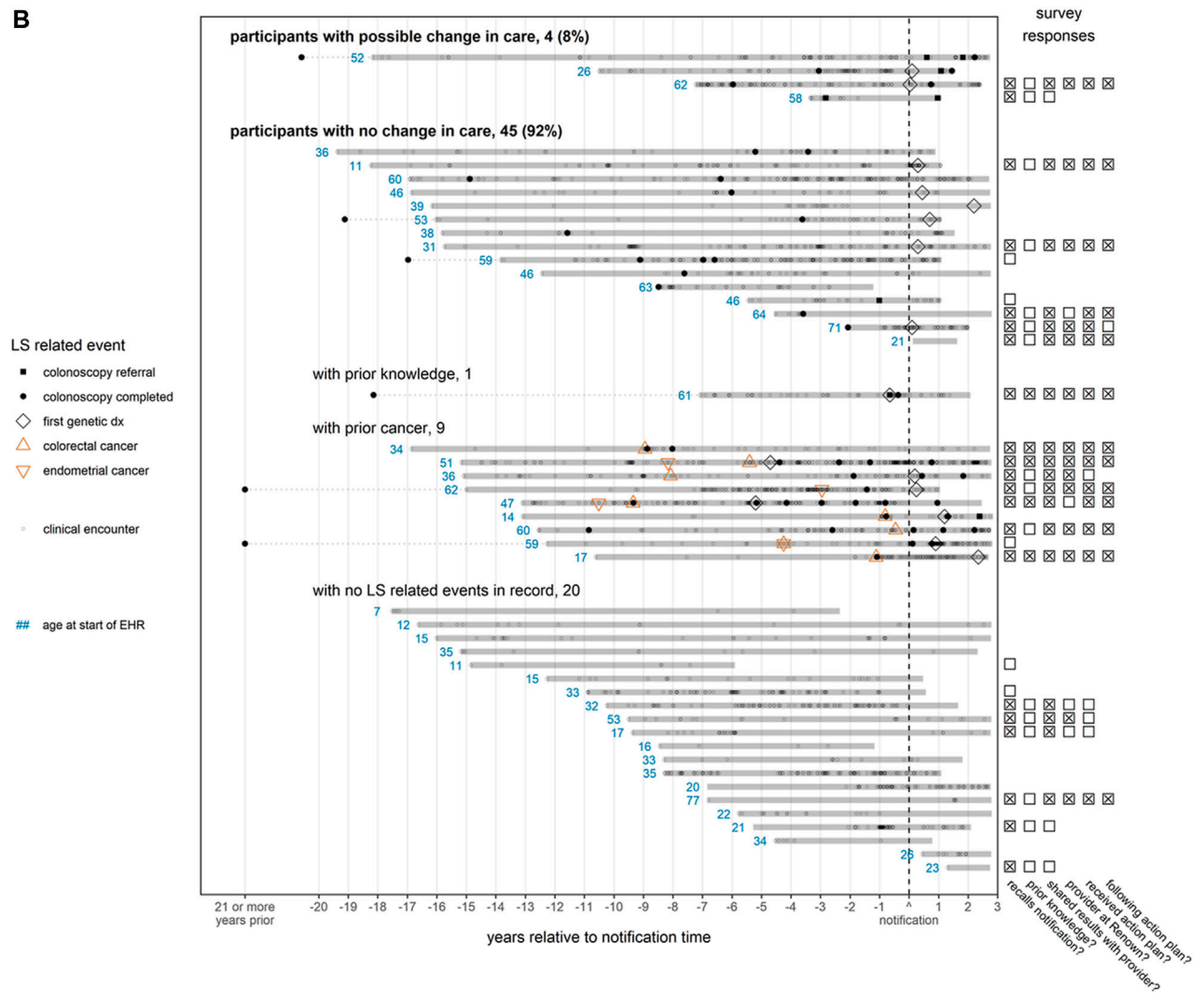

FIGURE 2 | Continued.

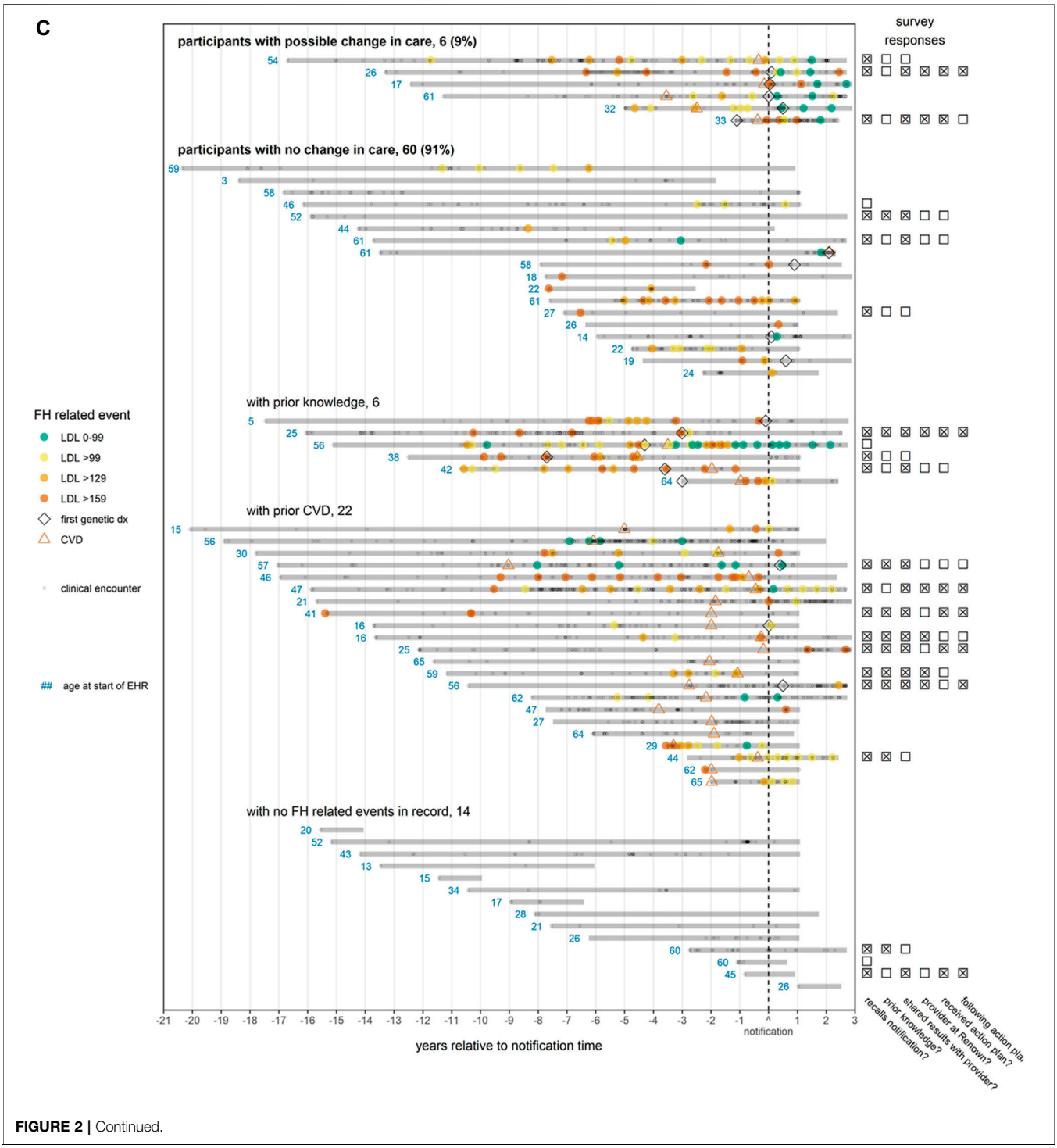

FIGURE 2 | Continued.

counseling. This approach provides an opportunity to examine how T1pos participants respond to notification and how efficiently those responses are recorded in the EHR and acted upon. Thus, the results of this analysis could provide a guide to other projects that are returning genetic results, and thereby enhance the effectiveness of population-based genetic screening (PbGS) in general.

Many studies that examine the outcomes of delivering actionable genetic findings to previously undiagnosed individuals do so in a clinical setting, and the clinical documentation of the finding is a given (Godino et al., 2016; Menko et al., 2019; David et al., 2021). It cannot be assumed that participants will act upon the information entrusted to them, even when the information is potentially life altering (as clearly

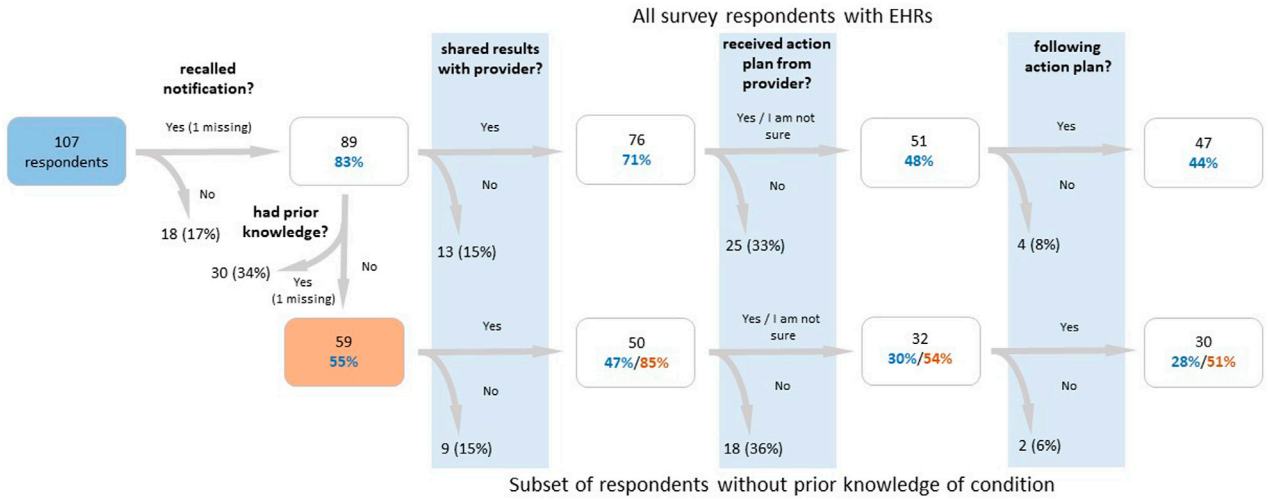

FIGURE 3 | Flow chart of participant survey responses for participants with a finding, who were notified of their finding, and who had an electronic health record. The lower branch of the flow chart examines participants who did not have prior knowledge of their findings, while the upper branch examines all participants. Percentages in blue text are calculated out of the total number of respondents, percentages in red text are calculated out of the number of respondents who reported no prior knowledge (or whose response was missing for that question), and percentages in black are calculated out of the number of respondents in the previous box. From the left to right, the survey questions are as follows: (1) "Did you receive positive genetic findings from the Healthy Nevada Project?", (2) "Were you aware of your genetic variant prior to participating in the Healthy Nevada Project?", (3) "Have you shared your results with any of your healthcare providers?", (4) "Did your provider design an action plan for you to follow?", (5) "Are you currently following the action plan suggested by your provider?".

indicated in their initial informed consent) and the individual is provided with professional advice regarding recommended action. This is especially true when testing was unsolicited as part of a research project, but even when testing was solicited, responses to pathogenic genetic findings may be influenced by an individual's culture, family interactions, and life philosophy (Press et al., 2000; Binetti et al., 2006; Godino et al., 2016; Bijlsma et al., 2018). For instance, an individual's balance between desire for control versus belief in fate may play a significant role in their response (Zimmermann et al., 2020). Additional factors such as age or prior presentation of T1pos related disease (such as breast cancer for an individual with HBOC) play a role as well. For these and other reasons, it has been shown that the uptake of pre-symptomatic genetic testing is considerably lower than 100% even for at-risk individuals (Finlay et al., 2008; George et al., 2015; Menko et al., 2019; Actkins et al., 2021; David et al., 2021). Considering that 9.1% of surveyed T1pos participants with an EHR record had prior, EHR-documented knowledge of their condition and additional participants already had interventions due to prior presentation of their underlying risk, it is perhaps not surprising that just 71% of T1pos Participants with EHR record indicated that they shared their results with their healthcare providers (**Figure 3**).

Shortcomings of Documentation in the EHR

Although most participants shared their pathogenic genetic screening T1pos results with their healthcare providers, we observed a much lower rate of documentation of those results in their EHR (**Figure 1**). Survey results indicate that participants' sharing their previously unknown genetic finding with their provider increases the likelihood of its documentation in the medical record. However, even when a participant says they have shared their results, less than 11% of such participants had a sufficiently specific diagnosis in their PLs. Since the PL is the primary method for indicating and sharing a patient's active health problems between providers, these low documentation rates in the PL are especially worrisome. The discordance between sharing the results with providers and recording the finding in the EHR was not due to participants' reluctance to have the finding documented and thus argues that the "hands-off" approach is not necessarily problematic but would benefit from overcoming some of the gaps in knowledge providers have with genetic testing and clinical decision support of genetic testing positive findings. The low EHR documentation rate does not appear to be due to participants' reluctance to have the finding documented. It occurs despite significant promotional efforts within Renown in support of the HNP.

Even when findings were recorded, quite often diagnoses were not as specific as they could have been, considering the available nDxs in the EHR system. A diagnosis of "Genetic susceptibility to other malignant neoplasm" (Z15.09, 54 instances, **Table 2**) is too vague to inform clinical action. Similarly, recording "Genetic susceptibility to malignant neoplasm of ovary" (Z15.01) as a single code to document a finding of *BRCA1* or *BRCA2* does not convey the scope of the risk (as *BRCA1* and *BRCA2* also increase the risk of cancer of the breasts and other organs). Such non-specific coding may prevent appropriate risk-reduction interventions from being implemented. However, codes documenting specific variants were occasionally used (**Table 2**), indicating that more specific nDxs are available to providers.

We also observe cases where specific codes were used for documenting FH without the support of required clinical criteria.

"Familial hypercholesterolemia" diagnosis (ICD-10-CM E78.01) is mostly used for patients without documented genetic findings of FH or evidence that a clinical criteria such as the DLCN was applied, thus reducing its significance, and necessitating the recording of a genetic variant for a provider to be certain that a patient was FH-T1pos. However, we could only find two such records for T1pos participants with FH.

The frequent use of non-specific diagnoses may simply reflect the widespread use of ICD-10-CM codes for clinical documentation and their relative inappropriateness for documenting genetic findings (Topaz et al., 2013; DeAlmeida et al., 2014; Fung et al., 2014). In contrast to ICD-10-CM, SNOMED CT[6] has specific codes for *BRCA1* or *BRCA2* variants (SNOMED CD IDs 412734009/412738007 respectively). The use of non-specific diagnoses may also reflect documented issues in current EHRs with effective integration of genetic data with patient medical records (Kho et al., 2013) as well as issues with template designs, such as having to select codes from exhaustive lists.

However, another possibility may be that healthcare personnel are uncomfortable dealing with genetic testing and the resulting findings. Numerous studies have shown that healthcare personnel, especially in the primary care setting, do not feel adequately equipped to order genetic tests or interpret, communicate, and follow up on such results (Overby et al., 2014; George et al., 2015; Hamilton et al., 2017; Hann et al., 2017; Briggs et al., 2018; Hauser et al., 2018; Laforest et al., 2019; Menko et al., 2019; Demeshko et al., 2020). Reservations regarding insurance discrimination and the social impact the findings might have for the patient play a role as well, although we note that only one person in the results herein asked to have no mention of the finding in the medical record. Additionally, physicians may not pay attention to unsolicited genetic results within EHRs (eMERGE (Gottesman et al., 2013; Williams et al., 2019; Nestor et al., 2021)) and it may be unclear to healthcare personnel who is responsible for positive genetic testing results (Pet et al., 2019). Ours was not a usability study and we cannot attribute the relative weight of the factors that may contribute to the observed poor documentation. Nevertheless, it is likely that if integrated clinical decision support tools were available for the PCPs seeing patients with CDCT1 findings, better documentation rates would follow. Such tools might suggest the appropriate diagnostic codes for the condition, the risk and the genetic variant detected, as well as recommended follow up steps and intervals.

Importance of Testing Early

Although we could not demonstrate improved practice patterns following T1Pos-finding notification for most participants (**Figures 2A–C**), many of the participants failed to benefit due to their old age, prior knowledge of their condition, prior presentation of outcomes, and prior interventions related to their findings. It is also possible that, because of the voluntary nature of the HNP, participants tend to be more health conscious than the general population and that this paradoxically contributed to our inability to detect improved practice patterns. Nevertheless, our results suggests that the timing of the genetic testing was a key factor. Had genetic screening been conducted earlier in life, many more participants would have benefited from T1Pos notification. Other studies (including our previous HNP publication) have reported similar findings (Grzymski et al., 2020; Guzauskas et al., 2020; Patel et al., 2020).

Since genetic testing after the presentation of a disease is clearly suboptimal, mandated testing in younger adult populations should be considered as a possible solution. In Nevada, a recently signed bill (SB251 (Nevada Legislature, 2021)), based on 42 U.S.C. 300gg-13 (GOVINFO, 2010), requires PCPs to obtain genetic counseling in compliance with the USPSTF recommendation (US Preventive Services Task Force, Owens et al., 2019) for risk assessment and possible genetic counseling and testing for all women with "a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility". Even though the USPSTF recommendations were published in 2019, our review of the EHR indicates that widespread genetic screening under those circumstances is not yet common practice, especially if there was no evidence of relevant family history. Others have reported similarly low rates (Cham et al., 2022). Mandates such as Nevada's may help identify many individuals at a younger age, prevent additional malignancies, and expand the scope of prevention by cascade testing. However, without sustained educational efforts within the general and medical communities, these types of efforts are more likely to increase screening after the presentation of symptoms rather than improve the ascertainment of family history in the medical record that will yield much earlier detection and risk reduction.

Similar Studies

We are not aware of directly comparable studies attempting to measure the clinical outcomes of a "hands-off" return of results approach. The most similar study is probably Buchanan et al. (2020), which reported on the clinical outcomes of Geisinger's genomic medicine experience (Williams et al., 2018), and their clinical data extraction and evaluation methods were similar. They provide similar information concerning diagnostic documentation and risk management, but in a different clinical setting and initiative design. In their report, post-disclosure diagnoses were evident in the EHRs of 13.4% of participants without prior knowledge, a rate comparable to the rate we observed in the PL. However, Buchanan *et al.* reported a much higher rate of post-disclosure risk management activities (70.2%) than we observed in our study. This may be because the definition of risk management activities used by Buchanan *et al.* for the T1pos conditions was significantly more encompassing (especially for FH) than our definition of behavior change. Nevertheless, the most likely cause of the difference in outcomes between our study and Buchanan *et al.* is the more integrative and proactive design of the Geisinger initiative.

Limitations

A limitation of our study was the structure of healthcare in northern Nevada, where some subspecialties are predominantly private practice groups that have not provided us with access to their medical records. However, our review of the clinical notes

[6]SNOMED International. https://www.snomed.org/.

indicated that procedures outside the reach of Renown's Epic EHR are often documented in clinical notes during subsequent visits at Renown. Thus, even if a participant's PCP was not an affiliated Renown physician and user of Renown's Epic EHR system, it is reasonable that a significant genetic finding would eventually appear in the EHR record, given the typical rate of encounters at Renown and follow up time. We believe that the partial availability of clinical data due to the gradual implementation of Renown's EHR from 2006 to 2011 had a minimal effect with regards to the recorded date of the finding but no effect on its actual documentation. When possible, additional specific dates were incorporated upon review of clinical notes.

Our review of EHR data was conducted at least 10 months after T1pos notification by the HNP. This was deemed sufficient time to allow T1pos participants to share their results with their physicians and for the findings to appear in the medical record. The existence of private practice groups was also the reason that for procedures such as colonoscopies, we considered orders as well as completed procedures. Although Renown's coverage of primary care is roughly 50% in northern Nevada, at least 59% of survey respondents who shared their results shared with a Renown provider, suggesting a higher capture rate in our population. Although this was a single center study, the training and practice of medicine are comparable to other integrated networks and medical centers and our results should be considered in that broader context.

Additional Observations

While our survey was not designed to evaluate how likely participants were to share their results with different types of family members, more than 90% of respondents indicated that they shared their finding with family. This level of uptake is comparable to the highest levels reported by others (Menko et al., 2019).

From the limited data set obtained from the third-party vendor that provides the genetic counseling, it is worth noting that more than half declined confirmatory testing and only 19% completed confirmatory testing. Thus, it seems that there is little value in recommending confirmatory testing. Financial or insurance considerations did not appear to be a significant contributing factor to the low rate of confirmatory testing. It may have been that HNP assurances regarding the robustness of the genetic testing results negated the importance of seeking confirmation for some participants.

The COVID-19 pandemic overlapped with our study period. We examined the possibility that this might have reduced participant utilization of healthcare, and thus affected our ability to detect responses to notification in the EHR. However, after a 2–4-month period of decreased utilization at the beginning of the pandemic, utilization rebounded to pre-pandemic levels (**Supplementary Figure S1**). Given that the minimum observation time was at least 10 months, we believe the pandemic had a minimal effect on our ability to detect responses to T1pos notification.

Only 60% of T1pos consenting participants with EHR were successfully notified and counselled, but the HNP has observed that the notification success rate was significantly higher when participants were contacted by Renown physicians than when they were contacted by the third-party vendor. This is likely due to Renown's name recognition by participants. However, the third-party vendor success rate appears to be comparable to the rest of the industry. This highlights the need to find much more effective ways of reaching out to T1pos participants. Lack of notification was also associated with being non-white, who are underrepresented in the HNP (**Table 1**). This is likely a reflection on the socioeconomic disparities of certain non-white ethnic groups in northern Nevada[7], negatively affecting their communication means and access to healthcare. Modifications to the HNP protocol including integration of the study into the EHR and improvements to the clinical decision support available to Renown Health providers will help address these disparity gaps moving forward.

Conclusion

As a result of these findings and in conjunction with the new state law, SB251, Renown and the HNP have made significant changes including obtaining informed consent to report positive findings directly into the medical record of the consented patient. We have expanded physician and other provider education, created order sets within the EHR specific to the CDC Tier 1 conditions, as well as study- and CDC Tier 1-specific tip sheets for providers.

Altogether, our findings indicate significant missed opportunity to maximize the benefit of the HNP voluntary population-based genetic screening and suggests that a change of design is required when it comes to the integration of the results into the participants' medical record. Relying on participants to share their T1pos status with their healthcare providers appears to be inefficient, suggesting that a much more proactive approach should be taken. To improve results, we propose that participants' consent be obtained at the time of recruitment for the study to automatically integrate T1pos findings with their EHR and to directly contact the participants' healthcare providers. Persistent training of medical staff regarding CDC Tier 1 conditions is also needed to maintain a high level of awareness of the significance of such results and ensure appropriate documentation. Medical staff should use the most specific available codes and should document the findings in the PL. Failing to document findings in the PL could result in a loss of knowledge regarding the patients' at-risk status for years to come. However, as Nestor et al. (2021) showed, even documented findings can often be ignored. This highlights the need for continued outreach to T1pos participants and especially their healthcare providers on follow-up steps and documentation that needs to be taken to effectively manage disease risk and to ensure optimal outcomes of PbGS.

[7]United states Census Bureau. https://data.census.gov/cedsci/. Washoe County, NV Tables: Personal Income—B19301A-G,I, Household Tenure—B25003A-G, I, Geographic Mobility—S0701, Educational Attainment—S1501, Uninsured—S2702, Internet by Household Income—S2801.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Nevada, Reno Institutional Review Board (IRB, project 956068-12). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG contributed to conception and design of the Healthy Nevada Project. JG, GE, JL contributed to the design of this study. DK and GE performed the analysis. JM organized the data. IN developed and analyzed survey data. SD was integral to return of results. GE and DK wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.866169/full#supplementary-material

REFERENCES

Actkins, K. E. V., Srinivasan, S., Spees, L. P., Turbitt, E., Allen, C. G., and Roberts, M. C. (2021). Uptake of Genetic Testing Among Patients with Cancer at Risk for Lynch Syndrome in the National Health Interview Survey. *Cancer Prev. Res. (Phila).* 14 (10), 927–932. doi:10.1158/1940-6207.CAPR-21-0073

Bijlsma, R. M., Wessels, H., Wouters, R. H. P., May, A. M., Ausems, M. G. E. M., Voest, E. E., et al. (2018). Cancer Patients' Intentions towards Receiving Unsolicited Genetic Information Obtained Using Next-Generation Sequencing. *Fam. Cancer* 17 (2), 309–316. doi:10.1007/s10689-017-0033-7

Binetti, G., Benussi, L., Roberts, S., Villa, A., Pasqualetti, P., Sheu, C.-F., et al. (2006). Areas of Intervention for Genetic Counseling of Dementia: Cross-Cultural Comparison between Italians and Americans. *Patient Educ. Couns.* 64 (1-3), 285–293. doi:10.1016/j.pec.2006.03.008

Briggs, A., Nouri, P. K., Galloway, M., O'Leary, K., Pereira, N., and Lindheim, S. R. (2018). Expanded Carrier Screening: A Current Survey of Physician Utilization and Attitudes. *J. Assist. Reprod. Genet.* 35 (9), 1631–1640. doi:10.1007/s10815-018-1272-8

Buchanan, A. H., Lester Kirchner, H., Schwartz, M. L. B., Kelly, M. A., Schmidlen, T., Jones, L. K., et al. (2020). Clinical Outcomes of a Genomic Screening Program for Actionable Genetic Conditions. *Genet. Med.* 22 (11), 1874–1882. doi:10.1038/s41436-020-0876-4

Centers for Disease Control and Prevention (2021). Office of Public Health Genomics. Tier 1 Genomic Applications Toolkit for Public Health Departments. Available at: https://www.cdc.gov/genomics/implementation/toolkit/index.htm (Accessed January 24, 2022).

Cham, S., Landrum, M. B., Keating, N. L., Armstrong, J., and Wright, A. A. (2022). Use of Germline BRCA Testing in Patients with Ovarian Cancer and Commercial Insurance. *JAMA Netw. Open* 5 (1), e2142703. doi:10.1001/jamanetworkopen.2021.42703

David, S. P., Dunnenberger, H. M., Ali, R., Matsil, A., Lemke, A. A., Singh, L., et al. (2021). Implementing Primary Care Mediated Population Genetic Screening within an Integrated Health System. *J. Am. Board Fam. Med.* 34 (4), 861–865. doi:10.3122/jabfm.2021.04.200381

DeAlmeida, D. R., Watzlaf, V. J., Anania-Firouzan, P., Salguero, O., Rubinstein, E., Abdelhak, M., et al. (2014). Evaluation of Inpatient Clinical Documentation Readiness for ICD-10-CM. *Perspect. Health Inf. Manag.* 11, 1h.

Demeshko, A., Pennisi, D. J., Narayan, S., Gray, S. W., Brown, M. A., and McInerney-Leo, A. M. (2020). Factors Influencing Cancer Genetic Somatic Mutation Test Ordering by Cancer Physician. *J. Transl Med.* 18 (1), 431. doi:10.1186/s12967-020-02610-7

Evans, O., Gaba, F., and Manchanda, R. (2020). Population-Based Genetic Testing for Women's Cancer Prevention. *Best Pract. Res. Clin. Obstet. Gynaecol.* 65, 139–153. doi:10.1016/j.bpobgyn.2020.02.007

Ficarazzi, F., Vecchi, M., Ferrari, M., and Pierotti, M. A. (2021). Towards Population-Based Genetic Screenings for Breast and Ovarian Cancer: A Comprehensive Review from Economic Evaluations to Patient Perspectives. *Breast* 58, 121–129. doi:10.1016/j.breast.2021.04.011

Finlay, E., Stopfer, J. E., Burlingame, E., Evans, K. G., Nathanson, K. L., Weber, B. L., et al. (2008). Factors Determining Dissemination of Results and Uptake of Genetic Testing in Families with Known BRCA1/2 Mutations. *Genet. Test.* 12 (1), 81–91. doi:10.1089/gte.2007.0037

Fung, K. W., Richesson, R., and Bodenreider, O. (2014). Coverage of Rare Disease Names in Standard Terminologies and Implications for Patients, Providers, and Research. *AMIA Annu. Symp. Proc.* 2014, 564–572.

George, R., Kovak, K., and Cox, S. L. (2015). Aligning Policy to Promote Cascade Genetic Screening for Prevention and Early Diagnosis of Heritable Diseases. *J. Genet. Counsel* 24 (3), 388–399. doi:10.1007/s10897-014-9805-5

Godino, L., Turchetti, D., Jackson, L., Hennessy, C., and Skirton, H. (2016). Impact of Presymptomatic Genetic Testing on Young Adults: A Systematic Review. *Eur. J. Hum. Genet.* 24 (4), 496–503. doi:10.1038/ejhg.2015.153

Gottesman, O., Kuivaniemi, H., Tromp, G., Faucett, W. A., Li, R., Manolio, T. A., et al. (2013). The Electronic Medical Records and Genomics (eMERGE) Network: Past, Present, and Future. *Genet. Med.* 15 (10), 761–771. doi:10.1038/gim.2013.72

GOVINFO (2010). 42 U.S.C. 300gg-13 - Coverage of Preventive Health Services. Available at: https://www.govinfo.gov/app/details/USCODE-2010-title42/USCODE-2010-title42-chap6A-subchapXXV-partA-subpartii-sec300gg-13 Accessed January 24, 2022.

Grzymski, J. J., Elhanan, G., Morales Rosado, J. A., Smith, E., Schlauch, K. A., Read, R., et al. (2020). Population Genetic Screening Efficiently Identifies Carriers of Autosomal Dominant Diseases. *Nat. Med.* 26 (8), 1235–1239. doi:10.1038/s41591-020-0982-5

Guzauskas, G. F., Garbett, S., Zhou, Z., Spencer, S. J., Smith, H. S., Hao, J., et al. (2020). Cost-Effectiveness of Population-Wide Genomic Screening for Hereditary Breast and Ovarian Cancer in the United States. *JAMA Netw. Open* 3 (10), e2022874. doi:10.1001/jamanetworkopen.2020.22874

Hamilton, J. G., Abdiwahab, E., Edwards, H. M., Fang, M.-L., Jdayani, A., and Breslau, E. S. (2017). Primary Care Providers' Cancer Genetic Testing-Related Knowledge, Attitudes, and Communication Behaviors: A Systematic Review and Research Agenda. *J. Gen. Intern. Med.* 32 (3), 315–324. doi:10.1007/s11606-016-3943-4

Hann, K. E. J., Fraser, L., Fraser, L., Side, L., Gessler, S., Waller, J., et al. (2017). Health Care Professionals' Attitudes towards Population-Based Genetic Testing and Risk-Stratification for Ovarian Cancer: A Cross-Sectional Survey. *BMC Women's Health* 17 (1), 132. doi:10.1186/s12905-017-0488-6

Hauser, D., Obeng, A. O., Fei, K., Ramos, M. A., and Horowitz, C. R. (2018). Views of Primary Care Providers on Testing Patients for Genetic Risks for Common Chronic Diseases. *Health Aff.* 37 (5), 793–800. doi:10.1377/hlthaff.2017.1548

Helix (2017). Personal Genomics Platform White Paper. Available at: https://cdn.shopify.com/s/files/1/0004/5416/4542/files/Helix-Performance-White-Paper_v2.pdf?3324109126506576509 Accessed January 24, 2022.

Jasperson, K. W., Tuohy, T. M., Neklason, D. W., and Burt, R. W. (2010). Hereditary and Familial Colon Cancer. *Gastroenterology* 138 (6), 2044–2058. doi:10.1053/j.gastro.2010.01.054

Jellinger, P. S., Handelsman, Y., Rosenblit, P. D., Bloomgarden, Z. T., Fonseca, V. A., Garber, A. J., et al. (2017). American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. *Endocr. Pract.* 23 (Suppl. 2), 1–87. doi:10.4158/EP171764.APPGL

Kho, A. N., Rasmussen, L. V., Connolly, J. J., Peissig, P. L., Starren, J., Hakonarson, H., et al. (2013). Practical Challenges in Integrating Genomic Data into the Electronic Health Record. *Genet. Med.* 15 (10), 772–778. doi:10.1038/gim.2013.131

Laforest, F., Kirkegaard, P., Mann, B., and Edwards, A. (2019). Genetic Cancer Risk Assessment in General Practice: Systematic Review of Tools Available, Clinician Attitudes, and Patient Outcomes. *Br. J. Gen. Pract.* 69 (679), e97–e105. doi:10.3399/bjgp18X700265

Lambert, S. A., Abraham, G., and Inouye, M. (2019). Towards Clinical Utility of Polygenic Risk Scores. *Hum. Mol. Genet.* 28 (R2), R133–R142. doi:10.1093/hmg/ddz187

Lee, A., Moon, B.-I., and Kim, T. H. (2020). BRCA1/BRCA2 Pathogenic Variant Breast Cancer: Treatment and Prevention Strategies. *Ann. Lab. Med.* 40 (2), 114–121. doi:10.3343/alm.2020.40.2.114

Manchanda, R., Lieberman, S., Gaba, F., Lahad, A., and Levy-Lahad, E. (2020). Population Screening for Inherited Predisposition to Breast and Ovarian Cancer. *Annu. Rev. Genom. Hum. Genet.* 21, 373–412. doi:10.1146/annurev-genom-083118-015253

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome Sequencing-Based Screening for BRCA1/2 Expected Pathogenic Variants Among Adult Biobank Participants. *JAMA Netw. Open* 1 (5), e182140. doi:10.1001/jamanetworkopen.2018.2140

Menko, F. H., Ter Stege, J. A., van der Kolk, L. E., Jeanson, K. N., Schats, W., Moha, D. A., et al. (2019). The Uptake of Presymptomatic Genetic Testing in Hereditary Breast-Ovarian Cancer and Lynch Syndrome: A Systematic Review of the Literature and Implications for Clinical Practice. *Fam. Cancer* 18 (1), 127–135. doi:10.1007/s10689-018-0089-z

Miller, D. T., Lee, K., Chung, W. K., Gordon, A. S., Herman, G. E., Klein, T. E., et al. (2021). ACMG SF v3.0 List for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing: A Policy Statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (8), 1381–1390. doi:10.1038/s41436-021-01172-3

Murray, M. F., Evans, J. P., and Khoury, M. J. (2020). DNA-Based Population Screening: Potential Suitability and Important Knowledge Gaps. *JAMA* 323 (4), 307–308. doi:10.1001/jama.2019.18640

Nestor, J. G., Fedotov, A., Fasel, D., Marasa, M., Milo-Rasouly, H., Wynn, J., et al. (2021). An Electronic Health Record (EHR) Log Analysis Shows Limited Clinician Engagement with Unsolicited Genetic Test Results. *JAMIA Open* 4 (1), ooab014. doi:10.1093/jamiaopen/ooab014

Nevada Legislature (2021). SB251. Available at: https://www.leg.state.nv.us/App/NELIS/REL/81st2021/Bill/7773/Overview Accessed January 24, 2022.

Overby, C., Erwin, A., Abul-Husn, N., Ellis, S., Scott, S., Obeng, A., et al. (2014). Physician Attitudes toward Adopting Genome-Guided Prescribing through Clinical Decision Support. *J. Pers Med.* 4 (1), 35–49. doi:10.3390/jpm4010035

Patel, A. P., Wang, M., Fahed, A. C., Mason-Suares, H., Brockman, D., Pelletier, R., et al. (2020). Association of Rare Pathogenic DNA Variants for Familial Hypercholesterolemia, Hereditary Breast and Ovarian Cancer Syndrome, and Lynch Syndrome with Disease Risk in Adults According to Family History. *JAMA Netw. Open* 3 (4), e203959. doi:10.1001/jamanetworkopen.2020.3959

Pet, D. B., Holm, I. A., Williams, J. L., Myers, M. F., Novak, L. L., Brothers, K. B., et al. (2019). Physicians' Perspectives on Receiving Unsolicited Genomic Results. *Genet. Med.* 21 (2), 311–318. doi:10.1038/s41436-018-0047-z

Peterse, E. F. P., Naber, S. K., Daly, C., Pollett, A., Paszat, L. F., Spaander, M. C. W., et al. (2020). Cost-Effectiveness of Active Identification and Subsequent Colonoscopy Surveillance of Lynch Syndrome Cases. *Clin. Gastroenterol. Hepatol.* 18 (12), 2760–2767. doi:10.1016/j.cgh.2019.10.021

Press, N., Fishman, J. R., and Koenig, B. A. (2000). Collective Fear, Individualized Risk: The Social and Cultural Context of Genetic Testing Forbreast Cancer. *Nurs. Ethics* 7 (3), 237–249. doi:10.1177/096973300000700306

Read, R. W., Schlauch, K. A., Lombardi, V. C., Cirulli, E. T., Washington, N. L., Lu, J. T., et al. (2021). Genome-Wide Identification of Rare and Common Variants Driving Triglyceride Levels in a Nevada Population. *Front. Genet.* 12, 639418. doi:10.3389/fgene.2021.639418

Tafe, L. J. (2015). Targeted Next-Generation Sequencing for Hereditary Cancer Syndromes: A Focus on Lynch Syndrome and Associated Endometrial Cancer. *J. Mol. Diagn.* 17 (5), 472–482. doi:10.1016/j.jmoldx.2015.06.001

Topaz, M., Shafran-Topaz, L., and Bowles, K. H. (2013). ICD-9 to ICD-10: Evolution, Revolution, and Current Debates in the United States. *Perspect. Health Inf. Manag.* 10, 1d.

US Preventive Services Task Force, Owens, D. K., Davidson, K. W., Krist, A. H., Barry, M. J., Cabana, M., et al. (2019). Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA-Related Cancer. *JAMA* 322 (7), 652–665. doi:10.1001/jama.2019.10987

Williams, M. S., Buchanan, A. H., Davis, F. D., Faucett, W. A., Hallquist, M. L. G., Leader, J. B., et al. (2018). Patient-Centered Precision Health in A Learning Health Care System: Geisinger's Genomic Medicine Experience. *Health Aff.* 37 (5), 757–764. doi:10.1377/hlthaff.2017.1557

Williams, M. S., Taylor, C. O., Walton, N. A., Goehringer, S. R., Aronson, S., Freimuth, R. R., et al. (2019). Genomic Information for Clinicians in the Electronic Health Record: Lessons Learned from the Clinical Genome Resource Project and the Electronic Medical Records and Genomics Network. *Front. Genet.* 10, 1059. doi:10.3389/fgene.2019.01059

Winters, S., Martin, C., Murphy, D., and Shokar, N. K. (2017). Breast Cancer Epidemiology, Prevention, and Screening. *Prog. Mol. Biol. Transl Sci.* 151, 1–32. doi:10.1016/bs.pmbts.2017.07.002

Youngblom, E., Pariani, M., and Knowles, J. W. (2014). "Familial Hypercholesterolemia," in *GeneReviews® (Internet)*. Editors MP Adam, HH Ardinger, RA Pagon, SE Wallace, LJH Bean, KW Gripp, et al. (Seattle (WA): University of Washington, Seattle), 1993–2021.

Zimmermann, B. M., Shaw, D., Heinimann, K., Knabben, L., Elger, B., and Koné, I. (2020). How the "Control-Fate Continuum" Helps Explain the Genetic Testing Decision-Making Process: A Grounded Theory Study. *Eur. J. Hum. Genet.* 28 (8), 1010–1019. doi:10.1038/s41431-020-0602-3

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Parental Attitudes Toward Standard Newborn Screening and Newborn Genomic Sequencing: Findings From the BabySeq Study

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Introduction: With increasing utility and decreasing cost of genomic sequencing, augmentation of standard newborn screening (NBS) programs with newborn genomic sequencing (nGS) has been proposed. Before nGS can be integrated into newborn screening, parents' perspectives must be better understood.

Objective: Using data from surveys administered to parents of healthy newborns who were enrolled in the BabySeq Project, a randomized clinical trial of nGS alongside NBS, this paper reports parents' attitudes regarding population-based NBS and nGS assessed 3 months after results disclosure.

Methods: Parental attitudes regarding whether all newborns should receive, and whether informed consent should be required for, NBS and nGS, as well as whether nGS should be mandated were assessed using 5-point scales from strongly disagree (=1) to strongly agree (=5). Parents' interest in receiving types of results from nGS was assessed on a 5-point scale from not at all interested (=1) to very interested (=5). Survey responses were analyzed using Fisher's exact tests, paired t-tests, and repeated measures ANOVA.

Results: At 3 months post-disclosure, 248 parents of 174 healthy newborns submitted a survey. Support for every newborn receiving standard NBS (mean 4.67) was higher than that for every newborn receiving nGS (mean 3.60; $p < 0.001$). Support for required informed consent for NBS (mean 3.44) was lower than that for nGS (mean 4.27, $p < 0.001$). Parents' attitudes toward NBS and nGS were not significantly associated with self-reported political orientation. If hypothetically receiving nGS outside of the BabySeq Project, most parents reported being very interested in receiving information on their baby's risk of developing a disease in childhood that can be prevented, treated, or cured

(86.8%) and their risk of developing a disease during adulthood that can be prevented, treated, or cured (84.6%).

Discussion: Parents' opinions are crucial to inform design and delivery of public health programs, as the success of the program hinges on parents' trust and participation. To accommodate parents' preferences without affecting the current high participation rates in NBS, an optional add-on consent to nGS in addition to NBS may be a feasible approach. Trial Registration ClinicalTrials.gov Identifier: NCT02422511.

Keywords: newborn screening (NBS), newborn sequencing, genomic sequencing, ELSI, ethics, exome sequencing, newborn genomic sequencing

INTRODUCTION

Since starting in the 1960s as a single screening test for phenylketonuria (PKU), developed by Dr. Robert Guthrie, newborn screening (NBS) has expanded in the United States into an extremely successful mandated public health program (Koppaka 2011; CDC 2020; Baby's First Test 2021). While there are differences between states on the number and types of conditions that are screened, most states use a similar approach to mandating newborn screening, including an opt-out policy that does not require parental informed consent (Lewis and Botkin 2019). Current state-based programs can use tandem mass spectrometry to screen for over 50 different conditions to allow for presymptomatic detection, diagnosis, and treatment of conditions for which early intervention can reduce morbidity, mortality, and the social burden of disease (Cipriano et al., 2007; Therrell et al., 2015; Johnson and Wile 2017).

Building on the established success of NBS programs, some have proposed that there could be even greater public health impact if genomic sequencing (GS) were incorporated alongside current screening modalities (Genetic Alliance and District of Columbia Department of Helath 2010; Groft et al., 2017). Increases in the speed and affordability of GS have rendered it a feasible option for consideration as a population-based screening tool (Groft et al., 2017). The addition of newborn GS (nGS) to NBS programs would enable screening for more conditions than current methods alone, with the potential to benefit more families (Berg and Powell 2015; Wojcik et al., 2021). A study comparing screening results between nGS by exome sequencing and standard public health dried blood spot NBS found that the two modalities provided complementary information, with exome sequencing identifying genetic risk for conditions not detected through standard NBS in 9.4% of sequenced newborns (Wojcik et al., 2021). Additionally, although genomic sequencing has not been found to be adequately sensitive or specific to be an appropriate stand-alone screening test, combining standard NBS with nGS could increase the specificity of NBS and reduce the rates of false positives.(Bodian et al., 2016; Adhikari et al., 2020; Wojcik et al., 2021). In the same study comparing nGS and standard NBS results, nine infants were standard NBS positive but negative on exome sequencing. Seven of these infants were determined to be falsely positive on standard NBS (Wojcik et al., 2021).

Despite its potential, nGS raises both ethical concerns and implementation challenges that would need to be addressed before the integration of GS into existing NBS programs could be seriously considered (Pereira et al., 2021; Tarini 2021). In order to define and understand all relevant features of implementation, policy makers must consider input from many stakeholders, including parents. Consideration of parent perspectives is crucial in the development of ethical policies regarding the inclusion of nGS into NBS. Hypothetical parental interest in GS as a newborn screening tool has been reported (Goldenberg et al., 2014; Waisbren et al., 2015). However, opinions on many policy-relevant questions, such as whether all newborns should receive nGS, whether informed consent should be required (unlike most current NBS programs), and which types of results should be returned, have only recently started to be explored (Goldenberg et al., 2014; Lewis et al., 2018; Moultrie et al., 2020). In this paper, we present findings from surveys conducted with parents of healthy newborns who were enrolled in the BabySeq Project, a randomized clinical trial of nGS. We examine parental opinions regarding NBS and nGS universal application, parental informed consent, and types of nGS results to be disclosed that can inform discourse and policymaking regarding the addition of nGS to NBS.

MATERIALS AND METHODS

Study Participants and Design

The BabySeq Project is a series of randomized clinical trials designed to assess the medical, behavioral, and economic impact of nGS on infant care. The full study design of the first trial, from which we report results here, has been previously published (Holm et al., 2018). In the initial trial, two cohorts of parents and newborns were recruited to participate: parents with newborns admitted to the intensive care units (ICUs) at Brigham and Women's Hospital (BWH), Massachusetts General Hospital, and Boston's Children's Hospital; and parents with apparently healthy newborns admitted to the BWH Well Baby Nursery. Each family was randomly assigned to receive either the standard NBS and a detailed family history report only (control group), or the same plus their infant's exome sequencing report (nGS group). The exome sequencing report included monogenic disease risk results, i.e., pathogenic or likely pathogenic variants in approximately 1000 genes associated with actionable or non-

actionable childhood-onset conditions. Carrier status for recessive conditions was also returned. Monogenic disease risk results on highly actionable adult-onset conditions with available prevention strategies or treatment options that could impact outcome (as per the ACMG SF v2.0 list), as well as pharmacogenomic variants relevant during childhood, were also returned (Kalia et al., 2017). Adult-onset conditions were not included in the original study protocol but were later added in response to ethical concerns that arose around withholding actionable findings that may benefit the child by benefitting the parents or other family members (Holm et al., 2019). For participants enrolled after the protocol change, accepting results on actionable adult-onset conditions was a condition for enrollment. Participants who were enrolled prior to the change were contacted and given the option to consent to receive results related to adult-onset conditions (Holm et al., 2019). Reports were disclosed to families by a genetic counselor associated with the study before the reports were integrated into the electronic medical record and sent to pediatricians. Throughout the study, parents were surveyed on their experiences and their perspectives on the value of nGS. Surveys were administered at baseline, immediately post-disclosure, 3 months post-disclosure, and 10 months post-disclosure.

While the initial protocol involved limited recruitment of parents whose infants were in the ICUs, here we present findings only from surveys administered to parents enrolled from the healthy baby cohort, as this group is likely to be most representative of the general population of parents for whom population-based screening *via* nGS, to augment NBS, would be relevant. At baseline and 3 months post-disclosure, we assessed parental attitudes regarding whether every baby should receive NBS and GS at birth, whether informed consent should be required for these tests, and whether the state should require all newborns to receive GS at birth. We focus here on post-disclosure responses, as baseline survey results have been reported elsewhere, and this allows parents' responses to be informed by their participation in the study (Pereira et al., 2019). Further, we examine attitudes assessed at 3 months post-disclosure regarding the types of results parents would want to receive from GS.

Available data from both parents of a newborn from the first trial were included in the analytic data set, and missing values were not imputed. Baylor College of Medicine's Institutional Review Board (IRB), The Partners (now Mass General Brigham) Human Research Committee, and Boston Children's IRB approved all aspects of the BabySeq Project. This trial is registered at ClinicalTrials.gov (NCT02422511). The data supporting the assertions of this article will be made available by the authors upon request.

Measures

Parental attitudes regarding whether all newborns should receive, and whether informed consent should be required for, NBS and nGS, as well as whether nGS should be mandated, were assessed using five items in both the baseline and the 3-month post-disclosure surveys. This section of each survey began with a description of NBS and nGS. Novel survey items were designed to assess whether parents' agreed or disagreed with the following statements: *1*) every newborn should receive standard NBS, *2*) parental informed consent should be required for standard NBS, *3*) every newborn should receive genomic sequencing, *4*) parental informed consent should be required for genomic sequencing of a newborn, and *5*) the state should require that all newborns receive genomic sequencing. Responses were collected on a 5-point Likert-type scale ("agreement scale") from strongly disagree (=1) to strongly agree (=5).

Additionally, all parents were asked at 3 months post-disclosure how interested they would be in receiving the following types of information about their baby outside of the BabySeq Project, for example with their doctor or *via* a third-party service as a non-research participant. Options included: *1*) diseases that develop during *childhood* that can be prevented, treated or cured (i.e., actionable); *2*) diseases that develop during *childhood* that can NOT be prevented, treated, or cured, (i.e., non-actionable); *3*) diseases that develop during *adulthood* that can be prevented, treated, or cured; 4) diseases that develop during *adulthood* that can NOT be prevented, treated, or cured; *5*) carrier status, and *6*) variants of uncertain significance (VUSs). Carrier status was defined for parents as "information about genetic changes that my baby may have that would not cause disease in my baby but that he/she could potentially pass on to his or her own future children, or that could affect my other children." A VUS was defined for parents as "information that the researchers or doctors have not seen before or do not fully understand." For each type of information, parents were asked to indicate their interest on a 5-point Likert-type scale ("interest scale") from not at all interested (=1) to very interested (=5).

If a parent agreed or strongly agreed that every newborn should receive GS at 3 months post-disclosure, they were asked to indicate whether results in each of the categories described above (actionable and non-actionable childhood onset conditions, actionable and non-actionable adult-onset conditions, carrier status, and VUS) should be returned to parents, with multiple selections possible. This question was designed to assess parents' views on which results they felt were appropriate to include in screening reports to all newborn parents after mandated nGS screening, as this may differ from the types of results they would want for their own child (asked of all parents, as described in the previous paragraph).

We collected information about parents' demographic characteristics at baseline. Parents' political orientation was measured at 3 months post-disclosure using the 11-point political orientation scale from 0 to 10 with labels of Liberal (=0), Moderate (=5), and Conservative (=10) (Kroh 2007).

Data Analysis

Descriptive statistics were calculated for parents' demographic characteristics (at baseline and 3 months post-disclosure) and survey responses at 3 months post-disclosure. Responses to the 5-point agreement and interest scales were analyzed using Wilcoxon rank sum tests to compare parents' level of agreement with statements or interest in receiving various types of information from genomic sequencing between parents of families who were randomized to the control and

TABLE 1 | Demographic characteristics of parents who completed baseline and 3 months post-disclosure surveys.

	Control (*n* = 106)	nGS (*n* = 142)	Total (*n* = 248)	*p*-value
Gender				0.318
Female	62 (58.5%)	74 (52.1%)	136 (54.8%)	—
Male	44 (41.5%)	68 (47.9%)	112 (45.2%)	—
Race				0.299
Asian	8 (8.1%)	18 (14.1%)	26 (11.5%)	—
Black or African American	4 (4.0%)	2 (1.6%)	6 (2.6%)	—
More than one race	4 (4.0%)	2 (1.6%)	6 (2.6%)	—
Other	3 (3.0%)	2 (1.6%)	5 (2.2%)	—
White	80 (80.8%)	104 (81.2%)	184 (81.1%)	—
Ethnicity				0.098
Non-Hispanic	82 (90.1%)	115 (95.8%)	197 (93.4%)	—
Hispanic or Latino	9 (9.9%)	5 (4.2%)	14 (6.6%)	—
Education level				0.892
Less than Bachelor's	7 (6.6%)	10 (7.0%)	17 (6.9%)	—
Bachelor's or higher	99 (93.4%)	132 (93.0%)	231 (93.1%)	—
Household income				0.334
$0–$99,999	18 (17.1%)	19 (13.7%)	37 (15.2%)	—
≥ $100,000–199,999	47 (44.8%)	54 (38.8%)	101 (41.4%)	—
≥ $200,000	40 (38.1%)	66 (47.5%)	106 (43.4%)	—
Patient is parents' first child				0.133
No	48 (50.5%)	53 (40.5%)	101 (44.7%)	—
Yes	47 (49.5%)	78 (59.5%)	125 (55.3%)	—
Monogenic disease risk finding				
No monogenic disease risk	N/A	127 (89.4%)	127 (89.4%)	N/A
Monogenic disease risk finding	N/A	15 (10.6%)	15 (10.6%)	N/A

nGS, newborn genomic sequencing. NA, not applicable

nGS groups. For each attitude question asked at 3 months post-disclosure, we used paired sample t-tests to compare parents' responses regarding NBS to those regarding nGS. Additionally, attitudes assessed at 3-month post-disclosure were analyzed on the 5-point agreement scale by randomization arm and political orientation using Fisher's exact tests. To facilitate analysis, we combined responses on the political orientation scale to create three categories: liberal (0–3 on original scale), moderate (4–6), or conservative (7–10). We used repeated measures analysis of variance (ANOVA) to assess the effect of randomization arm on parents' attitudes regarding whether every newborn should receive each test at birth, whether informed consent should be required for each test, and whether the state should require that all newborns receive genomic sequencing at birth from baseline to 3 months post-disclosure. For ANOVA, Survey responses on the 5-point agreement scale were combined for "disagree" and "strongly disagree" (=1) and "agree" and "strongly agree" (=3) and analyzed on a 3-point scale with neither agree nor disagree as the midpoint (=2).

RESULTS

A total of 406 parents of 257 healthy newborns were enrolled in the healthy baby cohort and responded to demographic questions in the baseline survey (Pereira et al., 2019). Among these parents, 248 parents of 174 healthy newborns also submitted a survey at 3 months post-disclosure. Demographic characteristics did not differ between parents who responded at baseline and who responded at 3 months post-disclosure, except for educational attainment; a higher proportion of parents who responded at both time points had a bachelor's degree or higher (93%), compared to those who only responded at baseline (86%; p = 0.028). **Table 1** presents self-reported characteristics of parents who responded at 3 months post-disclosure. Thirty parents who responded to the 3 months post-disclosure survey did not respond to the baseline survey, and therefore their demographic characteristics are not available.

Parental Attitudes Regarding Standard NBS and nGS

Table 2 presents parents' attitudes regarding standard newborn screening and newborn genomic sequencing by study arm at 3 months post-disclosure. A majority of parents in both the control arm (96/122, 78.7%) and in the nGS arm (115/162, 71.0%) strongly agreed that every newborn should receive NBS. There was not a statistically significant interaction between the effect of study arm and time on agreement that every newborn should receive NBS ($F(1, 250) = 0.20$, $p = 0.655$). Average agreement among parents that every newborn should receive standard NBS (mean 4.67) was higher than that every newborn should receive GS (mean 3.60; $p < 0.001$). At 3 months post-disclosure, 18.5% (23/124) of parents in the control arm and 16.7% (27/162) of parents in the nGS arm strongly agreed that every newborn should receive nGS. There was no statistically significant interaction between study arm and time on agreement that every newborn should receive nGS ($F(1, 252) = 0.66$, p = 0.416). Parents' average agreement that informed consent should be required to perform NBS (mean 3.44) was lower than that for

TABLE 2 | Parents' attitudes regarding standard newborn screening and newborn genomic sequencing by study arm.

	Control	nGS	Total	*p*-value
Every newborn should receive standard newborn screening	*n* = 122	*n* = 162	*n* = 284	0.652
Strongly disagree	0 (0.0%)	1 (0.6%)	1 (0.4%)	—
Disagree	1 (0.8%)	2 (1.2%)	3 (1.1%)	—
Neither agree nor disagree	4 (3.3%)	7 (4.3%)	11 (3.9%)	—
Agree	21 (17.2%)	37 (22.8%)	58 (20.4%)	—
Strongly agree	96 (78.7%)	115 (71.0%)	211 (74.3%)	—
Every newborn should receive genomic sequencing	*n* = 124	*n* = 162	*n* = 286	0.435
Strongly disagree	3 (2.4%)	7 (4.3%)	10 (3.5%)	—
Disagree	10 (8.1%)	14 (8.6%)	24 (8.4%)	—
Neither agree nor disagree	43 (34.7%)	42 (25.9%)	85 (29.7%)	—
Agree	45 (36.3%)	72 (44.4%)	117 (40.9%)	—
Strongly agree	23 (18.5%)	27 (16.7%)	50 (17.5%)	—
The state should require that all newborns receive genomic sequencing at birth	*n* = 123	*n* = 159	*n* = 282	0.654
Strongly disagree	11 (8.9%)	13 (8.2%)	24 (8.5%)	—
Disagree	28 (22.8%)	41 (25.8%)	69 (24.5%)	—
Neither agree nor disagree	47 (38.2%)	52 (32.7%)	99 (35.1%)	—
Agree	23 (18.7%)	39 (24.5%)	62 (22.0%)	—
Strongly agree	14 (11.4%)	14 (8.8%)	28 (9.9%)	—
Parental informed consent should be required for standard newborn screening	*n* = 124	*n* = 162	*n* = 286	0.436
Strongly disagree	9 (7.3%)	19 (11.7%)	28 (9.8%)	—
Disagree	28 (22.6%)	26 (16.0%)	54 (18.9%)	—
Neither agree nor disagree	18 (14.5%)	30 (18.5%)	48 (16.8%)	—
Agree	33 (26.6%)	44 (27.2%)	77 (26.9%)	—
Strongly agree	36 (29.0%)	43 (26.5%)	79 (27.6%)	—
Parental informed consent should be required for genomic sequencing	*n* = 124	*n* = 161	*n* = 285	0.884
Strongly disagree	2 (1.6%)	4 (2.5%)	6 (2.1%)	—
Disagree	3 (2.4%)	6 (3.7%)	9 (3.2%)	—
Neither agree nor disagree	7 (5.6%)	12 (7.5%)	19 (6.7%)	—
Agree	51 (41.1%)	67 (41.6%)	118 (41.4%)	—
Strongly agree	61 (49.2%)	72 (44.7%)	133 (46.7%)	—

nGS (mean 4.27, $p < 0.001$). At 3 months post-disclosure, 29.0% (36/124) of parents in the control arm and 26.5% (43/162) of parents in the nGS arm strongly agreed that parental informed consent should be required for NBS, while 49.2% (61/124) of parents in the control arm and 44.7% (72/161) of parents in the nGS arm strongly agreed that parental informed consent should be required for nGS. There was not a statistically significant interaction between study arm and time on agreement that informed consent should be required for either NBS ($F(1, 251) = 0.52$, $p = 0.470$) or for nGS ($F(1, 250) = 0.07$, $p = 0.794$).

Parents' opinions were divided as to whether states should require nGS in a manner similar to state mandated NBS. Overall, while 9.9% of parents strongly agreed that the state should require nGS, 8.5% strongly disagreed, and 35.1% of parents neither agreed nor disagreed. Only 11.4% (14/123) of parents in the control arm and 8.8% (14/159) of parents in the nGS arm agreed that the state should require that all newborns receive genomic sequencing at birth. There was not a statistically significant interaction between study arm and time on agreement that the state should require that all newborns receive genomic sequencing at birth ($F(1, 248) = 1.74$, $p = 0.187$).

Parents' attitudes regarding NBS and nGS were not associated with self-reported political orientation (**Table 3**). Strong agreement that every newborn should receive standard NBS was high among self-identified liberals (77.6%), moderates (78.5%), and conservatives (74.3%; $p = 0.187$). While 26.4% of liberals, 34.2% of moderates, and 20.0% of conservatives strongly agreed that informed consent should be required for NBS ($p = 0.359$), 48.5, 50.6, and 26.7%, respectively, strongly agreed that informed consent should be required for nGS ($p = 0.247$).

Parent Preferences on Results

At 3 months post-disclosure, parents indicated their interest in receiving several possible types of GS results for their baby if their baby were to receive GS outside of the BabySeq Project (**Table 4**). A majority of parents reported being very interested in receiving information on their baby's risk of developing a disease in *childhood* that can be prevented, treated, or cured (86.8%); risk of developing a disease during *childhood* that can NOT be prevented, treated, or cured (50.7%), baby's risk of developing a disease during *adulthood* that can be prevented, treated, or cured (84.6%); and carrier status (70.8%). Only 42.0% of parents reported being very interested in receiving VUS results, and only 47.7% reported being very interested in learning their baby's risk of developing a disease during *adulthood* that can NOT be prevented, treated, or cured. There were no differences in interest levels for receiving any result type between the control and nGS group (all $p > 0.144$).

Among parents who strongly agreed or agreed that every newborn should receive nGS at 3 months post-disclosure ($n = 167$), the most frequently selected categories of findings that should be returned to parents were actionable findings in childhood (98.8%) and adulthood (94.0%; **Figure 1**).

TABLE 3 | Parents' attitudes regarding newborn screening and genomic sequencing by political orientation.

	Liberal	Moderate	Conservative	*p*-value
Every newborn should receive standard newborn screening	*n* = 161	*n* = 79	*n* = 30	0.187
Strongly disagree	1 (0.6%)	0 (0.0%)	0 (0.0%)	—
Disagree	2 (1.2%)	1 (1.3%)	0 (0.0%)	—
Neither agree nor disagree	4 (2.5%)	3 (3.8%)	3 (10.0%)	—
Agree	29 (18.0%)	13 (16.5%)	10 (33.3%)	—
Strongly agree	125 (77.6%)	62 (78.5%)	17 (56.7%)	—
Every newborn should receive genomic sequencing	*n* = 163	*n* = 79	*n* = 30	0.448
Strongly disagree	5 (3.1%)	4 (5.1%)	0 (0.0%)	—
Disagree	18 (11.0%)	6 (7.6%)	0 (0.0%)	—
Neither agree nor disagree	49 (30.1%)	22 (27.8%)	10 (33.3%)	—
Agree	67 (41.1%)	30 (38.0%)	13 (43.3%)	—
Strongly agree	24 (14.7%)	17 (21.5%)	7 (23.3%)	—
The state should require that all newborns receive genomic sequencing at birth	*n* = 163	*n* = 79	*n* = 30	0.354
Strongly disagree	10 (6.1%)	9 (11.4%)	3 (10.0%)	—
Disagree	40 (24.5%)	20 (25.3%)	7 (23.3%)	—
Neither agree nor disagree	66 (40.5%)	20 (25.3%)	9 (30.0%)	—
Agree	34 (20.9%)	19 (24.1%)	7 (23.3%)	—
Strongly agree	13 (8.0%)	11 (13.9%)	4 (13.3%)	—
Parental informed consent should be required for standard newborn screening	*n* = 163	*n* = 79	*n* = 30	0.359
Strongly disagree	17 (10.4%)	7 (8.9%)	2 (6.7%)	—
Disagree	34 (20.9%)	14 (17.7%)	5 (16.7%)	—
Neither agree nor disagree	30 (18.4%)	7 (8.9%)	8 (26.7%)	—
Agree	39 (23.9%)	24 (30.4%)	9 (30.0%)	—
Strongly agree	43 (26.4%)	27 (34.2%)	6 (20.0%)	—
Parental informed consent should be required for genomic sequencing of a newborn	*n* = 163	*n* = 79	*n* = 30	0.247
Strongly disagree	4 (2.5%)	1 (1.3%)	1 (3.3%)	—
Disagree	5 (3.1%)	3 (3.8%)	1 (3.3%)	—
Neither agree nor disagree	13 (8.0%)	3 (3.8%)	1 (3.3%)	—
Agree	62 (38.0%)	32 (40.5%)	19 (63.3%)	—
Strongly agree	79 (48.5%)	40 (50.6%)	8 (26.7%)	—

DISCUSSION

In this analysis of survey responses from parents of healthy newborns in the BabySeq Project, parents were more supportive of every newborn receiving NBS than receiving nGS. We found no significant difference in nGS support between parents in the control arm and parents who had experienced receiving nGS results for their newborn, and results suggest that the experience of receiving nGS results did not affect parents' attitudes over time. While a majority of parents supported the notion that every newborn should receive GS, only a minority thought that the state should require nGS. Additionally, a larger proportion of parents agreed that parental informed consent should be required for nGS than for standard NBS. Previous studies examining parent attitudes toward standard NBS and nGS have also reported parent concern about not requiring informed consent for nGS, increased parent support for standard NBS compared to nGS, and disagreement between parents about which results should be reported (Bombard et al., 2014; Joseph et al., 2016; Lewis et al., 2018; Moultrie et al., 2020). Though most parents indicated they would be interested in receiving all available result types if their baby received GS outside the BabySeq Project, enthusiasm varied among result types.

NGS in newborns may provide health benefits and information complementary to standard NBS. A previously published study from the BabySeq Project showed that families experienced no sustained negative psychosocial effects from participating in the GS process or receiving results, a concern frequently raised in the discussion surrounding the addition of nGS (Pereira et al., 2021; Wojcik et al., 2021). However, even highly successful programs like standard NBS can come under scrutiny if policies are not acceptable to parents (National Institute of Child Health and Human Development 2017). It is critical to consider parent buy-in before implementing policies that impact NBS programs; not doing so may risk negatively affecting parent trust, participation, and thus the overall success of the program.

Even among our group of parents who had enough interest in nGS to volunteer to participate in the BabySeq Project, a majority of parents thought informed consent should be required for nGS and many were still hesitant about adding nGS to current state mandated NBS programs. Considering that parents who participated in the BabySeq Project may likely be more supportive of nGS than the average parent, our study results suggest that implementing nGS without addressing parental concerns could create parent backlash. Another study comparing parent views on nGS vs standard NBS in Canada came to a similar conclusion after finding parents were significantly less willing to participate in a NBS program that included whole genome or exome sequencing (Bombard et al., 2014). Notably, a majority of our parents thought that informed consent should also be required for standard NBS, which is not legally required in most states. It may be possible that, although

TABLE 4 | Parents' attitudes regarding desired results from newborn genomic sequencing by study arm.

	Control	nGS	Total	*p*-value
My baby's risk of developing a disease during childhood that can be prevented, treated, or cured	*n* = 124	*n* = 163	*n* = 287	0.809
Not at all interested	1 (0.8%)	0 (0.0%)	1 (0.3%)	—
Not very interested	1 (0.8%)	1 (0.6%)	2 (0.7%)	—
Neutral	4 (3.2%)	5 (3.1%)	9 (3.1%)	—
Somewhat interested	11 (8.9%)	15 (9.2%)	26 (9.1%)	—
Very interested	107 (86.3%)	142 (87.1%)	249 (86.8%)	—
My baby's risk of developing a disease during childhood that can NOT be prevented, treated, or cured	*n* = 125	*n* = 163	*n* = 288	0.201
Not at all interested	7 (5.6%)	5 (3.1%)	12 (4.2%)	—
Not very interested	9 (7.2%)	9 (5.5%)	18 (6.2%)	—
Neutral	15 (12.0%)	17 (10.4%)	32 (11.1%)	—
Somewhat interested	35 (28.0%)	45 (27.6%)	80 (27.8%)	—
Very interested	59 (47.2%)	87 (53.4%)	146 (50.7%)	—
My baby's risk of developing a disease during adulthood that can be prevented, treated, or cured	*n* = 124	*n* = 161	*n* = 285	0.976
Not at all interested	1 (0.8%)	0 (0.0%)	1 (0.4%)	—
Not very interested	1 (0.8%)	2 (1.2%)	3 (1.1%)	—
Neutral	3 (2.4%)	4 (2.5%)	7 (2.5%)	—
Somewhat interested	14 (11.3%)	19 (11.8%)	33 (11.6%)	—
Very interested	105 (84.7%)	136 (84.5%)	241 (84.6%)	—
My baby's risk of developing a disease during adulthood that can NOT be prevented, treated, or cured	*n* = 124	*n* = 161	*n* = 285	0.144
Not at all interested	7 (5.6%)	10 (6.2%)	17 (6.0%)	—
Not very interested	18 (14.5%)	8 (5.0%)	26 (9.1%)	—
Neutral	11 (8.9%)	19 (11.8%)	30 (10.5%)	—
Somewhat interested	34 (27.4%)	42 (26.1%)	76 (26.7%)	—
Very interested	54 (43.5%)	82 (50.9%)	136 (47.7%)	—
Carrier status	*n* = 125	*n* = 163	*n* = 288	0.556
Not at all interested	2 (1.6%)	2 (1.2%)	4 (1.4%)	—
Not very interested	2 (1.6%)	2 (1.2%)	4 (1.4%)	—
Neutral	10 (8.0%)	7 (4.3%)	17 (5.9%)	—
Somewhat interested	24 (19.2%)	35 (21.5%)	59 (20.5%)	—
Very interested	87 (69.6%)	117 (71.8%)	204 (70.8%)	—
Variants of uncertain significance	*n* = 125	*n* = 161	*n* = 286	0.967
Not at all interested	4 (3.2%)	9 (5.6%)	13 (4.5%)	—
Not very interested	13 (10.4%)	10 (6.2%)	23 (8.0%)	—
Neutral	25 (20.0%)	33 (20.5%)	58 (20.3%)	—
Somewhat interested	30 (24.0%)	42 (26.1%)	72 (25.2%)	—
Very interested	53 (42.4%)	67 (41.6%)	120 (42.0%)	—

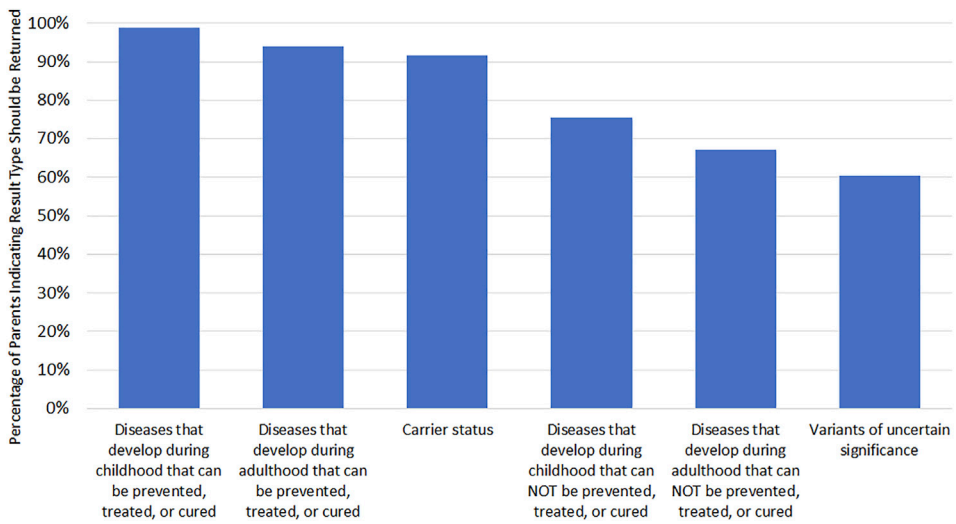

FIGURE 1 | Attitudes toward results types to be returned to parents if every newborn received GS. Only asked if parent agreed or strongly agreed that every newborn should receive GS (*n* = 167). Respondents could select multiple options.

parents may ideally want an informed consent process, they tolerate a lack of informed consent because such a strong majority feel that every newborn should receive standard NBS. However, nGS does not share this same level of support in our study sample.

One approach to accommodate parents' preferences while preserving participation in current newborn screening programs would be for nGS to be an optional addition to state mandated NBS that requires explicit informed consent. This optional add-on consent model gives the opportunity for counseling on GS screening to ensure parents understand the capacity, utility, and limitations of GS. This approach was successfully implemented for expanded NBS using tandem mass spectrometry. For example, when Massachusetts added mass spectrometry to their NBS program as an optional add-on program in 1999, 98% of parents chose to participate, prompting other states to expand their newborn screening programs (Marsden 2003). More recent studies examining newborn genetic screening for SMA and Duchenne Muscular Dystrophy have also used this model and experienced high parent participation rates (Kraszewski et al., 2017; Parad et al., 2021). While an optional add-on model could help demonstrate the health benefits of GS screening without compromising existing mandated public health programs, it induces the burden of additional informed consent and documentation on hospital staff. One California study examining the introduction of mass spectrometry to NBS that required informed consent demonstrated significant burden of documentation, resulting in many families not being offered the additional screening (Feuchtbaum et al., 2007). If hospital systems are not prepared to incur the burden of additional screening, increased documentation, follow-up and parent counseling that would be required to incorporate nGS into NBS, the addition of these programs may fail to produce the desired result and overall compromise parent satisfaction and trust. There are also concerns that requiring informed consent for any portion of the NBS may reduce overall participation rates (Davis et al., 2006; Feuchtbaum et al., 2007).

Interestingly, while other studies have found some association between political orientation and interest in genomic sequencing (Dodson et al., 2015), political orientation was not significantly associated with opinions of whether states should require GS in our study. This suggests that it may be possible to garner bipartisan support for policies regarding nGS. Finally, there is the issue of what results should be returned to parents. In our study, there was variation among parents on which nGS results they would want to receive. Differences in parent preferences may best be supported by an informed consent model that incorporates parental choice about the return of results, although this would likely be highly burdensome to NBS programs. Parent preferences may also not align with what results professional guidelines deem ethically justified to report for minors. NBS mandates are justified on the ethical basis that screening in the newborn period provides the opportunity to initiate early intervention after birth to prevent harm, and they are justified on the legal basis that significant public health benefits provide a compelling government interest. To maintain this justification, genetic testing results should only be disclosed if there is clear clinical value (Ross et al., 2013; Botkin et al., 2015). However, not all GS results have the promise of early or even certain direct benefit to the child being tested (Timmermans and Buchbinder 2010; Berg and Powell 2015; Johnston et al., 2018; Lewis 2019). The contrast between which results are considered ethical to return and which results parents want may pose challenges if whole genome or exome sequencing is used for nGS, as parents may be able to invoke a legal right to the entirety of their child's genomic data.

Our results should be considered within the limitations of our study. Study participants were parents willing to participate in a genomics study from three hospitals in the Boston, Massachusetts area. As such, opinions may differ significantly between study participants and the general population. It is also important to note that our study demographics are not representative of the general US population, with a high proportion of non-Hispanic white individuals, high household income, and high educational attainment. Representative surveys are warranted to provide more generalizable information suited to inform federal and state policy discussions. The second iteration of the BabySeq Project, BabySeq2, currently underway, will prioritize the inclusion of a more racially, ethnically, and geographically diverse cohort of families (https://www.genomes2people.org/research/babyseq/) and will provide additional data on parents' attitudes. Finally, our surveys were not designed to capture nuanced views; it is possible that parents may have expressed more tempered attitudes toward screening and results types in interviews or focus groups.

Currently, the NBS program has parents' trust and near universal participation. Any policies created to expand the NBS program to include nGS should strive to protect this trust and preserve parent support by considering parent values. We propose that should nGS be added to current NBS programs, parent values could be respected if it were initially added as an optional supplemental screen that requires an informed consent process with preservation of the default mandatory NBS using traditional methods.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by Baylor College of Medicine's Institutional Review Board (IRB), The Partners (now Mass General Brigham) Human Research Committee, and Boston Children's IRB. Participants provided written informed consent.

AUTHOR CONTRIBUTIONS

BA, SP, and HS designed the project and contributed to interpretation of the results. HS conducted the statistical analysis. BA took the lead in writing the first draft of the manuscript. SP and HS oversaw all aspects of the project. SP, BA, AM, JR, KC, and RP provided input on analysis. All authors contributed to the framing of the manuscript, revised the work critically for intellectual content, agreed to be named as authors, and agreed to be accountable for all aspects of the work.

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REFERENCES

Adhikari, A. N., Gallagher, R. C., Wang, Y., Currier, R. J., Amatuni, G., Bassaganyas, L., et al. (2020). The Role of Exome Sequencing in Newborn Screening for Inborn Errors of Metabolism. *Nat. Med.* 26, 1392–1397. doi:10.1038/s41591-020-0966-5

Baby's First Test (2021). Newborn Screening 101. Available at: https://www.babysfirsttest.org/newborn-screening/screening-101 (Accessed May 26, 2021).

Berg, J. S., and Powell, C. M. (2015). Potential Uses and Inherent Challenges of Using Genome-Scale Sequencing to Augment Current Newborn Screening. *Cold Spring Harb. Perspect. Med.* 5 (12), a023150. doi:10.1101/cshperspect.a023150

Bodian, D. L., Klein, E., Iyer, R. K., Wong, W. S. W., Kothiyal, P., Stauffer, D., et al. (2016). Utility of Whole-Genome Sequencing for Detection of Newborn Screening Disorders in a Population Cohort of 1,696 Neonates. *Genet. Med.* 18 (3), 221–230. doi:10.1038/gim.2015.111

Bombard, Y., Miller, F. A., Hayeems, R. Z., Barg, C., Cressman, C., Carroll, J. C., et al. (2014). Public Views on Participating in Newborn Screening Using Genome Sequencing. *Eur. J. Hum. Genet.* 22 (11), 1248–1254. doi:10.1038/ejhg.2014.22

Botkin, J. R., Belmont, J. W., Berg, J. S., Berkman, B. E., Bombard, Y., Holm, I. A., et al. (2015). Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am. J. Hum. Genet.* 97 (3), 501. doi:10.1016/j.ajhg.2015.07.013

CDC (2020). Newborn Screening. Available at: https://www.cdc.gov/nceh/features/newbornscreening-program/index.html#:~:text=This%20process%2C%20known%20as%20newborn,the%20laboratory%20is%20CDC's%20NSQAP (Accessed July 15, 2021).

Cipriano, L. E., Rupar, C. A., and Zaric, G. S. (2007). The Cost-Effectiveness of Expanding Newborn Screening for up to 21 Inherited Metabolic Disorders Using Tandem Mass Spectrometry: Results from a Decision-Analytic Model. *Value in Health* 10 (2), 83–97. doi:10.1111/j.1524-4733.2006.00156.x

Davis, T. C., Humiston, S. G., Arnold, C. L., Bocchini, J. A., Bass, P. F., Kennen, E. M., 3rd, et al. (2006). Recommendations for Effective Newborn Screening Communication: Results of Focus Groups with Parents, Providers, and Experts. *Pediatrics* 117 (5 Pt 2), S326–S340. doi:10.1542/peds.2005-2633M

Dodson, D. S., Goldenberg, A. J., Davis, M. M., Singer, D. C., and Tarini, B. A. (2015). Parent and Public Interest in Whole-Genome Sequencing. *Public Health Genomics* 18 (3), 151–159. doi:10.1159/000375115

Feuchtbaum, L., Cunningham, G., and Sciortino, S. (2007). Questioning the Need for Informed Consent: A Case Study of California's Experience with a Pilot Newborn Screening Research Project. *J. Empirical Res. Hum. Res. Ethics* 2 (3), 3–14. doi:10.1525/jer.2007.2.3.3

Genetic Alliance and District of Columbia Department of Health (2010). *Chapter 4 Newborn Screening*. in *Understanding Genetics: A District of Columbia Guide for Patients and Health Professionals*. Washington, DC: Genetic Alliance.

Goldenberg, A. J., Dodson, D. S., Davis, M. M., and TarinI, B. A. (2014). Parents' Interest in Whole-Genome Sequencing of Newborns. *Genet. Med.* 16 (1), 78–84. doi:10.1038/gim.2013.76

Groft, S. C., Taruscio, D., and Posada de la Paz, M. (2017). *Rare Diseases Epidemiology: Update and Overview*. New York: Springer International Publishing.

Holm, I. A., Mcguire, A., Pereira, S., Rehm, H., Green, R. C., and Beggs, A. H. (2019). Returning a Genomic Result for an Adult-Onset Condition to the Parents of a Newborn: Insights from the BabySeq Project. *Pediatrics* 143 (Suppl. 1), S37–S43. doi:10.1542/peds.2018-1099H

Holm, I. A., Agrawal, P. B., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18 (1), 225. doi:10.1186/s12887-018-1200-1

Johnson, T., and Wile, M. (2017). State Newborn Health Screening Policies. Available at: https://www.ncsl.org/research/health/state-newborn-health-screening-policies.aspx (Accessed July 13, 2021).

Johnston, J., Lantos, J. D., Goldenberg, A., Chen, F., Parens, E., and Koenig, B. A. (2018). Sequencing Newborns:A Call for Nuanced Use of Genomic Technologies. *Hastings Cent. Rep.* 48 (S2), S2–S6. doi:10.1002/hast.874

Joseph, G., Chen, F., Harris-Wai, J., Puck, J. M., Young, C., and Koenig, B. A. (2016). Parental Views on Expanded Newborn Screening Using Whole-Genome Sequencing. *Pediatrics* 137, S36–S46. doi:10.1542/peds.2015-3731h

Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., et al. (2017). Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): a Policy Statement of the American College of Medical Genetics and Genomics. *Genet. Med.* 19 (2), 249–255. doi:10.1038/gim.2016.190

Koppaka, R. (2011). Ten Great Public Health Achievements — United States, 2001-2010. *Morb. Mortal. Wkly. Rep.* 60 (19), 619–623.

Kraszewski, J. N., Kay, D. M., Stevens, C. F., Koval, C., Haser, B., Ortiz, V., et al. (2017). Pilot Study of Population-Based Newborn Screening for Spinal Muscular Atrophy in New York State. *Genet. Med.* 20 (6), 608–613. doi:10.1038/gim.2017.152

Kroh, M. (2007). Measuring Left-Right Political Orientation: The Choice of Response Format. *Public Opin. Q.* 71 (2), 204–220. doi:10.1093/poq/nfm009

Lewis, M. A., Stine, A., Paquin, R. S., Mansfield, C., Wood, D., Rini, C., et al. (2018). Parental Preferences toward Genomic Sequencing for Non-medically

Actionable Conditions in Children: a Discrete-Choice experiment. *Genet. Med.* 20 (2), 181–189. doi:10.1038/gim.2017.93

Lewis, M. H., and Botkin, J. R. (2019). "Newborn Screening in the United States: Ethical Issues," in *The Oxford Handbook of Public Health Ethics*. Editor A. C. Mastroianni (Oxford University Press), 653–664. doi:10.1093/oxfordhb/9780190245191.013.59

Lewis, T. (2019). 23 and Baby. *Nature* 576 (7785), S8–S12. doi:10.1038/d41586-019-03715-w

Marsden, D. (2003). Expanded Newborn Screening by Tandem Mass Spectrometry: the Massachusetts and New England Experience. *Southeast. Asian J. Trop. Med. Public Health* 34 Suppl 3 (Suppl. 3), 111–114.

Moultrie, R. R., Paquin, R., Rini, C., Roche, M. I., Berg, J. S., Powell, C. M., et al. (2020). Parental Views on Newborn Next Generation Sequencing: Implications for Decision Support. *Matern. Child. Health J.* 24 (7), 856–864. doi:10.1007/s10995-020-02953-z

National Institute of Child Health and Human Development (2017). How many Newborns Are Screened in the united states? Available at: https://www.nichd.nih.gov/health/topics/newborn/conditioninfo/infants-screened (Accessed July 15, 2021).

Parad, R. B., Sheldon, Y., and Bhattacharjee, A. (2021). Implementation of Hospital-Based Supplemental Duchenne Muscular Dystrophy Newborn Screening (sDMDNBS): a Pathway to Broadening Adoption. *Ijns* 7 (4), 77. doi:10.3390/ijns7040077

Pereira, S., Robinson, J. O., Gutierrez, A. M., Petersen, D. K., Hsu, R. L., Lee, C. H., et al. (2019). Perceived Benefits, Risks, and Utility of Newborn Genomic Sequencing in the Babyseq Project. *Pediatrics* 143 (Suppl. 1), S6–S13. doi:10.1542/peds.2018-1099C

Pereira, S., Smith, H. S., Frankel, L. A., Christensen, K. D., Islam, R., Robinson, J. O., et al. (2021). Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project. *JAMA Pediatr.* 175 (11), 1132–1141. doi:10.1001/jamapediatrics.2021.2829

Ross, L. F., Saal, H. M., David, K. L., and Anderson, R. R. (2013). Technical Report: Ethical and Policy Issues in Genetic Testing and Screening of Children. *Genet. Med.* 15 (3), 234–245. doi:10.1038/gim.2012.176

Tarini, B. A. (2021). The Effect of BabySeq on Pediatric and Genomic Research-More Than Baby Steps. *JAMA Pediatr.* 175 (11), 1107–1108. doi:10.1001/jamapediatrics.2021.2826

Therrell, B. L., Padilla, C. D., Loeber, J. G., Kneisser, I., Saadallah, A., Borrajo, G. J. C., et al. (2015). Current Status of Newborn Screening Worldwide: 2015. *Semin. Perinatology* 39, 171–187. doi:10.1053/j.semperi.2015.03.002

Timmermans, S., and Buchbinder, M. (2010). Patients-in-Waiting. *J. Health Soc. Behav.* 51 (4), 408–423. doi:10.1177/0022146510386794

Waisbren, S. E., Bäck, D. K., Liu, C., Kalia, S. S., Ringer, S. A., Holm, I. A., et al. (2015). Parents Are Interested in Newborn Genomic Testing during the Early Postpartum Period. *Genet. Med.* 17 (6), 501–504. doi:10.1038/gim.2014.139

Wojcik, M. H., Zhang, T., Ceyhan-Birsoy, O., Genetti, C. A., Lebo, M. S., Yu, T. W., et al. (2021). Discordant Results between Conventional Newborn Screening and Genomic Sequencing in the BabySeq Project. *Genet. Med.* 23 (7), 1372–1375. doi:10.1038/s41436-021-01146-5

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Education and Consent for Population-Based DNA Screening: A Mixed-Methods Evaluation of the Early Check Newborn Screening Pilot Study

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A challenge in implementing population-based DNA screening is providing sufficient information, that is, understandable and acceptable, and that supports informed decision making. Early Check is an expanded newborn screening study offered to mothers/guardians whose infants have standard newborn screening in North Carolina. We developed electronic education and consent to meet the objectives of feasibility, acceptability, trustworthiness, and supporting informed decisions. We used two methods to evaluate Early Check among mothers of participating infants who received normal results: an online survey and interviews conducted via telephone. Survey and interview domains included motivations for enrollment, acceptability of materials and processes, attitudes toward screening, knowledge recall, and trust. Quantitative analyses included descriptive statistics and assessment of factors associated with knowledge recall and trust. Qualitative data were coded, and an inductive approach was used to identify themes across interviews. Survey respondents (n = 1,823) rated the following as the most important reasons for enrolling their infants: finding out if the baby has the conditions screened (43.0%), and that no additional blood samples were required (20.1%). Interview respondents (n = 24) reported the value of early knowledge, early intervention, and ease of participation as motivators. Survey respondents rated the study information as having high utility for decision making (mean 4.7 to 4.8 out of 5) and 98.2% agreed that they had sufficient information. Knowledge recall was relatively high (71.8–92.5% correct), as was trust in Early Check information (96.2% strongly agree/agree). Attitudes about Early Check screening were positive (mean 0.1 to 0.6 on a scale of 0–4, with lower scores indicating more positive attitudes) and participants did not regret participation (e.g., 98.6% strongly agreed/agreed Early Check was the right decision). Interview respondents further reported positive attitudes about Early Check materials and processes. Early Check provides a model for education and consent in large-scale DNA screening. We found evidence of high acceptability, trustworthiness and knowledge recall, and positive attitudes among

respondents. Population-targeted programs need to uphold practices that result in accessible information for those from diverse backgrounds. Additional research on those who do not select screening, although ethically and practically challenging, is important to inform population-based DNA screening practices.

Keywords: informed consent, electronic consent, newborn screening, DNA screening, participant attitudes, evaluation

1 INTRODUCTION

Precision public health implements DNA-based screening to identify individuals with specific characteristics and then target relevant interventions. Achieving the promise of equitable precision public health necessitates a basic understanding of genetic concepts among those offered DNA-based screening. Well-established challenges include the complexity of genetic and genomic information (Morgenstern et al., 2015) together with the relatively low health (Greenberg et al., 2007) and genomic literacy (Hurle et al., 2013) among U.S. residents.

Population-based DNA-based screening also creates feasibility challenges associated with scale. It is impractical for professionals to use traditional, face-to-face approaches to education and informed consent when implementing screening in public health and large-scale research settings. Electronic, user-driven approaches may improve practicability by alleviating professional and administrative burden, by making educational content more accessible to the target population, and through increasing the consistency of information provision. The development of end-user-focused education and informed consent procedures is critical to the success and feasibility of public health integration of genetics and genomics.

Early Check is a voluntary, large-scale expanded newborn screening (NBS) research study in North Carolina, established to address substantial gaps in newborn screening evidence and to inform policy (Bailey et al., 2019). The study is led by researchers at RTI International, in partnership with the University of North Carolina at Chapel Hill, the North Carolina State Laboratory of Public Health (NCSLPH), Duke University, and Atrium Health Wake Forest Baptist (formerly Wake Forest Baptist Medical Center). Early Check offers new and expectant mothers or legal guardians screening for conditions that are not currently included in state NBS; the Early Check panel has included spinal muscular atrophy (SMA), fragile X syndrome (FXS), and Duchenne muscular dystrophy (DMD). Early Check currently does not use sequencing in the initial screening. Targeted genetic analysis was used for SMA and FXS, and creatine kinase isoenzyme (CK-MM) was used for DMD screening.

Babies who receive NBS through the NCSLPH and live in North or South Carolina are eligible for participation in Early Check. Mothers or legal guardians can enroll if they are at least 13 weeks pregnant or have a baby up to 4 weeks of age. All mothers or legal guardians who have given birth in North Carolina and whose babies have newborn screening are mailed an invitation letter and flyer from the NCSLPH. Collaboration with partners at University of North Carolina at Chapel Hill and Duke University supports in-person recruitment at those affiliated birthing hospitals and prenatal invitations sent via MyChart. Early Check also has a social media presence via Facebook, Twitter, and Pinterest.

The research screening is done using residual dried blood spots obtained for standard NBS and retained by the NCSLPH (North Carolina Department of Health and Human Services, 2020). The Institutional Review Board at the University of North Carolina at Chapel Hill determined that the Early Check study is minimal risk; thus, only the mother is required to give permission for the child to participate, though the study materials encourage both parents to be involved in the decision making, as relevant. Because traditional education and consent approaches are impracticable given the approximately 1,20,000 births per year in North Carolina, the study team developed a user-driven, participant-centered digital education and electronic consent approach. Our development objectives were:

- Feasibility for the research team;
- Acceptability and trustworthiness for potential participants; and
- Supportive of informed decision-making.

Electronic consent refers to the use of digital means to obtain informed consent from potential study participants. The U.S. Food and Drug Administration (2015) defines this as "the use of electronic systems and processes that may employ multiple electronic media, including text, graphics, audio, video, podcasts, passive, and interactive Web sites …. to convey information related to the study and to obtain and document informed consent." Electronic consent may enhance knowledge and engagement of study participants in comparison to traditional informed consent, and improve quality and consistency of the consent process (Rowbotham et al., 2013; Rothwell et al., 2014; Simon et al., 2016; Cadigan et al., 2017; Buckley et al., 2018; Biesecker et al., 2019). Additionally, electronic consent leverages digital tools to improve visual clarity and focus on content most important to decision making and reduces the length, complexity, and literacy demand of consent materials. Such approaches may be more engaging, participant-centered, and help address long-reported issues with standard informed consent (Biesecker et al., 2019; Grant, 2021).

Early Check's approach was created by a multidisciplinary team that included experts in health communication, informed consent, clinical genetics, behavioral science, user interface development, and bioethics. We employed user-centered design that integrated community engagement and rounds of formative research with diverse participants. The resulting electronic consent includes 16 screens with core information

TABLE 1 | Early Check electronic consent overview.

Section title	Components in addition to standard text
Welcome to Early Check! Let's get started!	Video; Eligibility screener; Visual overview of e-consent process
How is Early Check done? What health problems does Early Check look for in newborns? What happens when parents get results from Early Check?	Video; Infographic Learn more about [condition name] from our experts Information for parents of twins or multiple babies
Do you have to pay for Early Check?	
How is Early Check different from state newborn screening? Are the screening tests perfect? How is your information protected and shared?	Learn more about regular North Carolina newborn screening from our experts Learn more about Early Check's false positive rates; Learn more about screening tests from our experts Learn more about protecting information from our experts
Why might you say Yes to Early Check? And why might you say No?	Video; Interactive checklist
Let's Review Agreement and electronic signature	Review questions, multiple choice format with correct responses shown and explained Option to continue to electronic signature page, or take more time to decide (with option to enter email address to receive a reminder) or to contact study team with questions

presented in lay language, and which offer additional detail in layered (optional) content. The electronic consent includes an interactive eligibility tool and employs simple graphics, infographics, and videos. The content provides a brief values clarification that provides reasons a mother might participate or decline. It concludes with summarizing self-assessment questions. All screens include optional voiceover to reduce literacy demands, options for contacting the study team, and a list of the collaborating institutions. The electronic consent sections and a brief description of section components (in addition to standard text elements) are described in **Table 1**.

All materials are available in English and Spanish. We developed the education and consent process so that it does not require investigator involvement unless clarification or assistance is requested by a parent. A copy of the Early Check e-consent content is available for reader review: https://testportal.earlycheck.org/. Here we present results from an evaluation of the Early Check electronic education and consent.

2 MATERIALS AND METHODS

We implemented a mixed-methods evaluation using data from mothers or legal guardians who enrolled their newborns in Early Check. Our survey aims were to assess, among mothers who chose to enroll their child and received a normal result:

- Motivation for enrolling the child in Early Check,
- Whether the process was acceptable and information sufficient,
- Attitudes about Early Check screening and participation in the research,
- Knowledge recall of key facts about Early Check, and
- The degree to which Early Check was perceived as trustworthy.

For knowledge recall and trust, an additional aim was to determine whether there were differences based on race/ethnicity and educational attainment. We also tested our hypothesis that trust ratings would be higher in those who rated themselves as sufficiently informed to make the decision to enroll in Early Check, those with more positive attitudes toward screening, and those with higher knowledge recall.

The evaluation also included semi-structured interviews with mothers of infants enrolled in Early Check to explore similar concepts in more depth and to allow for the emergence of unexpected attitudes or experiences with the study.

2.1 Inclusion and Recruitment

Between 7/7/2020 and 11/17/2021, mothers aged 18 or older whose child received a normal Early Check screening result were invited to participate in the evaluation survey. Interviews were conducted between 7/13/2020 and 8/31/2020 with mothers who met the same criteria. These evaluation efforts were directed to mothers of children with normal results. We are also conducting mixed-methods research, which is still underway and will be reported separately, on parents whose children received an abnormal, actionable result. Given the different experience and level of engagement that families of screen positive infants have with Early Check, the assessment of parents whose children receive an abnormal result is conducted using a longitudinal, mixed methods approach, with greater depth to the questioning about the impact of the study result.

Participants were recruited via email and the Early Check return of results website. Those who completed the survey were entered in a monthly drawing to receive a $20 gift card, and all interview participants received a $20 gift card.

The evaluation activities were approved by the University of North Carolina at Chapel Hill Institutional Review Board as a modification to the overall Early Check study (#18–0009).

2.2 Evaluation Survey

The evaluation survey was a 36-question questionnaire conducted online. The survey instrument included the following constructs and demographic questions.

2.2.1 Motivations for Enrolling the Baby in Early Check

Respondents were asked to select the reasons they enrolled their baby in Early Check, using response options informed by the consent information and prior formative research (Peay et al., 2018). Respondents first chose up to three responses from the following options: "It was free," "To help babies in the future," "It was easy to sign up," "It did not require a doctor visit," "There were not additional blood samples taken from my baby," "To find out if my baby has the conditions screened," "For my peace of mind," "To help research," "I don't recall," and "Other." They were then asked to select the single most important reason from the three they initially selected.

2.2.2 Acceptability and Sufficiency of Information in the Enrollment Process

Respondents' preference for learning about and signing up for Early Check was assessed with a single ranking item, with options that included, "get information about Early Check online and sign up on my own", "Get information from a healthcare provider/health educator and also get information about Early Check online and sign up on my own", and "Get information from a healthcare provider/health educator and sign up with them".

Respondents answered three questions about Early Check information using a 5-point rating scale ranging from not at all to a good amount. The items were "Did the Early Check information make it easier to make a decision about whether to sign up?"; "How helpful was the information provided by Early Check in making the decision to sign up?"; and "How much did the information about Early Check help you understand what you were signing up for?"

Respondents were then asked a yes/no question, "Did you get enough information about Early Check?" If respondents marked that they did not get enough information, they were asked a follow-up question to indicate what more they hoped to learn, with items including "More about the conditions screened," "More about the Early Check process," "More about newborn screening," "More about my child's participation and expectations," or "Other." Respondents were then asked (yes/no), "With the same information you got, do you think other parents will be able to make a decision about signing up for Early Check?"

2.2.3 Attitudes About Early Check Screening and Participation

We included five items on attitudes toward the screening, using items originally from Marteau et al. (2001), as adapted by Lewis and colleagues (2016). Respondents marked their answers to semantic differential items anchored by opposite descriptors, with response options ranging from 0 to 4: "For me, having Early Check was. . .beneficial/harmful, important/unimportant, a good thing/a bad thing, reassuring/not reassuring, and desirable/undesirable" (Lewis et al., 2016). We selected three items from the Decision Regret Scale (O'Connor et al., 2003) that are relevant to the decision context: "It was the right decision," "I regret the choice that was made," and "I would go for the same choice if I had to do it over again." Response options were on a 5-item Likert-type response ranging from strongly agree to strongly disagree.

2.2.4 Knowledge Recall About Early Check

We included a series of six questions to assess knowledge recall of Early Check concepts. Response options were True/False/Unsure. Respondents marked the answers to the following questions (correct response noted in parenthesis):

- Early Check screening tests will not find every single baby with the health problems. (True)
- If the screening result is not normal that means the baby definitely has the health problem. (False)
- Early Check screens for health problems that currently cannot be cured. (True)
- Early Check does the test on the same blood spot taken from the baby's foot after delivery. (True)
- There are treatments that can help babies with the health problems screened by Early Check. (True)
- Finding health problems early gives babies a chance for better development and health outcomes. (True)

2.2.5 Trust in the Information Provided About the Early Check Study

Respondents were queried about how much they agreed or disagreed with the statement "I trust the information provided by Early Check." Response options were on a 5-point scale from strongly agree to strongly disagree.

The survey included additional questions related to condition familiarity and perspectives on the return of results process, which are not included in this analysis.

2.2.6 Analysis

Statistical analysis was performed using SAS version 7.15. Descriptive statistics were used to characterize participant demographics. Chi-square and t-tests were completed to assess differences in participant characteristics between mothers who completed the survey (using race, ethnicity and education data provided in the survey) and the population of mothers who enrolled their infants in Early Check during the same time period but did not complete the survey (using race, ethnicity and education data provided at the time of enrolling the infant in Early Check).

Descriptive analysis was used to summarize responses to the survey items. Several planned analyses to assess factors associated with acceptability and participant attitudes could not be conducted because of highly skewed data.

Knowledge recall items were summed, based on scoring a one for a correct response and 0 for an incorrect or uncertain response, resulting in a range of 0–6. An unadjusted, ordered logistic regression was used to determine whether there were significant differences in knowledge recall scores between White and non-White participants; between Hispanic/Latino and non-Hispanic/Latino participants; among those with less than a bachelor's degree, a bachelor's degree, or more than a bachelor's degree; and based on participant age. Those who did not provide race or ethnicity were

TABLE 2 | Characteristics of parents who enrolled their infants in Early Check and received negative screening results, survey respondents, and interview participants.

	Parents who enrolled infant in EC (*n* = 7,702) 7/7/2020–11/17/2021	Survey respondents (*n* = 1,823) 7/7/2020–11/17/2021	Interviewees (*n* = 24) 7/13/2020–8/31/2020
Median age (years)	32 (11–51)*	33 (18–46)**	35 (23–41)
Ethnicity			
Hispanic or Latino	1,067 (14%)	159 (9%)	2 (8%)
Not Hispanic or Latino	6,092 (79%)	1,395 (77%)	20 (83%)
Unknown/Not reported	543 (7%)	269 (14%)	2 (8%)
Race			
White	5,446 (71%)	1,250 (69%)	18 (75%)
African American/Black	691 (9%)	118 (6%)	4 (17%)
Asian	512 (7%)	104 (6%)	2 (8%)
American Indian/Alaska Native	36 (0.5%)	4 (0.2%)	0
Multi-race/Other	751 (9%)	66 (4%)	0
Unknown/Not reported	266 (4%)	281 (15%)	0
Education			
Did not finish high school	30 (0.4%)	18 (1%)	0
High school graduate	53 (0.7%)	109 (6%)	0
Some college	73 (1%)	123 (7%)	1 (4%)
College degree or higher	468 (6%)	1,343 (74%)	2 (8%)
Not reported	7,078 (92%)	232 (13%)	21 (88%)

**Those with reported maternal ages greater than 60 (n = 3) were excluded because of anticipated data entry error.*
***Derived from 983 participants with completion dates available to calculate age.*

removed from this analysis. An adjusted model with all significant characteristics was then conducted.

For trust, we dichotomized the dataset into those who strongly agreed/agreed with trusting Early Check versus those who were unsure, disagreed, or strongly disagreed. We then applied univariate statistical analysis (Chi-Square or Fisher's exact test for categorical, Kruskal-Wallis test for ordinal variables, and Wilcoxon-Mann-Whitney U test for interval data) to assess differences among the groups based on their race, education, mean attitude score about Early Check screening, knowledge recall score, and whether they perceived themselves to be sufficiently informed (yes/no). Output from the Wilcoxon-Mann-Whitney U tests results were used to display box plots of differences in Wilcoxon mean scores by trust category.

2.3 Semistructured Interviews

The evaluation interviews were conducted *via* telephone. Interviews were conducted by an experienced qualitative researcher from Wake Forest School of Medicine who was not involved in the day-to-day operations of the study. Interviews lasted between 20 and 30 min.

The interviewer used a semi-structured interview guide. Interview questions were designed to explore similar evaluation constructs as the survey. Domains included motivations for enrollment, perception of information sufficiency ease of using the Early Check electronic consent process, perceptions of trust, and satisfaction with the decision to enroll their infant. Data on mothers' age, race, ethnicity and educational attainment were obtained at the time of enrollment of the infant in Early Check.

2.3.1 Analysis

Interviews were recorded and transcribed verbatim for analysis. Two experienced coders from RTI who were not involved in the planning or conduct of the Early Check study iteratively coded all interview transcripts using *in vivo*. A codebook was first developed with inductive and deductive codes to organize and label the interview data. Coders then selected four interviews to code simultaneously to establish interrater reliability using Cohen's κ. Strong agreement was found between the two coders, κ = 0.92. An inductive approach was used to analyze the data and identify themes across interviews. Excerpts from verbatim transcripts were selected to illustrate themes.

3 RESULTS

3.1 Participant Characteristics

Of 1,837 survey respondents meeting study criteria (a 24% response rate), most remembered giving permission for their babies to be enrolled in the Early Check study (*n* = 1,823). Six respondents (0.003%) did not remember and eight (0.004%) who were unsure were excluded from the following analysis.

Of the resulting 1,823 respondents, 69% were White, 6% Black, 6% Asian, 15% missing race/preferred not to answer, and 9% were Hispanic/Latino. Seventy-four percent of survey respondents had a bachelor's degree or higher (**Table 2**). In contrast, the North Carolina population is approximately 60% White, 12% Black, and 6% Asian; and 10% Hispanic/Latino. Approximately 30% of the North Carolina population have a bachelor's degree or higher (U.S. Census, 2018; U.S. Census, 2020).

Twenty-four mothers participated in the in-depth interviews. Seventy-five percent of interviewees reported

their race as White, 17% as Black, and 8% Hispanic or Latino. Four percent reported some college experience and 8% a college degree, although the majority (88%) preferred not to report their education.

Comparing survey respondents to mothers of all Early Check participants who were recruited during the same time period but did not complete the survey (n = 7,702), there were significant differences in age (t (7,729.6) = 1,051.19, $p < 0.0001$), ethnicity [X_2 (2, n = 9,525) = 134.1, $p < 0.0001$], and race [X_2 (5, $p < 0.0001$], although the differences were modest. The amount of missing data about maternal education precluded education-based comparisons.

The sample size of interviewees was too small to make statistical comparisons. **Table 2** includes demographic data provided by mothers when they enrolled their infants in the Early Check study.

3.2 Motivations for Enrolling the Baby in Early Check

3.2.1 Evaluation Survey

The most frequently-endorsed reason for enrolling was to find out if the baby has the conditions screened (43.0%), followed by the need for no additional blood samples from their baby (20.1%) (see **Figure 1**).

3.2.2 Interviews

All but one interviewee reported that a main reason for signing up was to know if their child had one of the conditions screened. They indicated wanting to be armed with information, and many expressed the sentiment of, "I would rather know than not know." Many also reported that they thought getting normal results would give them peace of mind.

"It seemed like a nice opportunity to learn more about our child potentially—like obviously if there is a genetic condition that we were not already aware of, it would be nice to know."

> "I was interested [in] her [getting] screened for everything she possibly could. So, I could just clear my mind of any existing problems that she might have."

Many interviewees shared that knowing about the conditions early would allow them to be prepared and to seek necessary resources or treatment for their child.

> "The more screening you can do to understand your child and how you can help them, the better. . .. the more that you can see coming, the better prepared you are—if you know about it, then you can help them be prepared with early treatment."

A few noted specific reasons to be concerned about the health of their babies because of a high-risk pregnancy or a family history of one of the genetic disorders.

> "I'm a high-risk patient, so like anything that would give me a better insight towards anything that might affect my baby. . .. Basically, I would take the answers."

Ease of participation motivated enrollment among interviewees.

> "I read through the information and figured there was nothing to lose, so it's not like we had to do a whole bunch on our part. It was. . .signing up online and allowing his blood, or whatever it was, to get used from the hospital. So, it's not like we had to go in and do anything extra. . . I'm quite sure if we did have to go back to the hospital or something—I'm sure I wouldn't have done it. But it was easy enough just to use what the hospital already had."

Several interviewees reported that they wanted to contribute to research and viewed the program as a way of helping other families or children.

"In general, just having the information for ourselves and if we needed to do anything further, and then just helping out others to be able to have that information as well."

Participants were asked if they had any concerns when signing up for Early Check. Most respondents shared that they had no concerns. A few had concerns related to the privacy of their child's genetic information.

"We had the slightest, slightest hesitation in thinking the only possible downside of this is that now like the state has our child's genetic material and she's like an infant, right?. . .. I don't think they're going to do anything weird with our information. It is obviously all confidential.. . . So that was just like the slightest little hesitation, but we don't think that there's anything negative that will come out of it in that way, really."

3.3 Acceptability and Sufficiency of the Early Check Enrollment Process

3.3.1 Evaluation Survey

When asked about preferences for getting information about and enrolling in Early Check, the most preferred option was to get information from a healthcare provider and from Early Check online, and sign up on my own (51.6%), followed by get information about Early Check online and sign up on my own (28.1%). The least-preferred option was to sign up with a healthcare provider (20.4%) (**Figure 2**).

On a scale of 0–5, survey respondents reported that the Early Check information made it easier to decide whether to sign up (mean = 4.73), was helpful in making the decision (mean = 4.81), and helped them understand what they were signing up for (mean = 4.83) (**Figure 3**).

Most survey respondents (98.2%) reported that they received enough information about Early Check, and 99.1% indicated that other parents would be able to decide with the same information (**Table 3**).

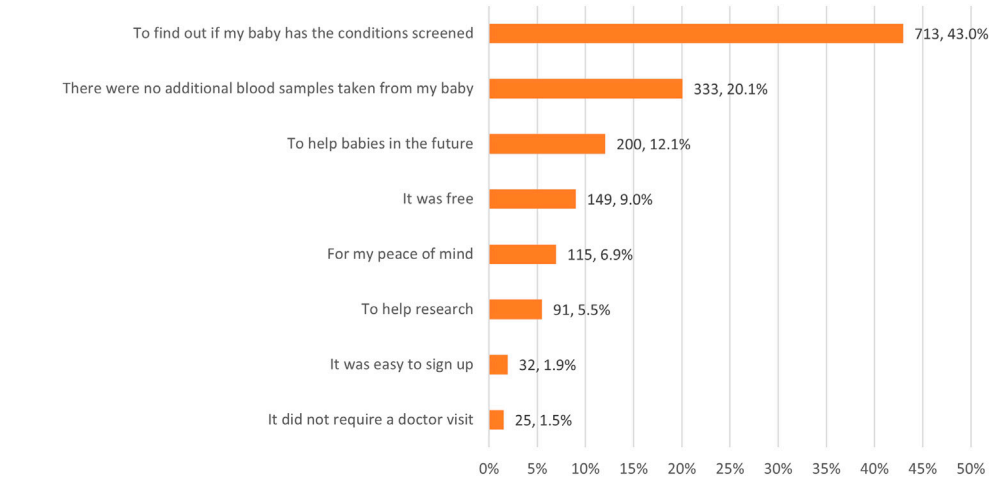

FIGURE 1 | Most important reasons for enrolling the baby in Early Check (n = 1,665).

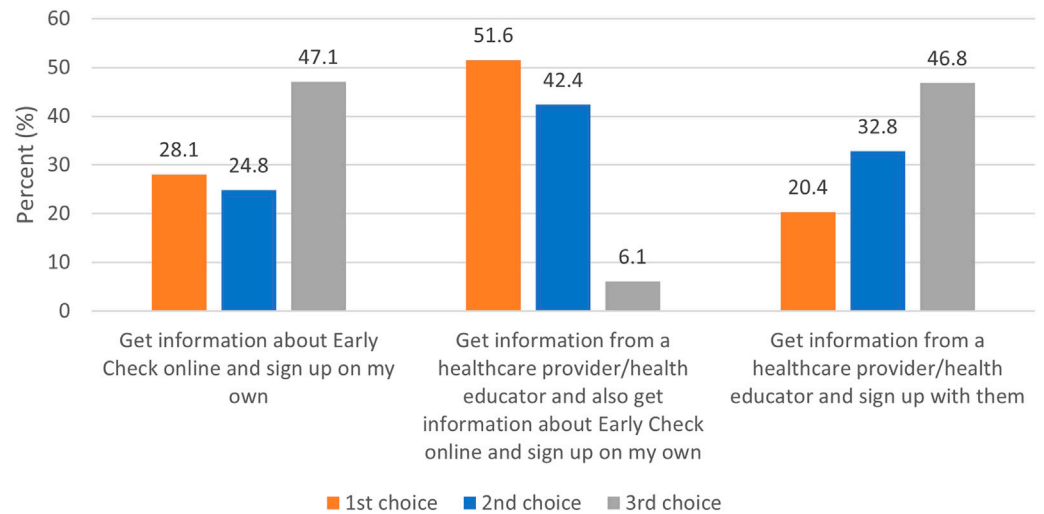

FIGURE 2 | Ranking of preference for education and consent (n = 1,542).

Those who indicated that they did not get enough information (n = 31, 1.8%) were asked what else they hoped to learn (**Table 4**.) The most common response was to learn more about the conditions screened (n = 22), followed by the Early Check process and standard newborn screening (n = 12).

3.3.2 Interviews

All but one interviewee reported that it was easy to sign up; that respondent reported that it was neither easy nor difficult. Ease of enrollment was described as a motivating factor for most respondents. Reasons for perceiving the enrollment process as easy included: information that was easy to understand, an entirely online enrollment process, no need for additional information from parents to sign up (e.g., from medical records), and that it did not take long to sign up.

"Yeah, the fact that it was really easy to do. It was just like: 'Oh, just click here, click here.' If I were to go on the page and it would have been confusing or messy [. . .] I would not have clearly been shown how to sign up, I'm sure that I would not have done [it]. But it was so easy that I just was like 'click, click', you know?"

When asked to describe how they felt when visiting the Early Check website, the most common response was feeling more informed. Several described the content as "straightforward" and that they did not have many questions after viewing the portal.

> "I did not have a lot of questions about it. I thought, 'why would anybody not do this?' And I remember it wasn't challenging. It was just do X, Y, and Z."

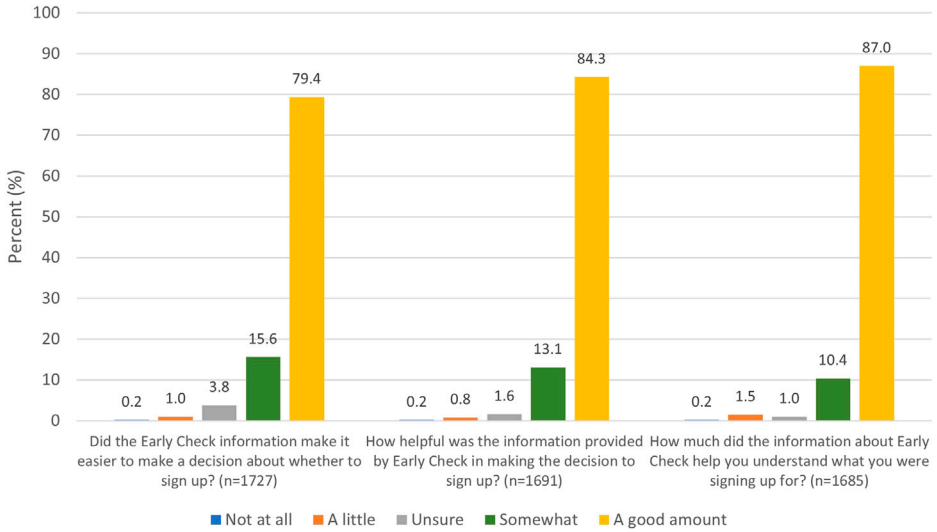

FIGURE 3 | Perceived utility of study information to decision making.

TABLE 3 | Information sufficiency (n = 1,708).

	All	
	N	**%**
Did you get enough information about Early Check?		
No	31	1.8
Yes	1,677	98.2
With the same information you got, do you think other parents will be able to make a decision about signing up for Early Check?		
No	15	0.9
Yes	1,693	99.1

TABLE 4 | What respondents who felt they did not get enough information about Early Check hoped to learn (n = 31).

	N
More about the conditions screened	22
More about the Early Check process	12
More about newborn screening	12
More about the child's participation and expectations	9
Other	4

Interview respondents were asked whether they received enough information to sign up, whether the information was clear and complete, and if they understood which conditions were screened. Most responded in the affirmative to these questions. Respondents were asked whether there was any information not included on the website that they would have wanted. Most said no information was missing and they did not need to search for more information beyond what was provided. Two respondents had to look elsewhere for information on whether the screening was only available for newborns (or if it was also available for older children) and the conditions screened in standard newborn screening.

3.4 Attitudes About Early Check Screening and Participation

3.4.1 Evaluation Survey

Attitudes about the screening were positive among survey respondents. Mean scores on the attitude items, measured on a scale of 0–4 with lower scores indicating better attitudes, are shown in **Table 5**. Survey respondents reported that Early Check screening was "important" (0.58), "desirable" (0.32), "reassuring" (0.18), a "good thing" (0.12), and "beneficial" (0.17).

In responses to the three items selected from the Decision Regret Scale (Brehaut et al., 2003), 98.6% strongly agreed or agreed that participation was the right decision; 96.7% strongly disagreed or disagreed with regretting participation; and 99.3% strongly agreed or agreed that they would make the same choice again (**Table 6**).

3.4.2 Interviews

Interviewees indicated high satisfaction with participation. All stated that they would sign up if given the chance to make the decision over again, for reasons that were similar to their motivations for enrollment: ease of participating, being armed

TABLE 5 | Attitudes about screening.

For me, having early check screening was	N (%)					Mean (SD)	
	0	1	2	3	4		
Beneficial	620 (87.82%)	57 (8.07%)	23 (3.26%)	5 (0.71%)	1 (0.14%)	Harmful	0.17 (0.52)
Important	436 (61.84%)	149 (21.13%)	102 (14.47%)	16 (2.27%)	2 (0.28%)	Unimportant	0.58 (0.84)
A good thing	641 (90.92%)	43 (6.10%)	19 (2.70%)	2 (0.28%)	0 (0.00%)	A bad thing	0.12 (0.42)
Reassuring	614 (87.46%)	54 (7.69%)	31 (4.42%)	3 (0.43%)	0 (0.00%)	Not reassuring	0.18 (0.51)
Desirable	539 (76.89%)	106 15.12%)	50 (7.13%)	4 (0.57%)	2 (0.29%)	Undesirable	0.32 (0.66)

TABLE 6 | Decision regret for Early Check participation.

	Frequency	Percent
It was the right decision		
Strongly agree	564	80.6
Agree	126	18.0
Neither agree nor disagree	9	1.3
Strongly disagree	1	0.1
Frequency missing = 93		
I regret the choice that was made		
Strongly agree	12	1.7
Agree	5	0.7
Neither agree nor disagree	6	0.9
Disagree	87	12.5
Strongly disagree	585	84.2
Frequency missing = 98		
I would go for the same choice if I had to do it over again		
Strongly agree	598	85.4
Agree	97	13.9
Neither agree nor disagree	3	0.4
Strongly disagree	2	0.3
Frequency missing = 93		

with the information about their child, and contributing to research. Further, nearly all stated that they would recommend Early Check to a friend; the one respondent who would not recommend it indicated that she would not think to do so.

3.5 Knowledge Recall About Early Check

3.5.1 Evaluation Survey

Most survey respondents correctly recalled key concepts from the electronic consent materials. A large majority (92.5%) correctly recalled that Early Check performs the test on the same blood spot taken from the baby's foot after delivery and 89.5% that the screening tests will not find every baby with the health problems. Most (78.4%) correctly identified that there are treatments that can help identified babies; but that Early Check screens for health problems that currently cannot be cured (71.8% correct); and 79.5% correctly identified as false the concept that an abnormal result means the baby definitely has the health problem (**Figure 4**).

Using a summed knowledge recall score, an unadjusted, ordered logistic regression was used to determine whether there were significant differences based on mothers' age, between White and non-White participants, between Hispanic/Latino and non-Hispanic/Latino participants, and among those with less than a bachelor's degree, a bachelor's degree, or more than a bachelor's degree. Maternal age was not significant in the unadjusted model and thus was not included in the adjusted model. An adjusted model with all significant characteristics found that, similar to the adjusted model (**Table 7**), White, non-Hispanic, and more-highly-educated respondents were more likely to score higher on knowledge recall.

3.5.2 Interviews

All interviewees agreed that the information on the Early Check website was clear and complete, but most did not remember any specific information or sections of the consent content. Those who did remember specifics most often reported remembering the video elements on the website.

"I think the video is easier to understand and I think some people don't have the patience to read all those words and they prefer the video. I think though the video is good for that kind of parent. . ."

3.6 Trust in the Information Provided About the Early Check Study

3.6.1 Evaluation Survey

Most survey participants reported that they trusted the information provided by Early Check, with 57.9% selecting "strongly agree" and 38.3% selecting "agree" (**Figure 5**).

In assessing those who reported trust (n = 1,598) versus those who indicated being unsure or distrusting Early Check (n = 63), there were significant differences based on race and education. In addition, those reporting less trust were significantly more likely to report more negative attitudes toward the screening ($p < 0.001$) and to indicate that they were not sufficiently informed (p = <0.0001). The mean knowledge recall score is higher for those who trust the information versus those who do not ($Z = -3.51$, $p < 0.001$) (**Table 8** and **Figure 6**.)

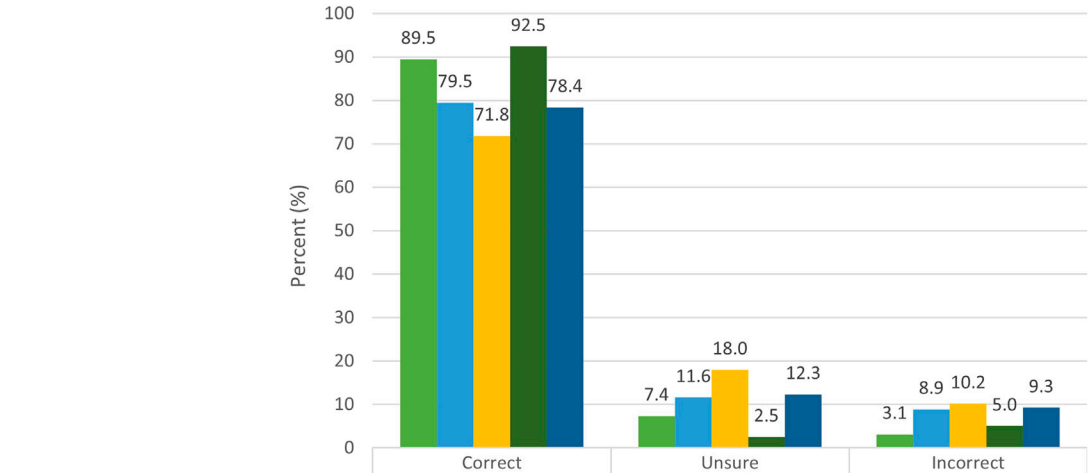

FIGURE 4 | Recall of key Early Check concepts (n = 1,630).

TABLE 7 | Ordered logistic regression: Knowledge recall score[a].

n = 1,346	Unadjusted		Adjusted	
	OR[b]	95% CI	OR[b]	95% CI
Race				
White	5.74***	(4.03, 8.17)	4.0***	(2.78, 5.76)
Non-White (ref.)				
Ethnicity				
Non-Hispanic	2.14***	(1.57, 2.92)	1.63**	(1.13, 2.33)
Hispanic (ref.)				
Education				
< Bachelor's degree	0.40***	(0.31, 0.52)	0.45***	(0.34, 0.59)
Bachelor's degree (ref.)				
> Bachelor's degree	1.63***	(1.31, 2.0)	1.64***	(1.13, 2.33)

$^{**}p < 0.01$.
$^{***}p < .0001$.
[a]*Knowledge recall score is the sum of the number of recall questions answered correctly. Range is 0–6.*
[b]*OR (Odds Ratio) greater than one means the participant characteristic is positively associated with a higher knowledge recall score, and a less than one means the characteristic is negatively associated with a knowledge recall score.*

3.6.2 Interviews

All interviewees reported that they trusted the information provided by Early Check. Many said that the information was from a credible source and the website appeared legitimate. Several also noted that the organizations listed on the website made them trust the information, and most participants said that they were familiar with at least one of the institutions.

"Yeah. . .the fact that you're doing surveys on it, it looked like a lot of thought went into planning, how it was laid out and how it was worded. That even if I wasn't good at using a website, or even if I wasn't good at reading, what seemed very scientific or medical, I could still understand it. It seemed like there was care put into it to make it seem not intimidating and intentional and well-worded and stuff."

> "I mean as far as like you, the schools of Wake Forest and UNC and Duke, I mean, all those are, you know, I recognize that they're all like research organizations and local universities. So, I thought that they seemed reputable. It wasn't like here were a random company trying to collect your child's genetic information."

4 DISCUSSION

We developed a large-scale education and consent approach that was designed to be feasible for the study team, acceptable and trustworthy to parents making decisions about enrollment, and promoting of informed decisions. During our 16-month evaluation period we enrolled over 7,700 infants to Early

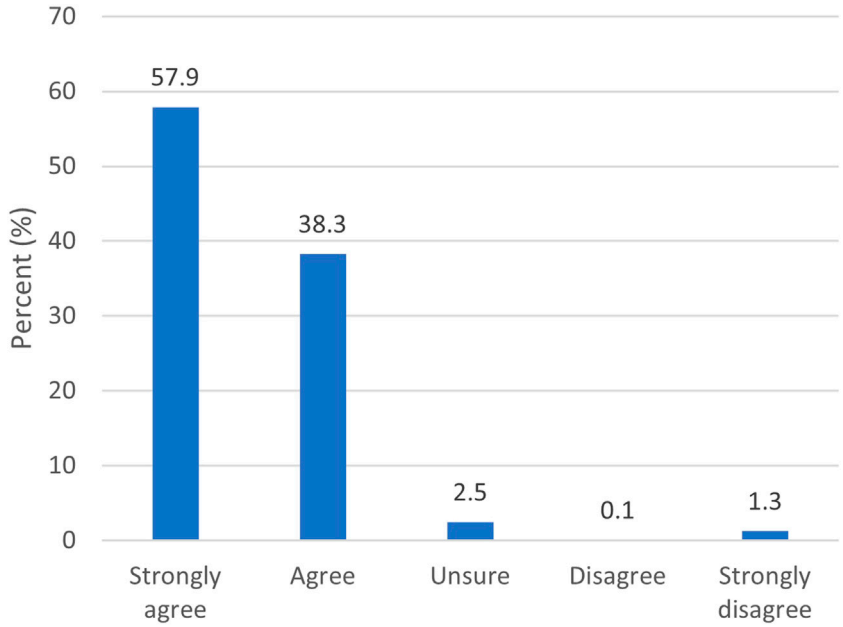

FIGURE 5 | Responses for "I trust the information provided by Early Check" (*n* = 1,661)

TABLE 8 | Factors associated with trust in Early Check participants.

	Trust (*n* = 1,598)	Unsure/Distrust (*n* = 63)	*p*-value
Race			**0.007**
White	1,208 (79.68%)	38 (64.41%)	
Non-White	274 (18.07%)	17 (28.81%)	
Prefer not to say	34 (2.24%)	4 (6.78%)	
Education			**0.039**
<Bachelor's degree	351 (22.99%)	22 (37.29%)	
Bachelor's degree	482 (31.57%)	15 (25.42%)	
>Bachelor's degree	694 (45.45%)	22 (37.29%)	
Attitude about screening [Mean (SD)]	1.39 (2.27)	2.70 (3.20)	**0.0002**
Knowledge recall score	4.12 (1.00)	3.54 (1.38)	**0.0005**
Informed enough			< **0.0001**
Yes	1,576 (98.62%)	57 (90.48%)	
No	22 (1.38%)	6 (9.52%)	

Bold values indicate p-value from Chi-Square or Fisher's exact test for categorical, Kruskal-Wallis test for ordinal variables, and Mann-Whitney U test for interval data.

Check, the large majority coming through our entirely participant-driven online education and consent process. We have demonstrated that our participant-driven, online approach makes it feasible to educate a large sample from the general population.

And yet developing an approach, that is, feasible for the study team only has utility if it also meets the needs of the end users. This requires developing study materials that provide sufficient information while maintaining a reasonable and acceptable level of complexity and literacy. Our survey respondents reported that the study information was sufficient and made it easier to make an enrollment decision and understand what they were signing up for. These sentiments were echoed by parents who participated in the qualitative interviews, who expressed that information was easy to understand, easy to navigate, and informative for decision making. Existing literature on the use of electronic consent is also promising with studies reporting positive attitudes and experiences of participants who use virtual approaches informed consent (Bollschweiler et al., 2008; Abujarad et al., 2018; Simon et al., 2018).

Our data indicate that our participant-driven, online approach was acceptable to those who agreed to participate. Survey respondents most preferred an approach that included healthcare provider and online information, with online sign up; this was followed by online only. Survey respondents and interviewees reported positive attitudes and limited regret about their decision to enroll their newborns. Ease and convenience were cited as motivations to enroll, which is a common-sense

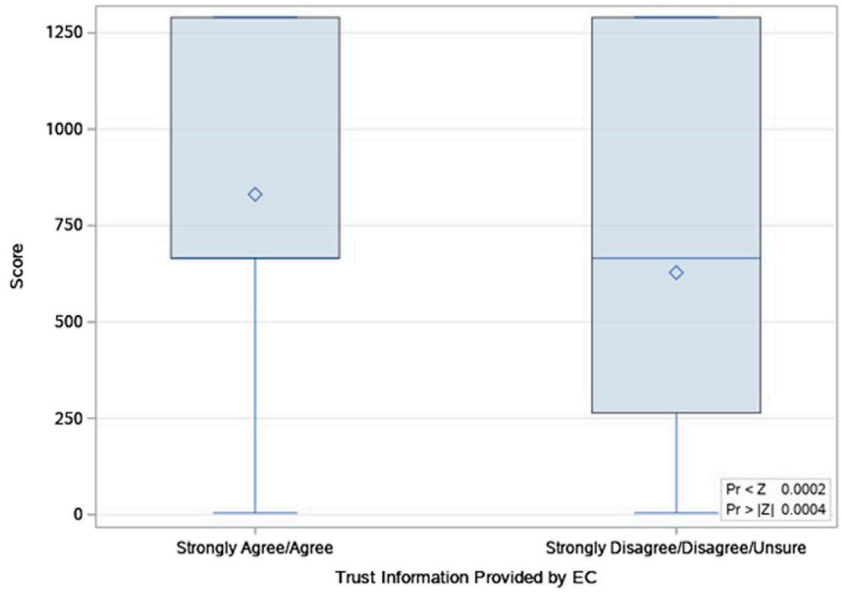

FIGURE 6 | Distribution of Wilcoxon Scores for knowledge score, by trust in Early Check.

finding. Study teams can, however, make it too easy to enroll. It is well-recognized that online users are accustomed to scrolling through content to get to the accept button without reading technical information (Doerr et al., 2016). The process of education for screening and consent for research participation must not take advantage of that learned behavior. It may be important for content and interface developers to build "friction" into the online education process; this includes purposefully-designed elements to slow and engage users (Doerr et al., 2016). Employing a variety of media may meet this goal while also offering different approaches to learning that do not rely solely on reading (Rowbotham et al., 2013; Kraft et al., 2017; Simon et al., 2018). In our website materials we employed voiceover, simple graphics, infographics, video, brief values clarification, and self-assessment questions. We designed the user interface to promote exposure to the core content and required participants to click through content rather than scrolling.

Most survey respondents correctly recalled key concepts of Early Check, similar to the evaluation of the All of Us research program's electronic consent (Doerr et al., 2021). Interviewees were not asked equivalent questions where specific concepts were assessed due to the exploratory nature of the interviews. Therefore, it is unclear whether interview participants recall these concepts similarly. Our survey data indicate areas for improvement in explaining educational concepts—particularly the differentiation between treatment and cure. Although the overall numbers are small, we acknowledge that our knowledge recall is lower in non-White populations and those with less education. It is paramount that population-focused programs continue efforts to develop education, that is, effective for those from diverse racial, ethnic, and education backgrounds.

Another critical goal of Early Check is trustworthiness. Regardless of the quality of educational materials, some degree of trust is required for parents to agree to enroll their child in screening. We found high trust in Early Check; our qualitative data indicate that having sufficient information and clearly identifying collaborating institutions, especially those known through the state, is important. Among the fewer than 4% of survey respondents who indicated distrust or being unsure about trusting the information, we observed more individuals identifying in race categories other than white, less positive attitudes toward Early Check, and lower information recall. Although our materials include multiple references to the voluntary nature of participation and brief values clarification component that reviews why parents may choose to decline Early Check participation for their children, parents who are unsure or untrusting of Early Check may still anticipate sufficient value from the resulting screening information to offset feelings of distrust.

A strength of our study is that we obtained both quantitative and qualitative data. The interviews allowed us to explore unexpected findings that would not have emerged from a survey. Although results from the interviews and surveys were complementary, the survey questions and the qualitative interview questions were not identical.

4.1 Limitations

A limitation to our data is that our evaluation participants have higher education than the average in the state of North Carolina. About 30% of the North Carolina working-age population has a bachelor's degree or higher (U.S. Census, 2020) compared to 74% in our evaluation survey respondents. As such, our findings have limited generalizability. In addition, we achieved only a 24% response rate in our survey. The relatively low response rate may be to some extent explained by a study team decision to de-emphasize the evaluation survey in favor of promoting

communication about the return of screening results; clearly it is more important to garner the attention of participants to their newborn's screening result than to recruit for the evaluation. Further, our data may be biased based on time between enrollment and data collection (recall bias) and social desirability bias. To help reduce the potential for bias in the qualitative data collection and interpretation, we employed an interviewer who was not involved in the day-to-day operations of Early Check and analysts who were completely uninvolved with the Early Check study prior to coding the data.

It should be noted that this evaluation comprised parents who received negative (or normal) screening results. Parents who received positive screening results may have differing views. We are conducting additional research on mothers of children who screen positive to explore the impact of the positive screen and their experiences and attitudes, and their recommendations for improving Early Check procedures. Another important limitation is that this study included only mothers who enrolled their children in Early Check and not those who declined participation. The study population must be taken into account when interpreting our findings, as these are individuals who perceived Early Check to be sufficiently trustworthy and the screening of sufficient value to warrant participation. Additional research on those who do not participate in Early Check, although ethically and practically challenging, is important to informing population-based DNA screening.

4.2 Implications

Large-scale research and public health use of DNA-based screening become increasingly feasible when quality electronic approaches are used to educate and/or consent impacted communities. Our evaluation of the Early Check newborn screening research study indicates that participant-focused materials provided in an entirely virtual format can be acceptable, trustworthy, and informative. Though developing participant-focused materials is a time-intensive process that requires a multidisciplinary development group and the use of community engagement and formative research, the result can be a user-directed process that requires little study team time. Early Check currently uses single-gene and analyte screening; we are in process of adapting and testing a similar approach for newborn screening using exome sequencing, where some educational concepts are of higher complexity. Additional evaluation data from programs that use virtual education and consent may lead to best practices in new material development and may increase the acceptance of participant-centered electronic consent among regulators. Finally, as DNA-based screening programs and screening-based studies are implemented, it is vital to explore new approaches to education and consent that account for the needs of diverse target populations.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, if the data request is in accordance with the IRB protocol and consent.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of North Carolina at Chapel Hill. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

HLP, AYG, RM, BL-B, KAP, MD, AAA, BBB, JC, DBB, and NMPK contributed to conception and design of the study. AYG, KAP, and HLP contributed to the analysis. HLP, AYG, RM, HC, and KAP wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCES

Abujarad, F., Alfano, S., Bright, T. J., Kannoth, S., Grant, N., Gueble, M., et al. (2018). Building an Informed Consent Tool Starting with the Patient: The Patient-Centered Virtual Multimedia Interactive Informed Consent (VIC). *AMIA Annu. Symp. Proc.* 2017, 374–383.

Bailey, D. B., Jr, Gehtland, L. M., Lewis, M. A., Peay, H., Raspa, M., Shone, S. M., et al. (2019). Early Check: Translational Science at the Intersection of Public Health and Newborn Screening. *BMC Pediatr.* 19 (1), 238. doi:10.1186/s12887-019-1606-4

Biesecker, B., Raspa, M., Rupert, D., Moultrie, R., Furberg, R., and McCormack, L. A. (2019). *Making Clinical Trials More Patient-Centered Using Digital Interactive E-Consent Tools*. Research Triangle Park, NC: RTI Press Occasional Papers.

Bollschweiler, E., Apitzsch, J., Obliers, R., Koerfer, A., Mönig, S. P., Metzger, R., et al. (2008). Improving Informed Consent of Surgical Patients Using a Multimedia-Based Program? *Ann. Surg.* 248 (2), 205–211. doi:10.1097/sla.0b013e318180a3a7

Brehaut, J. C., O'Connor, A. M., Wood, T. J., Hack, T. F., Siminoff, L., Gordon, E., et al. (2003). Validation of a Decision Regret Scale. *Med. Decis. Making* 23 (4), 281–292. doi:10.1177/0272989X03256005

Buckley, M. T., Lengfellner, J. M., Koch, M. J., Pacheco, H. O., Hoidra, C., Damron, D. J., et al. (2018). The Memorial Sloan Kettering (MSK) Electronic Informed Consent (eIC) Platform for Clinical Trials: An Operational Model and Suite of Tools for Obtaining Informed Consent, and Managing Consent Documents. *Jco* 36 (15_Suppl. l), e18577. doi:10.1200/jco.2018.36.15_suppl.e18577

Cadigan, R. J., Butterfield, R., Rini, C., Waltz, M., Kuczynski, K. J., Muessig, K., et al. (2017). Online Education and E-Consent for GeneScreen, a Preventive Genomic Screening Study. *Public Health Genomics* 20 (4), 235–246. doi:10.1159/000481359

Doerr, M., Moore, S., Barone, V., Sutherland, S., Bot, B. M., Suver, C., et al. (2021). Assessment of the *All Of Us* Research Program's Informed Consent Process. *AJOB Empirical Bioeth.* 12 (2), 72–83. doi:10.1080/23294515.2020.1847214

Doerr, M., Suver, C., and Wilbanks, J. (2016). *Developing a Transparent, Participant-Navigated Electronic Informed Consent for mobile-mediated Research*. Rochester, NY: SSRN. doi:10.2139/ssrn.2769129

Grant, S. C. (2021). Informed Consent-We Can and Should Do Better. *JAMA Netw. Open* 4 (4), e2110848. doi:10.1001/jamanetworkopen.2021.10848

Hurle, B., Citrin, T., Jenkins, J. F., Kaphingst, K. A., Lamb, N., Roseman, J. E., et al. (2013). What Does it Mean to Be Genomically Literate? National Human Genome Research Institute Meeting Report. *Genet. Med.* 15 (8), 658–663. doi:10.1038/gim.2013.14

Kraft, S. A., Constantine, M., Magnus, D., Porter, K. M., Lee, S. S., Green, M., et al. (2017). A Randomized Study of Multimedia Informational Aids for Research on Medical Practices: Implications for Informed Consent. *Clin. trials* 14 (1), 94–102. doi:10.1177/1740774516669352

Lewis, C., Hill, M., Skirton, H., and Chitty, L. S. (2016). Development and Validation of a Measure of Informed Choice for Women Undergoing Non-invasive Prenatal Testing for Aneuploidy. *Eur. J. Hum. Genet.* 24 (6), 809–816. doi:10.1038/ejhg.2015.207

Marteau, T. M., Dormandy, E., and Michie, S. (2001). A Measure of Informed Choice. *Health Expect. : Int. J. Public participation Health Care Health Pol.* 4 (2), 99–108. doi:10.1046/j.1369-6513.2001.00140.x

Morgenstern, J., Hegele, R. A., and Nisker, J. (2015). Simple Genetics Language as Source of Miscommunication between Genetics Researchers and Potential Research Participants in Informed Consent Documents. *Public Underst Sci.* 24 (6), 751–766. doi:10.1177/0963662514528439

National Center for Education Statistics Greenberg, E., Jin, Y., and White, S. (2007). *2003 National Assessment of Adult Literacy: Public-Use Data File User's Guide*. American Institutes for Research. Available from https://nces.ed.gov/NAAL/pdf/2007464.pdf.

North Carolina Department of Health and Human Services (2020). Newborn Screening. Available from https://slph.ncpublichealth.com/newborn/default.asp.

Peay, H., Duparc, M., Moultrie, R., Jordan, A., Lewis, M., and Bailey, D. (2018). "Informing the Implementation of a Large-Scale Genetic Research Study: Early Check," in Presented poster at the American College of Medical Genetics Annual Meeting, April 10-14 (Charlotte NC.

Rothwell, E., Wong, B., Rose, N. C., Anderson, R., Fedor, B., Stark, L. A., et al. (2014). A Randomized Controlled Trial of an Electronic Informed Consent Process. *J. Empirical Res. Hum. Res. Ethics* 9 (5), 1–7. doi:10.1177/1556264614552627

Rowbotham, M. C., Astin, J., Greene, K., and Cummings, S. R. (2013). Interactive Informed Consent: Randomized Comparison with Paper Consents. *PLoS ONE* 8 (3), e58603. doi:10.1371/journal.pone.0058603

Simon, C. M., Klein, D. W., and Schartz, H. A. (2016). Interactive Multimedia Consent for Biobanking: A Randomized Trial. *Genet. Med.* 18, 57–64. doi:10.1038/gim.2015.33

Simon, C. M., Schartz, H. A., Rosenthal, G. E., Eisenstein, E. L., and Klein, D. W. (2018). Perspectives on Electronic Informed Consent from Patients Underrepresented in Research in the United States: A Focus Group Study. *J. Empirical Res. Hum. Res. Ethics* 13 (4), 338–348. doi:10.1177/1556264618773883

U.S. Census (2020). 2020 *Census*. Available from: https://www.census.gov/library/stories/state-by-state/north-carolina-population-change-between-census-decade.html.

U.S. Census (2018). Educational Attainment. Available from https://data.census.gov/cedsci/table?hidePreview=true&tid=ACSST1Y2018.S1501&tp=false&moe=false&g=0100000US%2404000%24001&t=Educational%20Attainment.

U.S. Food and Drug Administration (FDA) (2015). Use of Electronic Informed Consent in Clinical Investigations Questions and Answers Guidance for Industry Draft Guidance. Available from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436811.pdf?source=govdelivery&utm_medium=email&utm_source=govdelivery.

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Utilizing Public Health Frameworks and Partnerships to Ensure Equity in DNA-Based Population Screening

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DNA-Based population screening in the United States has the promise to improve the health of all people in all communities. We highlight recent DNA-based population screening examples at the state, local, and individual level. Key public health principles and concepts with a focus on equity appear to be lacking in current efforts. We request 'A Call to Action' that involves all partners in DNA-based population screening. Potential actions to consider include: a) identification and elimination of systemic barriers that result in health inequities in DNA-based population screening and follow-up; b) creation of a national multidisciplinary advisory committee with representation from underserved communities; c) revisiting well-described public health screening principles and frameworks to guide new screening decisions and initiatives; d) inclusion of the updated Ten Essential Public Health Services with equity at the core in efforts at the local, state and national level.

Keywords: genomic screening, DNA-based screening, public health, population screening, health equity

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INTRODUCTION

The vision of precision public health is 'providing the right intervention to the right population at the right time' (Khoury et al., 2016). In order to achieve this vision, it is critical to integrate current public health principles and frameworks in the development and implementation of population-level genomic screening (Andermann et al., 2008; The Futures Initiative, 2020). These revised frameworks have placed a stronger focus on equity. It is imperative that all DNA-based population screening efforts at all levels center equity to improve the health for all people in all communities. We discuss the public health framework for decision making and implementation using the example of population-based newborn screening (NBS). We also provide recent examples of DNA-based population screening at the individual, local, and state levels to highlight the importance of equity and partnerships.

EXISTING HEALTH INEQUITIES IN GENETIC SERVICES

Health care inequity is defined as a difference in treatment provided to members of different groups that is not justified by the underlying health conditions or treatment preferences of patients (National Academies of Sciences, Engineering, and Medicine, 2018). With the introduction of any new technology into health care, there are significant concerns that all segments of the population -

especially medically underserved groups—will not be reached (National Academies of Sciences, Engineering, and Medicine, 2018). This is especially true for genetic technologies and precision medicine. Access to genetic services in the United States is primarily gated by referrals from non-genetics providers for patients with a significant personal and/or family history based on clinical guidelines. This has resulted in stark inequities to genetic services with multiple barriers at the individual, provider, and healthcare system levels (Childers et al., 2018; Chapman-Davis et al., 2021; Weise et al., 2021). For example, physicians who serve a high proportion of minority patients are significantly less likely to have ever referred a patient for genetic counseling and testing (Shields et al., 2008). There is also less awareness of genetic testing among individuals who identify as Hispanic or non-Hispanic Black and live in rural areas (Salloum et al., 2018). Disparities in access to and awareness of genomic medicine is a complex issue that affects several populations, including underrepresented minorities, rural communities, medically underserved groups, and others (National Academies of Sciences, Engineering, and Medicine, 2018).

The experiences of Candace Henley, cancer survivor and Lynch syndrome patient, highlights these barriers and conveys the need for an urgent focus on equity:

> "The opportunity to have been proactive to avoid my cancer diagnosis and the devastating after-effects would have been ideal. The words "you have colon cancer" echoed in my head and left me numb, and everything else said to me afterward was lost to thoughts about my children and what would happen if I died. I was shocked because I was 35 years old, with a disease that occurs in people over 50; how?
>
> The first and last time Lynch Syndrome was mentioned was a brief conversation at the six-week visit after my surgery; genetic testing or referral to a counselor was never offered or suggested. Combing through medical records from my diagnosis in 2003, it simply said: "MSI associated." That was the pathology report.
>
> For years, I thought Lynch Syndrome was something I should be proud of until I learned from other survivors and medical professionals at conferences that it was not. 11 years after my diagnosis, I learned my father and two aunts were diagnosed post-autopsy with colon cancer.
>
> In communities of color, doctors are not recommending genetic testing at the same rate as whites are. In addition, patient barriers exist, such as access to information about and education about genetic testing, racial inequities in care, lack of trust, physician perception of barriers such as psychological distress, and unconscious or implicit bias. Knowledge leads to prevention, healthier patient outcomes, and builds trust. Everyone deserves the opportunity to fight their best fight against cancer or any other illness."

Additionally, the disparities across state and federal insurance health insurance plans fundamentally contribute to disparities for patients. Although percentages vary by state, 86% of Medicare beneficiaries are covered due to being age 65 and older and 14% are covered due to disability across the U.S. (Kaiser Family Foundation, 2019). Medicare coverage specifically creates two gaps that exacerbate disparities. First, genetic testing is only a covered benefit if the individual has the condition of interest, and the testing will be used for clinical decision-making. As such, those who are healthy but at risk are not eligible to have testing covered by Medicare. Second, genetic counselors are not currently recognized as providers by the Centers for Medicare & Medicaid Services, so individuals with Medicare are dependent on providers with less training in genetics to offer and manage the appropriate testing. This second issue is critical to all individuals seeking genetic testing, regardless of whether they have Medicare or a commercial third-party payor. A recent study by Lin et al. (2022) assessed the barriers to genetic testing access in academic medical centers and safety net hospitals in California and North Carolina. Both types of institutions reported that the lack of coverage of genetic counseling was a "major barrier to testing". These are important gaps that will require significant changes in payer policies to implement DNA-based population screening efforts. Currently, DNA-based population efforts are not funded by health insurers and therefore do not suffer from these same issues.

The traditional clinical guidelines referral approach has also resulted in incomplete and inaccurate information regarding genetic disease prevalence, penetrance and natural history. There are numerous recent studies that have demonstrated that DNA-based population screening efforts not only detect more individuals in the population with genetic disease, but also add to our knowledge regarding the spectrum of disease especially in disparate populations (Manickam et al., 2018; Yang et al., 2018; Buchanan et al., 2020; Grzymski et al., 2020).

NEWBORN SCREENING PRINCIPLES AND INFRASTRUCTURE: LESSONS FOR DNA-BASED POPULATION SCREENING

DNA-based population screening efforts can benefit from the lessons learned over the past 50 years of newborn screening. For instance, newborn screening utilizes an established framework to prioritize specific conditions, a strategy that would be beneficial for DNA-based population screening programs to adopt. The gold standard in screening policy decisions, not limited to newborn screening, is the Wilson and Jungner criteria (Andermann et al., 2008). Wilson and Jungner first published their instrumental work "Principles and Practice of Screening for Disease" in 1968 (Wilson and Junger, 1968). Their focus was mainly on screening for common chronic diseases rather than newborn screening. These principles guide policy decisions regarding appropriate screening targets, based on factors such as the feasibility of early detection and the availability of an acceptable treatment. Wilson and Jungner also described

the practices essential to operationalize screening, including data collection and analysis, provider education and community engagement. The criteria were updated in 2008 by Andermann et al. to reflect evolving societal and other influences with a focus on equity, autonomy, and quality assurance. Specifically, the revised framework includes a new criterion that 'the programme should promote equity and access to screening for the entire target population.' The Wilson and Jungner principles are not being widely utilized in current DNA-based population screening in the United States. Revisiting these criteria would be important in order for DNA-based population screening programs to reach their potential.

Current local and statewide DNA-based population screening efforts are being led by academic institutions and regional health systems. These programs could be enhanced by a national advisory committee with recommendations such as exists with NBS. State NBS systems evolved independently for more than 30 years before resulting disparities led to national calls for standardization. In response, the U.S. Department of Health and Human Services (HHS), Health Resources and Services Administration commissioned then American College of Medical Genetics to outline a process (Watson et al., 2006) for guidance to align and support efforts nationally. Primary outcomes were the development of the Recommended Uniform Screening Panel (RUSP) in 2002 and the establishment of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) in 2003. ACHDNC membership is professionally diverse, drawing from public health NBS systems, clinical experts, rare disease advocates, and federal regulatory and service agencies. The Committee advises the HHS Secretary on NBS system priorities and needs, applying a decision matrix aligned with the Wilson and Jungner framework to examine and prioritize conditions for universal screening. The Committee has recently recognized that various factors, including the lasting impacts of structural racism, demand increased attention and commitment to achieve equitable outcomes. These practices are crucial to maintaining the wide public support and success of NBS as a public health practice. Developing and applying similar frameworks to newer DNA-based population screening practices is imperative to avoid increasing existing disparities surrounding health outcomes for a growing number of treatable conditions. Without similar frameworks the implementation of DNA-based population screening has been haphazard, dependent upon the buy-in of leaders at various institutions and hospitals, technology-led, and consumer-driven. While these programs are not restricted by the payer issues discussed above, they depend on funding from partners (e.g., pharmaceutical companies, state and federal research funds) which can introduce financial drivers that are incompatible with equitable recruitment. Many of these studies are incentivized to recruit as quickly as possible, regardless of the make-up of the cohort, resulting in inherent disparities in attempts at comprehensive and equitable integration.

OTHER PUBLIC HEALTH AND GENETIC SCREENING FRAMEWORKS TO CONSIDER IN DNA-BASED POPULATION SCREENINGS

Several current DNA-based population screening efforts utilize lists of genetic tests developed for other purposes such as the Tier 1 applications from the Centers for Disease Control & Prevention (CDC). The CDC has categorized genetic tests into tiers based on the evidence and/or consensus for their use in practice. Tier 1 applications are those having significant potential for positive impact on public health in specific settings. These applications are based on available evidence-based guidelines and recommendations (Bowen et al., 2012). There is currently no list of genetic tests or framework in DNA-based population genomics that integrates and/or prioritizes inequities in populations.

Additionally, there currently is no national public health genomics infrastructure for DNA-based based population screening in the United States. Current DNA-based population screening efforts at the state and local levels are occurring independently with finite funding from industry, foundations, governmental and research entities. Given this limited and uncertain funding, sustainability and time, DNA-based screening programs are focused on volume and speed at the expanse of equity. The Evaluation of Genomic Application in Practice (EGAPP™) was a previously funded effort by the CDC (Veenstra et al., 2012). EGAPP™ existed from 2005 to 2014 and provided a framework and national advisory role to select and evaluate genomic screening applications for specific clinical indications and populations. While there were shortcomings of this process, EGAPP served as a model for a federally funded entity which could partner with local and statewide DNA-based population screening programs and provided guidance about how to ensure equity across screening efforts. There is also a need for federal and state policies that support DNA-based population screening efforts and provide secure funding to ensure sustainability and health equity.

Furthermore, current DNA-based population screening efforts do not appear to use other key public health concepts, such as the Ten Essential Public Health Services. The Ten Essential Public Health Services was initially created in 1994 to provide a framework to describe the activities that public health systems should undertake in all communities (Castrucci, 2021). The framework was revised in 2020 with an explicit focus on equity to reflect public health values and social justice. More specifically, the visual representation of this framework places equity at the core. This is meant to be 'a reminder of how public health must center on communities that have been historically marginalized in their work' (Castrucci, 2021). DNA-based population screening needs to similarly place equity at the core of all activities. We would like to suggest creation of a new network of DNA-based population screening programs with national, state and local partners to share best practices and to collaborate on development of a framework that priorities health equity.

TABLE 1 | Selected population genomic screening initiatives.

Project	Target population	Year initiated	Testing and return of results	Findings
Ohio Colorectal Cancer Prevention Initiative[a]	Ohio residents	2013	3,310 colorectal cancer patients (CRC) underwent universal tumor screening (UTS) for mismatch repair (MMR) deficiency Germline multigene panel testing (MGPT) was performed for patients with MMR deficiency	Approximately 16% of patients had MMR deficiency. Pathogenic germline variants in cancer susceptibility genes were found in 234 patients, representing 7.1% of the entire cohort and 16% of the 1,462 patients who received MGPT. Pearlman et al. (2021)
Renown Healthy Nevada (with 23 and Me, Helix)[b]	Nevada residents	2016 2018	>26,906 individuals from throughout the state of Nevada assessed for ancestry, LS, hereditary breast and ovarian cancer syndrome (HBOC), and familial hypercholesterolemia (FH)	1.33% (1 in 75) individuals had one of these three conditions. Among them, only 21.9% had clinically relevant disease, 25.2% had a family history of a relevant disease, and 90% had not been previously diagnosed. Grzymski et al. (2020)
Geisinger MyCode (with Regeneron Pharmaceuticals)[c]	Geisinger patients	2014	>142,000 participants had their data analyzed for actionable hereditary disorders. (MyCode Scorecard, April 2022)	Almost 3,400 participants have received results to date, 48.1% with LS, HBOC or FH diagnoses. (MyCode Results Reported, April 2022) Studies on this cohort revealed that 87% of 351 individuals with LS, HBOC, and FH diagnoses were unaware of their genetic status before testing and 84% were eligible for additional interventions to mitigate disease risk. Buchanan et al. (2020)
NorthShore DNA-10K (with Color)[d]	NorthShore patients	2019	10,000 participants and provided patients with results for 60 genes associated with hereditary cancer and cardiac conditions, a 14-gene panel for pharmacogenomics (PGx) testing, ancestry and common trait information (such as lactose intolerance)	99% of eligible physicians ordered testing for a patient and more than half said DNA-10K has already provided a direct clinical benefit to patients. Nearly 80% of participants consented to participate in third party research and 70% said that the program "enabled them to better manage their personal health". (Northshore Press Release)
Mayo Clinic Tapestry study (with Helix)[e,f]	Mayo Clinic patients	2020	Returning ancestry results and actionable genetic findings derived from whole exome sequencing (WES) testing, starting with LS, HBOC, and FH.	Results pending
Intermountain HerediGene: Population Study (with deCODE Genetics/Amgen)[g]	Utah and Idaho residents	2019	Return of results planned	Results pending

[a]*Cancer.osu.edu/our-impact/community-outreach-and-engagement/statewide-initiatives/statewide-colon-cancer-initiative.*
[b]*Healthynv.org/.*
[c]*Geisinger.org/precision-health/mycode.*
[d]*Northshore.org/personalized-medicine/our-services/color-genetics-test/.*
[e]*Genomeweb.com/genetic-research/regeneron-mayo-ink-pact-sequence-genotype-100k-patient-samples.*
[f]*Mayo.edu/research/centers-programs/center-individualized-medicine/research/clinical-studies/tapestry.*
[g]*Intermountainhealthcare.org/heredigene.*

EXAMPLES OF DNA-BASED SCREENING EFFORTS

Several institutions (**Table 1**) including Mayo, Geisinger, Intermountain Healthcare, and NorthShore University HealthSystem, have developed and implemented personalized medicine testing programs (Lemke et al., 2017; Schwartz et al., 2018; Pritchard et al., 2021). Northshore's DNA-10K program specifically targeted the idea that scalable delivery of genomic medicine requires collaboration between genetics and non-genetics providers, implementing a combined primary care-genetics provider approach. Individuals who agreed to testing consented online in advance of their annual preventive care visit, at which time their primary care physician could place an order for clinical testing. The framework for NorthShore's Personalized Medicine initiatives was developed at the local level *via* review and included assessment of CDC Tier 1 conditions and other guidelines, including the National Comprehensive Cancer Network (NCCN) Cancer Gene guidelines, American Heart Association (AHA)-supported cardiac genes, and ClinGen curated genes for disease association, as well as American College of Medical Genetics & Genomics (ACMG) incidental finding guidelines (a *de facto* guideline in the field of genomic population screening).

Two examples of state level DNA-based population screening strategies exist in Ohio and Nevada. Ohio leverages universal tumor screening with germline multigene panel testing for Lynch syndrome (LS) among all colorectal cancer patients. Nevada uses

population screening in the general public for three Tier 1 CDC applications that have been defined in more narrowly defined populations. The Ohio study provides an important example of centralized expertise that could be utilized by other DNA-based population screening efforts at the state and local levels. The study also demonstrates that DNA-based population screening efforts with germline multigene panel testing (MGPT) will detect more patients and that wide-spread screening efforts involving multiple health systems at the state level is feasible. The Healthy Nevada study provides support that DNA-based population screening efforts at the state level detect previously undiagnosed hereditary conditions with actionable prevention measures.

These programs have demonstrated significant success at recruiting participants, returning actionable genetic results at scale, and engaging local researchers and physicians to participate in the programs. However, they have been critiqued for a lack of racial and ethnic diversity. The races and ethnicities of the participants are often similar to the population served but favor white, non-Hispanic enrollment. Buchanan et al. (2020) reports that 96.1% of MyCode participants are white and 97.5% are non-Hispanic/non-Latino, compared to 93.2 and 96.0% of active Geisinger patients respectively. Grzymski et al. (2020) reported similar consistency between the racial and ethnic makeup of the Healthy Nevada cohort (81% white, 10% Hispanic/Latino, 3% Asian, 1% African American compared to the Renown Health System (72, 10, 3, 3%, respectively), but an oversampling of white participants and underrepresentation of racial and ethnic minorities compared to Washoe County (63, 25, 5, 2% respectively).

It is critical that this history not be established as the norm for population genomic studies. As recently highlighted by the *All of Us* Research Initiative, oversampling of racial and ethnic minorities and other marginalized groups is achievable with targeted and purposeful effort. Currently, >50% of the *All of Us* cohort identifies as a racial/ethnic minority and >80% are traditionally underrepresented in biomedical research based on gender identity, sexual preference, age, disability status, etc. (https://www.researchallofus.org/data-tools/data-snapshots/) In March 2022, *All of Us* announced the release of nearly 100,000 whole genome sequences from this population, demonstrating the ability to recruit diverse participants for population genomic sequencing efforts specifically. (https://allofus.nih.gov/news-events/announcements/program-releases-first-genomic-dataset).

Elyse Azriel, Lynch syndrome previvor, captures the success of such local efforts and the promise of DNA-based population screening:

> "As a healthy and active 26-year-old, I had no idea that I might have an underlying genetic condition. During an annual physical, my doctor told me about a partnership that our hospital system, located in the northern suburbs of Chicago, had with a genetic testing company. The initiative called 'DNA 10K' was a population health program with the goal to enroll 10,000 patients for genetic testing. She encouraged me to enroll due to my dad's history of colon cancer at age 48. At first, I was hesitant to participate because I had just received a negative result on a direct-to-consumer test six months prior. However, when my doctor explained that this genetic test was more comprehensive and could potentially detect a variant that was more relevant to my family history of colon cancer, I decided to go ahead with it.
>
> This is when I first heard the words "Lynch Syndrome". I found out that I am positive for this genetic variant, which is likely pathogenic and means that I have a higher likelihood of developing several different types of cancers including colorectal and endometrial cancer. Luckily, I am a previvor, which means that I found out that I have Lynch Syndrome prior to ever developing cancer. I also have the privilege of accessing healthcare providers and resources such as colonoscopies and uterine biopsies annually to monitor for any new cancer. Three years later, I am relieved that I am still cancer free"

DISCUSSION

DNA-based population screening has the promise to improve health of all people in all communities. However, if current efforts continue without clear principles and frameworks, there will be continued harm and health inequities especially for those populations in greatest need. There is an urgent need for 'A Call to Action' that keeps equity at the core and involves all partners in DNA-based population screening efforts. Precision public health can use the framework of past and current initiatives in newborn screening as a basis to expand access and equity of DNA-based population screening. Potential actions to consider are:

- Identification and dismantling of systemic barriers that result in health inequities of genomic screening efforts to assure equitable access for people in all communities
- Creation of a national multidisciplinary advisory committee with representation from multiple underserved populations to improve current and inform future DNA-based population screening efforts
- Utilization of well-described framework(s) and criteria such as the revised Wilson and Jungner to guide screening decisions about appropriate conditions to include in DNA-based population screening initiatives
- Adoption of the newly updated Ten Essential Public Health Services with the core of equity in all efforts at the local, state, and national levels

We must embrace the wisdom of Candace Henley to "work hard to take care of the neediest members of our community and provide them with unconditional support".

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

REFERENCES

Andermann, A., Blancquaert, I., Beauchamp, S., and Dery, V. (2008). Revisting Wilson and Jungner in the Genomic Age: a Review of Screening Criteria over the Past 40 Years. *Bull. World Health Organ* 86 (4), 317–319. doi:10.2471/BLT.07.050112

Bowen, M. S., Kolor, K., Dotson, W. D., Ned, R. M., and Khoury, M. J. (2012). Public Health Action in Genomics Is Now Needed beyond Newborn Screening. *Public Health Genomics* 15 (6), 327–334. doi:10.1159/000341889

Buchanan, A. H., Lester Kirchner, H., Schwartz, M. L. B., Kelly, M. A., Schmidlen, T., Jones, L. K., et al. (2020). Clinical Outcomes of a Genomic Screening Program for Actionable Genetic Conditions. *Genet. Med.* 22 (11), 1874–1882. doi:10.1038/s41436-020-0876-4

Castrucci, B. C. (2021). The "10 Essential Public Health Services" Is the Common Framework Needed to Communicate about Public Health. *Am. J. Public Health* 111 (4), 598–599. doi:10.2105/AJPH.2021.306189

Chapman-Davis, E., Zhou, Z. N., Fields, J. C., Frey, M. K., Jordan, B., Sapra, K. J., et al. (2021). Racial and Ethnic Disparities in Genetic Testing at a Hereditary Breast and Ovarian Cancer Center. *J. Gen. Intern Med.* 36, 35–42. doi:10.1007/s11606-020-06064-x

Childers, K. K., Maggard-Gibbons, M., Macinko, J., and Childers, C. P. (2018). National Distribution of Cancer Genetic Testing in the United States. *JAMA Oncol.* 4 (6), 876–879. doi:10.1001/jamaoncol.2018.0340

Grzymski, J. J., Elhanan, G., Morales Rosado, J. A., Smith, E., Schlauch, K. A., Read, R., et al. (2020). Population Genetic Screening Efficiently Identifies Carriers of Autosomal Dominant Diseases. *Nat. Med.* 26 (8), 1235–1239. doi:10.1038/s41591-020-0982-5

Kaiser Family Foundation (2019). Distribution of Medicare Beneficiaries by Eligibility Category. Available at: https://www.kff.org/state-category/medicare/(Accessed on February 27, 2021).

Khoury, M. J., Iademarco, M. F., and Riley, W. T. (2016). Precision Public Health for the Era of Precision Medicine. *Am. J. Prev. Med.* 50 (3), 398–401. doi:10.1016/j.amepre.2015.08.031

Lemke, A. A., Hutten Selkirk, C. G., Glaser, N. S., Sereika, A. W., Wake, D. T., Hulick, P. J., et al. (2017). Primary Care Physician Experiences with Integrated Pharmacogenomic Testing in a Community Health System. *Pers. Med.* 14, 389–400. doi:10.2217/pme-2017-0036

Lin, G. A., Trosman, J. R., Douglas, M. P., Weldon, C. B., Scheuner, M. T., Kurian, A., et al. (2022). Influence of Payer Coverage and Out-of-pocket Costs on Ordering of NGS Panel Tests for Hereditary Cancer in Diverse Settings. *J. Genet. Couns.* 31, 130–139. doi:10.1002/jgc4.1459

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome Sequencing-Based Screening for BRCA1/2 Expected Pathogenic Variants Among Adult Biobank Participants. *JAMA Netw. Open.* 1, e182140. doi:10.1001/jamanetworkopen.2018.2140

National Academies of Sciences, Engineering, and Medicine (2018). *Understanding Disparities in Access to Genomic Medicine: Proceedings of a Workshop*. Washington, DC: The National Academies Press. doi:10.17226/25277

Pearlman, R., Frankel, W. L., Swanson, B. J., Jones, D., Zhao, W., Yilmaz, A., et al. (2021). Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. *JCO Precis. Oncol.* 5, 779–791. doi:10.1200/PO.20.00525

Pritchard, D., Hulick, P. J., and Wells, C. J. (2021). The Integration of Personalized Medicine into Health Systems: Progress and a Path Forward. *Pers. Med.* 18, 527–531. doi:10.2217/pme-2021-0102

Salloum, R. G., George, T. J., Silver, N., Markham, M.-J., Hall, J. M., Guo, Y., et al. (2018). Rural-urban and Racial-Ethnic Differences in Awareness of Direct-To-Consumer Genetic Testing. *BMC Public Health* 18, 277. doi:10.1186/s12889-018-5190-6

Schwartz, M. L. B., McCormick, C. Z., Lazzeri, A. L., Lindbuchler, D. A. M., Hallquist, M. L. G., Manickam, K., et al. (2018). A Model for Genome-First Care: Returning Secondary Genomic Findings to Participants and Their Healthcare Providers in a Large Research Cohort. *Am. J. Hum. Genet.* 103 (3), 328–337. doi:10.1016/j.ajhg.2018.07.009

Shields, A. E., Burke, W., and Levy, D. E. (2008). Differential Use of Available Genetic Tests Among Primary Care Physicians in the United States: Results of a National Survey. *Genet. Med.* 10 (6), 404–414. doi:10.1097/GIM.0b013e3181770184

The Futures Initiative (2020). Celebrating 25 Years and Launching the Revised 10 Essential Public Health Services. Available at: https://phnci.org/national-frameworks/10-ephs (Accessed on February 26, 2021).

Veenstra, D. L., Piper, M., Haddow, J. E., Pauker, S. G., Klein, R., Richards, C. S., et al. (2013). Improving the Efficiency and Relevance of Evidence-Based Recommendations in the Era of Whole-Genome Sequencing: an EGAPP Methods Update. *Genet. Med.* 15, 14–24. doi:10.1038/gim.2012.106

Watson, M. S., Mann, M. Y., Lloyd-Puryear, M. A., Rinaldo, P., and Howell, R. R. (2006). Executive Summary. *Genet. Med.* 8, S1–S11. doi:10.1097/01.gim.0000223891.82390.ad

Weise, N., Shaya, J., Javier-Desloges, J., Cheng, H. H., Madlensky, L., and McKay, R. R. (2021). Disparities in Germline Testing Among Racial Minorities with Prostate Cancer. *Prostate Cancer Prostatic Dis.*, 1–8. doi:10.1038/s41391-021-00469-3

Wilson, J., and Junger, G. (1968). *Princples and Practice of Screening for Disease*. Geneva: World Health Organization.

Yang, S., Axilbund, J. E., O'Leary, E., Michalski, S. T., Evans, R., Lincoln, S. E., et al. (2018). Underdiagnosis of Hereditary Breast and Ovarian Cancer in Medicare Patients: Genetic Testing Criteria Miss the Mark. *Ann. Surg. Oncol.* 25 (10), 2925–2931. doi:10.1245/s10434-018-6621-4

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"Let's Just Wait Until She's Born": Temporal Factors That Shape Decision-Making for Prenatal Genomic Sequencing Amongst Families Underrepresented in Genomic Research

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Genomic sequencing has been increasingly utilized for prenatal diagnosis in recent years and this trend is likely to continue. However, decision-making for parents in the prenatal period is particularly fraught, and prenatal sequencing would significantly expand the complexity of managing health risk information, reproductive options, and healthcare access. This qualitative study investigates decision-making processes amongst parents who enrolled or declined to enroll in the prenatal arm of the California-based Program in Prenatal and Pediatric Genome Sequencing (P3EGS), a study in the Clinical Sequencing Evidence-Generating Research (CSER) consortium that offered whole exome sequencing for fetal anomalies with a focus on underrepresented groups in genomic research. Drawing on the views of 18 prenatal families who agreed to be interviewed after enrolling (n = 15) or declining to enroll (n = 3) in P3EGS, we observed that the timing of sequencing, coupled with unique considerations around experiences of time during pregnancy and prenatal testing, intersect with structural supports beyond the clinic to produce preferences for and against prenatal sequencing and to contain the threat of unwelcome, uncertain knowledge. Particularly for those without structural supports, finding out consequential information may be more palatable after the birth, when the first stage of the uncertain future has been revealed. Future research should examine the role of temporality in decision-making around prenatal genomic sequencing across diverse population cohorts, in order to observe more precisely the role that structural barriers play in patient preferences.

Keywords: ELSI, prenatal exome sequencing, temporality, equity, genomic medicine

INTRODUCTION

After a 22-week ultrasound of their fetus, Erica and David were told that the sonographer "couldn't find her brain–that was the first thing, and when that happens sometimes the baby dies in the stomach before she is born," Erica recalled. There was also an apparent heart defect. Their first worry was that their baby would not carry to term. They were invited and agreed to participate in our study, through which detailed genomic sequencing was performed for their fetus, to improve medical understanding of the multiple structural differences observed. The sequencing took 4 weeks to complete. This is a fast turnaround time for sequencing more generally; however in the prenatal context and for Erica and David it meant that by the time the results were returned, "the time to terminate the pregnancy was over." Besides, explained Erica, "I felt bad at that time because I could already feel her moving." The sequencing identified a pathogenic variant in a gene associated with a brain malformation called Dandy-Walker Syndrome, as well as developmental delay, heart defects, scoliosis and additional complications.

David reflected: "everything can change all of a sudden: Suddenly you look at life and in a moment the panorama completely changes. It is not easy; that's why many people make drastic decisions, like ending the pregnancy, or not doing the tests because people prefer not to know anything because it is not easy. Science is very advanced and that is nice, but sometimes with those news not everyone is prepared."

On the one hand, there was personal reassurance: finding a non-inherited genetic cause meant that it was "nobody's fault, it is something they don't know why it happened—that is the purpose of the tests, to clarify" (David). On the other hand, there was uncertainty: "what I'm worried about now is the heart surgery, because they told us it would be done when she is born (. . .) maybe in 2 months or maybe sooner, and if she's going to need medications too (. . .) we don't know about her brain, if it is minimum or if it will be a lot. We'll see" (Erica). "It is unpredictable, that's the word. We can't say anything because we don't know. Nobody knows. We know about her heart; we know that she has a cyst in the brain and that's our greatest concern. But regarding the rest, we don't know" (David).

Until the birth, nothing felt actionable yet. "We are not in this process yet," Erica said, "we don't know what we will have to deal with, we only have to wait. The only thing is that I think these tests should been done earlier. As I said, before you start feeling the baby moving inside."

The experience of time and decision-making during the prenatal period is fraught. There is a future-oriented tension between prenatal diagnostics—indicating a prognosis for the postnatal experience—and the lived experience of what the fetus already is as a prenatal entity (Völkle and Wettmann 2021). Both the visualizations of the fetus *via* ultrasound and the lived experience of fetal movement, as Erica explained, affirm the fetus as a present, living entity. Any concerning information revealed by structural anomalies on the (approximate) 20-week ultrasound can introduce "sudden" uncertainty about what is to come. The decision to undergo further testing from this point must thus be seen within the context of existing uncertainty, introduced by the ultrasound. For Erica and David, a heart defect was identified *via* ultrasound and, even though it was not clinically part of the genomic sequencing, they had conflated both concerns together. Decision-making is not always contingent on genetic findings; personal beliefs and expectations vary (Richardson and Ormond 2018), while decisions about termination (when available) are yet to rest on genomic sequencing results (Kalynchuk et al., 2015). Erica and David had passed their personal threshold for the time by which they might have terminated the pregnancy. They felt that they now could only wait for their future baby's needs to be revealed after birth. The genomic sequencing result offered some further explanation but ultimately not enough to act upon.

Prenatal genomic sequencing seeks to improve prenatal diagnosis by understanding the reasons for, and potential additional implications of, structural anomalies detected on routine prenatal ultrasound that are not detectable by standard chromosomal microarray or karyotype testing (Lord et al., 2019; Petrovski et al., 2019). Whole exome sequencing evaluates the protein-coding regions of the genome and identifies disease-causing genetic variants. For fetuses with undiagnosed structural abnormalities and otherwise 'normal' microarray results, exome sequencing can provide diagnostic information in as little as 6 percent and as many as 80 percent of cases (Best et al., 2018). This much variation is due to contextual factors, including the number of structural abnormalities observed and whether or not both parents in addition to the fetus can be sequenced (Mellis et al., 2018). While contested in its utility for whole population reproductive healthcare (ISPD et al., 2018), genomic sequencing is increasingly utilized in situations where a fetal structural anomaly is detected (Best et al., 2018). This trend is likely to continue (Fleck and Leslie, 2022).

There are, however, several logistical, experiential and equity challenges of prenatal genomic sequencing that warrant attention. First, timeliness is a huge barrier: turnaround time for sequencing results needs to be faster than in postnatal settings, where the window of potential action or treatment is wider (Kalynchuk et al., 2015). The late gestational age that anomalies are picked up when disorders are detected *via* imaging and the frequent need for another referral for a diagnostic procedure, which takes time, along with the current protocol requiring a microarray first, all compound the added delay of the sequencing process itself—not to mention the stakes now imposed by abortion bans pertaining to gestational age categories. Second, further research is needed to understand how genetic diseases manifest in a fetus and what the implications are of specific genetic variants identified *in utero*. Third, and related to the need for more timely sequencing, there is an impetus to provide access to adequate genetic counselling that takes into account the absence of clear phenotypes and prenatal reference data (Jelin and Neeta, 2018). Economic value for prenatal (and postnatal) interventions, encompassing a pipeline of testing *and* treatments, would need to be raised to meet health payer coverage (Trosman et al., 2020). Finally, patient acceptability of genomic testing across diverse population groups is not equal (Gutierrez and Hailu, 2021).

It is critical to capture the views of families who are underrepresented in genomic research. Populations who do not participate in genomic research remain underrepresented in two central ways. First, families are underrepresented in genomic databases, which thus use limited genetic ancestry information to drive the advancement of diagnostics and precision therapeutics (Sirugo et al., 2019). Individuals who are classified by European descent make up 81 per cent of genomic databases (Popejoy and Fullerton 2016). Second, underrepresented ancestry groups may also experience compounding structural inequalities, including systemic racism (Smith et al., 2016; Lee et al., 2019). For instance, Erica and David were from an ethno-racial minority group, they relied on government health insurance, and English was their second language. They had accessed further prenatal tests through participation in our study. Prenatal sequencing in the United States in its current form is available through exclusive and unequal access at the same time as adding another burden of 'choice' within prenatal care (Yurkiewicz et al., 2014). Yet, as Erica and David illuminated, revelations of uncertainty in prognosis do not just concern one intervention over another. Revelations of uncertainty begin with an ultrasound, before the sequencing option. Being able to pursue a prenatal diagnosis *via* any means is therefore associated with a burden of choice that gives rise to complex, time-pressured decision-making processes—particularly for groups who are underrepresented in genomic research.

This paper investigates how expectant parents from underrepresented groups in genomic research decide whether or not to pursue prenatal genomic sequencing—and the potential ongoing uncertainty it entails—in the context of limited opportunities for action before birth. As Erica and David described, pursuing prenatal genomic sequencing after a concerning ultrasound involves an "unpredictable" experiential process, despite the efforts of researchers and genetic counsellors to prepare expectant parents. Understandably, "people prefer not to know anything because it is not easy"—to hold uncertain information at the same time as, for the pregnant person, feeling at a visceral level the life of their unborn baby "moving inside" them, legitimizing hope and parental care.

Previous research on the temporality of pregnancy and prenatal tests suggests that there are experiential clashes between the linear stages of time informed by ultrasounds and biometric measurements, which give rise to gestational age and birth due dates, and how pregnant persons experience time during pregnancy as more precarious and ultimately negotiable in terms of when the birth takes place—as the first opportunity for post-test actionability (Sänger 2015). It has also been suggested that parents undergoing exome sequencing of their fetus can over-estimate the potential for answers and are likely to be unprepared for the increased uncertainty presented by results (Chandler et al., 2018; Richardson and Ormond 2018). Further, there are limitations to clinical capacities to manage uncertain results for those who pursue genetic testing prior to exome sequencing. Chromosomal microarray–identifying aneuploidy and structural changes in chromosomes that are typically not detectable by standard karyotype tests–places great demand on genetic counselors and obstetricians to account for diagnostic/prognostic uncertainty in a time-sensitive way. Thus microarray results have been described as sometimes imposing "toxic knowledge": knowledge that is not wanted and makes expectant parents feel anxious throughout the remainder of pregnancy, in fear of what might be to come (Bernhardt et al., 2013). Through attention to decision-making processes, temporality, and structural supports, our study ultimately considers the extent to which prenatal genomic sequencing produces more "toxic knowledge"—on top of ultrasound findings—for underrepresented groups in particular, and how experiences of time intersect with decision-making about that potential knowledge.

METHODS

Participants

The University of California, San Francisco (UCSF) initiated the California-based Program in Prenatal and Pediatric Genome Sequencing (P3EGS) in 2017. This was one of six NIH-funded sites in the Clinical Sequencing Evidence-Generating Research (CSER) consortium, investigating both prenatal and pediatric contexts. The main goal of P3EGS was to investigate the clinical and personal utility of exome sequencing, with a focus on underrepresented populations in genomic research. In the prenatal arm, utility applies to prenatal exome sequencing in situations of fetal structural anomalies. Most participating P3EGS families would otherwise be unable to access exome sequencing for their fetus' or child's suspected genetic condition, often due to a reliance on Medicaid/Medi-Cal coverage. Compared to the pediatric arm of the study where most parents (81.9%) relied on Medicaid/Med-Cal, expectant parents in the prenatal arm were predominantly privately insured (73.3%) and had higher incomes.

In addition to selecting participants to maximize inclusion of underrepresented groups, in the case of ongoing pregnancies inclusion also required participant willingness to undergo an amniocentesis first, for which a negative result was reported. We therefore had a selective subgroup of underrepresented populations who, with prior access to prenatal testing, were already dealing with an emotional toll of an anomalous pregnancy at baseline. Participants also underwent genetic counselling to help prepare them for the possibility of more uncertainty with the sequencing findings.

Data Collection

Our analytic sample included 18 families who agreed to be interviewed after either enrolling (n = 15) or declining to enroll (n = 3) in the prenatal arm of P3EGS. Parents of probands (the affected fetus) were invited to participate in semi-structured interviews. The interview sampling strategy aimed to reflect the greater P3EGS cohort, while capturing the specific populations' experiences (underrepresented families). The semi-structured interview guide was developed by the Ethical, Legal and Social Implications (ELSI) research team and included a wide range of topics, as well as specific

TABLE 1 | Participant demographics.

Interviewee(s) names or participant ID	Under represented in genomic research	Medicaid/Medi-Cal	Enrollment status	Sequencing result	Pregnancy status at time of interview
Erica and David	Y	Y	Participant	Positive, *de novo*	Ongoing
Eva	Y	N	Participant	Inconclusive	Ongoing
Jane	N	N	Declined enrollment		Ongoing
Mei	Y	N	Participant	Inconclusive	Terminated (prior to participation)
Melissa	Y	N/A	Declined enrollment		Ongoing
Rachel & Jay	Y	N	Participant	Positive, *de novo*	Ongoing
Susan	N	N	Declined enrollment		Ongoing
Vina & Jim	Y	N	Participant	Negative	Ongoing
Fam 309	N	N	Participant	Positive, *de novo*	Ongoing
Fam 11	Y	Y	Participant	Negative	Terminated
Fam 348	N	N	Participant	Negative	Terminated
Fam 370	Y	N	Participant	Negative	Ongoing
Fam 398	Y	N	Participant	Positive	Ongoing
Fam 41	Y	Y	Participant	Inconclusive	Terminated
Fam 442	N	N	Declined results		Terminated
Fam 596	Y	Y	Participant	Inconclusive, *de novo*	Ongoing
Fam 195	N	N	Participant	Positive, *de novo*	Ongoing
Fam 86	Y	N	Participant	Positive, *de novo*	Ongoing

questions related to the pursuit of prenatal genomic sequencing. Interviews were conducted either at the family's home, over the phone, or *via* videoconference. Each interview had a duration of between 30 and 60 min. All interviews were conducted by three members of the ELSI research team with training in ethnographic data collection. Most interviews were conducted in English or Spanish, the latter of which were transcribed and translated to English for coding and analysis.

Data Analysis

Qualitative analysis of interview transcripts involved thematic coding (Boyatzis 1998; Braun and Clarke 2006). An inductive approach was implemented whereby emerging patterns and themes were determined a *posteriori*. Data were analyzed using a pre-discussed set of qualitative codes. Codes were developed following what was being learned through initial observations and interviews. The ELSI research team iteratively conducted the process of coding and generating themes to increase the reliability of the iterative analysis. Themes were summarized to gain insight and provide an overall picture of the reasoning for each family's pursuit for prenatal genomic sequencing.

RESULTS

Below we describe how temporal factors shaped decision-making amongst 18 families who agreed to be interviewed after either enrolling (n = 14), enrolling and not receiving results (n = 1) or declining to enroll (n = 3). Building on Erica and David's case, we cite interviews from eight of these families, including five participants who enrolled and the three who declined to enroll. For families quoted in this paper, we use pseudonyms to balance the protection of participant identity and data integrity (Saunders et al., 2015). **Table 1** reports on select demographics for all families, including whether families are considered underrepresented in genomic research by ethno-racial status (yes or no) and whether families were enrolled in government insurance (Medicaid/Medi-Cal) (yes or no). Given that most people giving birth in California are enrolled in Medicaid/Medi-Cal, our study sample indicates disparities in access and a selection bias towards those who could access private health insurance for prenatal care.

We observed that decisions to participate in prenatal genomic sequencing are guided by time availability, social supports, and confidence in being able to plan for an uncertain future. These factors may be influenced by broader structural and socioeconomic conditions, which along with temporality ought to be better accounted for in considerations of the potential benefits and harms of prenatal sequencing and how these are distributed. We have categorized our results under two key findings: 1) Decision-making takes time and support beyond what the clinic can provide; and 2) In the absence of timeliness and actionability, expectant parents keep the future open for as long as possible.

Decision-Making Takes Time and Support Beyond What the Clinic can Provide

Making the decision about participation in prenatal sequencing takes time and personal assurance. The time it took participants to process relevant information may extend outside of when clinical advice is received, for several reasons. First, sorting through information in the clinical setting naturally invites more attention to medical concerns. Jane who declined to participate explained:

> I feel like being in the hospital setting and always kind of under that pressure or I feel like there's always this analysis going on about looking for potential

> risks—everything is very like risk-focused . . . I want to feel empowered.

Even expectant parents who, on the contrary, felt empowered while at the clinic to participate still sometimes changed their minds after leaving the clinic. For instance, after having blood drawn "with the intention of participating," Susan and her partner walked back on their decision:

> We talked to (the genetic counsellor) about it and . . . she was saying that they would use that to . . . narrow down, you know, [fetus'] sequence. So, I thought about that when we were talking to her, but then I thought more on it later, over the weekend, after we had talked about it. And we were like, you know what, let's just not . . . you can only do what you feel is best in that moment.

Second, for those who participated in our study, decision-making was often based on feeling more able to think clearly after leaving the clinical setting. Rachel explained, "it was a lot of information. She [the genetic counselor] gave us a lot of information that we . . . we hear everything here and then we just, in the car, right, we start processing it." Her partner, Jay, also described:

> Afterwards we thought about the implications. We didn't necessarily think about them all in the moment. I don't think in the conversation itself we necessarily said "do we actually—you know, what does this come back to? You know, what does that mean and how do we react to it?" That part is, you know, it took some time to kind of process that and think that through and get to that stage of conversation. It wasn't much longer. I think maybe on the car ride home.

Others felt overwhelmed regardless of the clinical or personal setting they were in. Melissa, who declined to participate, recalled:

> I kind of just stayed quiet and they gave me a call and I was like, "You know what, let's just, you know, let's not do this. I'm just really scared, just terrified." . . . me being stubborn and selfish and just scared, I was like, "Okay, I just don't want to know until she's born." . . . I just had so much going on, like my mind was, like, going blank.

Patients struggled to process the fetal anomalies, and the option of genetic testing on top of that was often just too much.

Mei, who participated in our study after terminating her pregnancy, described feeling similarly overwhelmed in processing information pertaining to the sequencing results. While inconclusive, there was an indication of "MEHMO," characterized by severe intellectual disability, epileptic seizures, hypogenitalism, microcephaly and obesity. Mei described that the order of delivery of information may have interfered with her ability to process what she was hearing:

> (the genetic counsellor) kind of went straight into "This mutation is called this thing." And it was so technical that I, A) could not really follow, even though I'm medically trained, I could not really follow . . . I was just surprised that there was a result at all. So, I wasn't really following the details and I just found it to be very technical for like a very long time. And hard to figure out, like, what does this mean? . . . I actually wished that I had gotten a synth"esis from a physician first, to set the stage for "This is where you are about to hear," and then go into, "Okay, there's this thing called MEHMO. There's this many identified pathogenic mutations." You know," you have a non-pathogenic, or a not identified variant," you know, like, all the details would've followed better after the high level synthesis, or just some kind of mental preparation. Like, you know, "Out of the spectrum of outcomes, "here's where you are and now let me tell you the details" . . . some kind of guiding statement would've helped.

Mei had made the decision to terminate based on both a follow-up fetal MRI, which "confirmed the diagnosis of agenesis of the corpus callosum," and the seeking a second opinion. She explained that participating in P3EGS came "quite some time after that—after we had the termination . . . And, I honestly wasn't expecting [the study] to find anything; I just thought, 'I support research and so I don't mind going through the process'." Upon receiving the results for which she felt completely unprepared for, she felt the need for personal space to process this new information:

> I had assumed that, just from the correspondence, there seemed to be no urgency, no rush. There was, I think (the genetic counselor) was even surprised that I was at work and not like somewhere, you know, more private . . . I don't think I was mentally prepared to be in a quiet place, you know, with some privacy, to really soak it in.

Finding "a quiet place" meant finding a supportive place—that would either affirm or challenge initial views. For Jane, who had "decided during the interview session" not to participate, it was in talking through the decision with her friends, who had "said, 'Good for you' . . . and just talking with other mothers, it seems like, you know, a lot of moms have felt like it has caused a lot of unnecessary stress in the pregnancy." There was a sense of solidarity and trust in others about her reasoning.

That said, sometimes final decision-making differed between partners. Melissa, who had declined genomic sequencing for their fetus due to feeling overwhelmed at the time, later agreed to have genetic testing on herself, however her partner refused. The test result brought her personal relief: "with me, there was no trait or anything that could have been passed down to (Proband) . . . that was a big thing for me . . . I felt so guilty for the longest time until

they told me, "No, it is not your fault . . ." It was just like eating me alive. It was horrible." Nonetheless, with this new knowledge about herself came the challenge of how to manage her family's expectations:

> it's just so hard to even like explain to my family now . . . my family has been driving me nuts, just asking all these questions . . . my family is just typical Mexican. They're like, "Oh, she'll get over it, she'll get over it, she'll get over it." You know, that's just them. So, I get frustrated when they ask me questions.

Finding a sense of ownership over the genomic sequencing experience takes time, which pregnancy cannot easily afford. Moreover, agreeing to participate in fetal sequencing can mean tempting a future that parents are not yet ready to accept.

In the Absence of Timeliness and Actionability, Expectant Parents Keep the Future Open for as Long as Possible

Expectant parents face a tension between appreciating the as-yet-known health status of their fetus and using information to prepare for the birth of their baby. As described in reference to Erica and David, obtaining more information while being unable to act until a baby is born can be anxiety-inducing because there are still many unknowns: "we are not in this process yet . . . we only have to wait (until the birth)." Melissa explicitly stated about her decision to decline:

> I just didn't want to know like something horrible was going to happen to her, just like know this could happen when she's born. It was just more like—then when she's born, if this happens, it's not more of a shock . . . It's like, "let's just wait until she's born, just to know when she's born." Not to, like, know beforehand. It's not a very pleasant feeling to know something is there.

After their daughter was born, Melissa had felt more inclined to have genetic testing not only for her own personal reassurance, but also because "now that her heart's working perfectly, she's looking good, it is like, 'let's just know, you know, now that she's here.' And if we could catch something now, that would be great . . . Now that she's here, yes, definitely, so we could just catch something before it is too late." It was only from birth onwards that the feeling of control over the future began to take hold.

Fear of finding out information before being able to act on it also took the form of declining to participate due to fears further down the line regarding secondary consequences of what might be disclosed:

> If we did discover that we had some kind of preexisting condition that might be adult onset, like do we want to live in fear or anxiety about this like our entire lives? . . . we just wanted to live and not really be thinking about all those things . . . it was just opening up a can of worms and where would it end, where would all of this testing end? . . . what do we do with all of this information? . . . I've already had a few ultrasounds where they had different information about my due date. And, so, I don't really like feeling all this anxiety.

While information about adult-onset conditions in a fetus was distinct and optional information, to be disclosed only if participants wanted, these expectant parents retained concern that there were no limits on the genetic information disclosed. Nonetheless, their decision-making seemed to involve having a greater sense of confidence in how knowledge can be put out of harm's way when it is not relevant to present circumstances.

Some expectant parents asserted that prenatal genomic sequencing "provides us [with] even more information and being just educated . . . one less thing that we have to worry about" (Vina), or that "it gives us choices, and where knowledge is better than not having nothing" (Vina's partner, Jim). Yet, as Erica described, this was perhaps dependent on how participants subjectively viewed the timeliness of the tests in regard to their personal (as well as the legal) thresholds for termination options.

Eva, who was not considering termination and decided to participate in P3EGS after a longer period of dealing with uncertainty having accessed a 12-week ultrasound, which revealed a potential heart anomaly, reflected:

> It was kind of amazing to find out like at 12 weeks that they recognize, "hey, there's something wrong," you know, "something doesn't look right with the heart." And to know that early on . . . it's not what you want to hear but it's beneficial in the big picture, in the sense that you can kind of prepare . . . what if we didn't . . . and we just went along thinking "everything's great, everything's fine," and then it's not until he's born that we're—you know, and it would just completely derail us. Whereas it gave us a lot more time to kind of mentally prepare and figure things out as we went along, [rather] than just getting hit really hard at the end.

This contrasts sharply with Erica and David's experiences, who, after receiving an abnormal ultrasound reading at 22 weeks and genomic sequencing results at 26 weeks, felt like the time to act had already passed. Again, selecting the appropriate social support can help buffer against fears of the future. In navigating the uncertainty of what was to come, David commented that "in life we have a person who . . . he wishes to share things with. It is nice because when I tell my mother, she will not say to me, 'it is because of this or because of that.' No, she tells me, 'It is in God's hands. He will know what do to'." David had not shared the information with his siblings because "sometimes you prefer not to worry people, especially when it is such a hard situation. So far, we have it under control and I prefer not to tell them." Only after baby's birth would the couple be confronted with familial reactions that they did not feel ready for.

Other parents who declined genomic sequencing were able to, for the duration of pregnancy at least, feel confident in the

hopeful information given through prior prenatal testing, rather than tempting more information through sequencing:

> I just don't feel like there's any reason to do further testing . . . the other test that we did came out normal. There wasn't anything unusual . . . I was comfortable with the results, where I felt like I didn't really need to delve deeper into the exome sequencing study . . . I think I just wanted to really trust my intuition and . . . I feel like the baby is healthy and I don't really want to go through further testing when all the test results that we've gotten back so far have been normal. (Jane)

Accepting prenatal genomic sequencing could also mean a burden to think even further down the line into the future. Jane, who explained that they were confident in the information already provided through ultrasound, thus declining sequencing, summarized the full extent of their concerns: "I didn't want to live in fear and anxiety based on the results of the study, and I also didn't want it to affect my child or our potential ability to get insurance." Beyond questions of healthcare coverage (which, contrary to some confusion, is protected under discrimination laws), there were legitime concerns about future life insurance coverage and the multitude of uncertain future implications for the future child. Susan, who had decided to pull out at the last minute, elaborated:

> We didn't feel that—specifically, that getting the information from the exome mapping for our daughter, [fetus], was going to change how we felt about her treatment or any decisions that we made about her treatment in the short term . . . it wasn't really going to affect us directly, but if it would be something that would be helpful for other families in the future . . . But then (the genetic counsellor) kind of reiterated, well, "there is information that you may find that may become helpful for you" . . . it was clear that there was potential for that . . . I remember it registering in my brain somewhere . . . but . . . we were still going to proceed and participate. And then the conversation with my husband about like, "oh, well, maybe this could negatively impact her in the future," you know, that was kind of the deciding factor for us to pull out.

Expectant parents can view the actionability of genetic testing results in pregnancy as limited by the lack of available fetal treatments. Especially if the results are uncertain, "it is not enough to make decisions on, it is not definitive but it is also not as reassuring," explained Mei.

For those seeking longer-term reassurance, prenatal genomic sequencing threatened to disrupt shorter-term confidence. Out of the 316 prenatal families who participated in exome sequencing in our study, nine families chose not to receive their results after the test results were ready. At least two of these families (that could be reached) said explicitly that they declined because they did not wish to learn the results. In these situations, there was nothing to act upon with the current pregnancy: one ended in termination and the other ended in miscarriage. The couple who terminated their pregnancy were from an underrepresented ethno-racial group who also relied on Medicaid. Further, 7/9 of the families that did not receive results relied on Medicaid and a respective 7/9 were identified as underrepresented ethno-racial group.

Expectant parents who chose to terminate their pregnancy appeared to feel that the information, while overwhelming to process at the time, became relevant upon further reflection when starting to plan for future pregnancies. Mei, who terminated her pregnancy before receiving the result, explained how she wished she had "screenshot" the information sent through after the consult rather than having to wait for it to be mailed out, because "the height of the issue was the couple of days after," when her and her partner, who had conceived the terminated pregnancy *via* IVF, were deciding—a few days after the sequencing result came through—whether to transfer one of their remaining embryos already available to do another IVF cycle and seek a preimplantation genetic diagnosis. In seeking more information, "if I had pushed this any further, we would have been past the decision point of which I'm going to transfer." They drew on information they recalled from return of results to "read more about it, understand more, and then to make a decision," which was to transfer a female embryo "to be safe" because the inconclusive result was an "X-linked" condition.

Parents also often erred on the side of hope, giving possible undesirable outcomes the benefit of doubt, when making decisions to pursue current or future pregnancies. Mei rationalized that the variant of unknown significance was reported "because it is a variant in a gene that has some kind of brain effect, even though it is the same thing that our fetus actually had . . . it was more of a conservative reporting" and "even though we don't know if it is a pathogenic or not pathogenic variant, I still suspect that probably not."

DISCUSSION

This paper has demonstrated the importance of experiences of temporality in considerations about prenatal genomic sequencing—both the unique timing factors imposed by the prenatal period of clinical timeframes and the lived experiences of time pressures and structural barriers when faced with making decisions about sequencing and waiting for results. Prenatal testing has long produced a 'tentative pregnancy' (Rothman 1986). For expectant parents, decision-making around genomic sequencing may rest on the extent to which sequencing makes their pregnancy feel even more tentative at a time when women like Erica are already "feeling the baby moving inside." Consistent with previous research on temporal experiences and conflicts imposed by prenatal testing (Sänger 2015), interviewees in our study described processing information and managing uncertainty in a non-linear way compared with clinical expectations. Declining prenatal genomic testing may help to suspend future uncertainties about outcomes, allowing parents to maximize control of the pregnancy. Critically, the greater ability to delay the possibilities of illness while a future baby remains *in utero* stands in contrast to newborn screening for genetic disease.

In the contrasting case of newborn screening, parents of newborns are left to navigate the possibility of 'illness in spite of symptoms or a diagnosis' such that they become 'patients-in-waiting,' navigating between 'an unremarkable state of "normalness" and "disease"' that ultimately requires 'patience' until clear symptoms manifest (Timmermans and Buchbinder 2010: 417; 418). In the prenatal period, expectant parents are more likely to experience a sense of indeterminability and inactionability, which lends to more empowerment to make decisions on their own terms.

At a practical level, the search for more information becomes more productive when information is actionable. While prenatal interventions are available for some fetal anomalies and genetic diseases, such as *in utero* transfusions for inherited anemias, prenatal interventions at this time do not exist for most disease and are generally not curative. Thus, finding out consequential information may be more palatable either before pregnancy (*via* expanded parental carrier genetic testing, which many are not offered) or else after the birth when the first stage of the uncertain future has been revealed.

In the absence of prenatal treatments or the possibility of termination (depending on both patient and provider views and state regulations), parents may feel that nothing is actionable until the point of birth. Melissa had described declining genomic sequencing because she wanted to "just wait until she's born . . . It is not a very pleasant feeling to know something is there," without being able to know for sure or to do anything about it. For others, like Eva, participating in prenatal genomic sequencing provided "a lot more time to kind of mentally prepare and figure things out as we went along [rather] than just getting hit really hard at the end." Eva, however, had begun the process of mental preparation at the 12-week ultrasound. Most parents eligible for prenatal genomic sequencing will not find out about structural anomalies until the 20-week ultrasound.

Prenatal genomic sequencing expands the orbit of managing health risk information, reproductive options, and systemic healthcare barriers introduced by earlier prenatal technologies. Racial disparities have long been a concern (Taylor et al., 2019), including in terms of access to prenatal genetic counseling (Christopher et al., 2022), a service that provides a critical opportunity for discussion about the level of uncertainty that might be acceptable to different expectant parents (Harris et al., 2018). Historically in California, declining earlier prenatal tests such as maternal serum alpha-fetoprotein (AFP), chorionic villus sampling (CVS) and amniocentesis was associated with racial and ethnic minority status and English language barriers (Kuppermann et al., 1996; Press and Browner 1998). Factors such as discomfort with and trust in clinical protocols and social rapport with clinicians, skepticism of statistical predictions, and religious beliefs were found to also shape declinations of amniocentesis, although these factors can be construed along social class lines as much as ethno-racial lines (Rapp 1998). For instance, acceptance of amniocentesis may be more likely amongst parents with higher education rather than ethnic or racial determinants per se (Saucier et al., 2005). In the case of today's genomic sequencing, less is known about the dynamics of prenatal social barriers beyond logistical and access issues (Bernhardt et al., 2013). For pediatric patients with rare disease, social demographic variables such as limited healthcare access and English language barriers can exclude parents from support groups, lowering the perceived utility of genomic sequencing for parents (Halley et al., 2022). Our study suggests that for expectant parents who have undergone ultrasound and amniocentesis to now be considering genomic sequencing, there may also be issues around what structural supports are in place to deal with return of results should they imply that further healthcare and support will be needed post-birth. English speaking barriers may compound these needs. Having supports in place to manage the outcomes of genomic sequencing is critical, and this factor may become more pressing the further along in the pregnancy parents are.

In terms of decision-making about whether to participate in genomic sequencing in the first instance, there were numerous temporal and structural factors at play. Some expectant parents appeared less likely to get reassurance about their decision-making process from within the clinical setting. Amongst the minority who decide while in the clinic, they still sometimes changed their minds upon talking it through with family. Earlier research on why expectant parents decline maternal serum alpha-fetoprotein (AFP) suggests there is an association between taking more time to decide to decline AFP and being able to talk it over with family (Press and Browner 1998). We were unable to test this hypothesis specifically, however our findings point to the need for expectant parents to seek guidance beyond the clinic. Given previous ethnographic findings that underrepresented groups may be more likely to decline amniocentesis following consultation with family members (Rapp 1998), it is pertinent to consider how a sense independence from clinical input is either collective (family) or individual. Even if family members are present during clinical conversations, they might remain silent until returning to private spaces where they feel more empowered, and less encumbered by a lack of social relatability with clinicians, to express their concerns (Rapp 1998). Our finding that there can be a divergence between expectant parents in their decisions to pursue their own exome sequencing as additional information for the fetus (demonstrated in the case of Melissa) suggests that whereas family-influenced decision-making may have been historically colored by gendered roles (Rapp 1998), female-identifying expectant parents can assert more independence in their decision-making while still consulting family.

The tendency to seek one's own information and social support in the prenatal period may depend on structural supports. This process may serve as a precursor to the ongoing "therapeutic odyssey" that parents face in the pediatric context, where genomic sequencing is only one part of a larger process that happens outside of the clinical setting (Childerhose et al., 2021). For other expectant parents, and perhaps more likely those with greater structural supports, they were more likely to feel confident in either the information presented in the clinical setting in the moment or to change their minds later after talking with their social supports. A previous Canadian study of decision-making about non-invasive prenatal testing (NIPT) to test for Down Syndrome observed that just over half of expectant parents envisaged being able to make a decision within the appointment where

information was given about NIPT, with the rest preferring to take a few days to consider (Laberge et al., 2019). The study also found that previous knowledge (about Down Syndrome and NIPT) played little role in decision-making: expectant parents 'do not necessarily need different types of information, but they simply need time to reflect on how to integrate this new knowledge into their decision-making process along with their values and preferences' (Laberge et al., 2019). Parents in Laberge et al.'s study were predominantly white, with access to universal prenatal healthcare. Our study suggests that, in practice, decision-making may be even less likely to happen within the same information session for expectant parents facing structural barriers.

The time taken to process information has important implications for informed consent. Amongst the larger P3EGS cohort, there was poor recollection of deciding whether or not to consent to broad data sharing of genomic information (Norstad et al., 2021). Previous research also suggests that, although expectant parents appreciate clinical support in their decision-making about prenatal whole exome sequencing, they would appreciate if the sequencing results were more timely, with more attention given to uncertainty, and with a preference for results to be repeated and delivered *via* multiple formats, as a way of ensuring more understanding of results (Quinlan-Jones et al., 2017). We have highlighted in this paper, however, that the delivery of information (and the timing of consent) is also complicated by the incongruence between the level of preparedness that might be expected from clinicians delivering information and the time, space and support that expectant parents may need beyond the clinical setting to sort through uncertain information and empower themselves in the decision-making process.

Implications for Future Research

Future research should examine the role of temporality in decision-making around prenatal genomic sequencing across diverse population cohorts, to observe more precisely the role those structural barriers play in patient preferences. Returning to our question posed in the Introduction, of whether prenatal genomic sequencing may produce more "toxic knowledge" for expectant parents and clinicians to navigate (Bernhardt et al., 2013), our study has demonstrated that the experience of liminal time in the prenatal period, as well as social supports beyond the clinic, may help families to contain the threat of unwelcome, uncertain knowledge. As underrepresented groups in genomic research are also disadvantaged by having less access to social and structural supports that shape health (Smith et al., 2016), it is critical consider how clinical supports may be better harnessed to enable timely planning toward the future and acting on uncertain information.

Often underrecognized by both patients and providers is that identifying a prenatal diagnosis also allows for advance preparation for continuing pregnancies. For example, plans can be made for a fetus found to have an inborn error of metabolism to be delivered at a tertiary care institution, with a metabolic geneticist and availability of enzyme replacement therapy. The utility of such considerations merit further exploration with patients as they weigh decisions about whether to undergo genomic sequencing during pregnancy. Even in the absence of an intervention, there may be opportunities for more frequent monitoring and meeting with subspecialists to plan for delivery and to manage expectations. That said, for those who decline sequencing, it is important to give expectant parents space to run with the hope that they might have about an alternative future, which keeps them from tempting the unknown. Refusing more information can in some circumstances be preferable and empowering during what is already such a stressful time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of California San Francisco Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

Conceptualization: SA; Data Curation: JB, AZ, SO, NS, and SA; Formal Analysis: JB and TS; Funding Acquisition: MEN; Writing-original draft: JB; Writing-reviewing and editing: JB, AZ, SO, TS, BL, MN, NS, MEN, and SA.

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REFERENCES

Bernhardt, B. A., Soucier, D., Hanson, K., Savage, M. S., Jackson, L., and Wapner, R. J. (2013). Women's Experiences Receiving Abnormal Prenatal Chromosomal Microarray Testing Results. *Genet. Med.* 15 (2), 139–145. doi:10.1038/gim.2012.113

Best, S., Wou, K., Vora, N., Van der Veyver, I. B., Wapner, R., and Chitty, L. S. (2018). Promises, Pitfalls and Practicalities of Prenatal Whole Exome Sequencing. *Prenat. Diagn* 38 (1), 10–19. doi:10.1002/pd.5102

Boyatzis, R. E. (1998). Transforming Qualitative Information: Thematic Analysis And Code Development. *Transforming Qualitative Information: Thematic Analysis and Code Development*. Thousand Oaks, CA, US: Sage Publications, Inc.

Braun, V., and Clarke, V. (2006). Using Thematic Analysis in Psychology. *Qual. Res. Psychol.* 3 (2), 77–101. doi:10.1191/1478088706qp063oa

Chandler, N., Best, S., Hayward, J., Faravelli, F., Mansour, S., Kivuva, E., et al. (2018). Rapid Prenatal Diagnosis Using Targeted Exome Sequencing: A Cohort Study to Assess Feasibility and Potential Impact on Prenatal Counseling and Pregnancy Management. *Genet. Med.* 20 (11), 1430–1437. doi:10.1038/gim.2018.30

Childerhose, J. E., Rich, C., East, K. M., Kelley, W. V., Simmons, S., Finnila, C. R., et al. (2021). The Therapeutic Odyssey: Positioning Genomic Sequencing in the Search for a Child's Best Possible Life. *AJOB Empir. Bioeth.* 12 (3), 179–189. doi:10.1080/23294515.2021.1907475

Christopher, D., Fringuello, M., Fought, A. J., Bolt, M., Micke, K., Elfman, H., et al. (2022). Evaluating for Disparities in Prenatal Genetic Counseling. *Am. J. Obstetrics Gynecol. MFM* 4 (1), 100494. doi:10.1016/j.ajogmf.2021.100494

Fleck, L. M., and Francis, L. (2022). Should Whole Genome Sequencing Be Publicly Funded for Everyone as a Matter of Healthcare Justice? *Camb Q. Healthc. Ethics* 31 (1), 5–15. doi:10.1017/s0963180121000426

Gutierrez, A. M., Robinson, J. O., Outram, S. M., Smith, H. S., Kraft, S. A., Donohue, K. E., et al. (2021). Examining Access to Care in Clinical Genomic Research and Medicine: Experiences from the CSER Consortium. *J. Clin. Transl. Sci.* 5 (1), e193. doi:10.1017/cts.2021.855,

Halley, M. C., Young, J. L., Fernandez, L., Kohler, J. N., Bernstein, J. A., Wheeler, M. T., et al.Undiagnosed Diseases Network (2022). Perceived Utility and Disutility of Genomic Sequencing for Pediatric Patients: Perspectives from Parents with Diverse Sociodemographic Characteristics. *Am. J. Med. Genet. Part A* 188 (4), 1088–1101. doi:10.1002/ajmg.a.62619

Harris, S., Gilmore, K., Hardisty, E., Lyerly, A. D., and Vora, N. L. (2018). Ethical and Counseling Challenges in Prenatal Exome Sequencing. *Prenat. Diagn.* 38 (12), 897–903. doi:10.1002/pd.5353

ISPDS; MFM; PQF (2018). Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the Use of Genome-wide Sequencing for Fetal Diagnosis. *Prenat. Diagn* 38 (1), 6–9. doi:10.1002/pd.5195

Jelin, A. C., and Vora, N. (2018). Whole Exome Sequencing. *Obstetrics Gynecol. Clin. N. Am.* 45 (1), 69–81. doi:10.1016/j.ogc.2017.10.003

Kalynchuk, E. J., Althouse, A., Parker, L. S., Saller, D. N., Jr, and Rajkovic, A. (2015). Prenatal Whole-Exome Sequencing: Parental Attitudes. *Prenat. Diagn* 35 (10), 1030–1036. doi:10.1002/pd.4635

Kuppermann, M., Gates, E., and Eugenewashington, A. (1996). Racial-Ethnic Differences in Prenatal Diagnostic Test Use and Outcomes: Preferences, Socioeconomics, or Patient Knowledge? *Obstetrics Gynecol.* 87 (5), 675–682. doi:10.1016/0029-7844(96)00017-8

Laberge, A.-M., Birko, S., Lemoine, M.-È., Le Clerc-Blain, J., Haidar, H., Affdal, A. O., et al. (2019). Canadian Pregnant Women's Preferences Regarding NIPT for Down Syndrome: The Information They Want, How They Want to Get it, and with Whom They Want to Discuss it. *J. Obstetrics Gynaecol. Can.* 41 (6), 782–791. doi:10.1016/j.jogc.2018.11.003

Lee, S. S-J., Cho, M. K., Kraft, S. A., Varsava, Nina., Gillespie, Katie., Kelly, E., et al. (2019). I Don't Want to Be Henrietta Lacks": Diverse Patient Perspectives on Donating Biospecimens for Precision Medicine Research. *Genet. Med.* 21 (1), 107–113. doi:10.1038/s41436-018-0032-6

Lord, J., McMullan, D. J., Eberhardt, R. Y., Hamilton, E., Rinck, G., Hamilton, S. J., et al. (2019). Prenatal Exome Sequencing Analysis in Fetal Structural Anomalies Detected by Ultrasonography (PAGE): A Cohort Study. *Lancet* 393 (10173), 747–757. doi:10.1016/s0140-6736(18)31940-8

Mellis, R., Chandler, N., and Chitty, L. S. (2018). Next-Generation Sequencing and the Impact on Prenatal Diagnosis. *Expert Rev. Mol. Diagnostics* 18 (8), 689–699. doi:10.1080/14737159.2018.1493924

Norstad, M., Outram, S., Brown, J. E., Zamora, A. N., Koenig, B. A., Risch, N., et al. (2021). The Difficulties of Broad Data Sharing in Genomic Medicine: Empirical Evidence from Diverse Participants in Prenatal and Pediatric Clinical Genomics Research. *Genet. Med.*

Petrovski, S., Aggarwal, V., Giordano, J. L., Stosic, M., Wou, K., Bier, L., et al. (2019). Whole-Exome Sequencing in the Evaluation of Fetal Structural Anomalies: A Prospective Cohort Study. *Lancet* 393 (10173), 758–767. doi:10.1016/s0140-6736(18)32042-7

Popejoy, A. B., and Fullerton, S. M. (2016). Genomics Is Failing on Diversity. *Nature* 538, 7624161–7624164. doi:10.1038/538161a

Press, N., and Browner, C. H. (1998). Characteristics of Women Who Refuse an Offer of Prenatal Diagnosis: Data from the California Maternal Serum Alpha Fetoprotein Blood Test Experience. *Am. J. Med. Genet.* 78 (5), 433–445. doi:10.1002/(sici)1096-8628(19980806)78:5<433::aid-ajmg8>3.0.co;2-m

Quinlan-Jones, Elizabeth., Hillman, Sarah. C., Kilby, Mark. D., and Greenfield, Sheila. M. (2017). Parental Experiences of Prenatal Whole Exome Sequencing (WES) in Cases of Ultrasound Diagnosed Fetal Structural Anomaly. *Prenat. Diagn.* 37 (12), 1225–1231.

Rapp, R. (1998). Refusing Prenatal Diagnosis: The Meanings of Bioscience in a Multicultural World. *Sci. Technol. Hum. Values* 23 (1), 45–70. doi:10.1177/016224399802300103

Richardson, A., and Ormond, K. E. (2018). Ethical Considerations in Prenatal Testing: Genomic Testing and Medical Uncertainty. *Seminars Fetal Neonatal Med.* 23, 1–6. doi:10.1016/j.siny.2017.10.001

Rothman, B. K. (1986). *The Tentative Pregnancy: Prenatal Diagnosis and the Future of Motherhood*. New York: Norton.

Sänger, Eva. (2015). Obstetrical Care as a Matter of Time: Ultrasound Screening, Temporality and Prevention. *Hist. Philosophy Life Sci.* 37 (1), 105–120. doi:10.1007/s40656-014-0056-4

Saucier, J. B., Johnston, D., Wicklund, C. A., Robbins-Furman, P., Hecht, J. T., and Monga, M. (2005). Racial-Ethnic Differences in Genetic Amniocentesis Uptake. *J. Genet. Couns.* 14 (3), 189–195. doi:10.1007/s10897-005-0641-5

Saunders, B., Kitzinger, J., and Kitzinger, C. (2015). Anonymising Interview Data: Challenges and Compromise in Practice. *Qual. Res.* 15 (5), 616–632. doi:10.1177/1468794114550439

Sirugo, G., Williams, S. M., and Tishkoff, S. A. (2019). The Missing Diversity in Human Genetic Studies. *Cell.* 177 (1), 26–31. doi:10.1016/j.cell.2019.04.032

Smith, C. E., Fullerton, S. M., Dookeran, K. A., Hampel, H., Tin, A., Maruthur, N. M., et al. (2016). Using Genetic Technologies to Reduce, rather Than Widen, Health Disparities. *Health Aff.* 358, 1367–1373. doi:10.1377/hlthaff.2015.1476

Taylor, J., Novoa, C, Hamm, K, and Phadke, S. (2019). *Eliminating Racial Disparities in Maternal and Infant Mortality: A Comprehensive Policy Blueprint*. Center for American Progress.Available at: https://www.americanprogress.org/issues/women/reports/2019/05/02/469186/eliminating-racial-disparities-maternal-infant-mortality/.

Timmermans, S., and Buchbinder, M. (2010). Patients-in-Waiting. *J. Health Soc. Behav.* 51 (4), 408–423. doi:10.1177/0022146510386794

Trosman, J. R., Weldon, C. B., Slavotinek, A., Norton, M. E., Douglas, M. P., and Phillips, K. A. (2020). Perspectives of US Private Payers on Insurance Coverage for Pediatric and Prenatal Exome Sequencing: Results of a Study from the Program in Prenatal and Pediatric Genomic Sequencing (P3EGS). *Genet. Med.* 22 (2), 283–291. doi:10.1038/s41436-019-0650-7

Völkle, Laura., and Wettmann, Nico. (2021). The Process of Pregnancy: Paradoxical Temporalities of Prenatal Entities. *Hum. Stud.* 44 (4), 595–614.

Yurkiewicz, I. R., Korf, L. S., and Lehmann., L. S. (2014). Prenatal Whole-Genome Sequencing? *Obstetrical Gynecol. Surv.* 69 (4), 197–199. doi:10.1097/01.ogx.0000446907.09890.ff

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Pursuing Public Health Benefit Within National Genomic Initiatives: Learning From Different Policies

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Introduction: Population-based genomic research is expected to deliver substantial public health benefits. National genomics initiatives are widespread, with large-scale collection and research of human genomic data. To date, little is known about the actual public health benefit that is yielded from such initiatives. In this study, we explore how public health benefit is being pursued in a selection of national genomics initiatives.

Methods: A mixed-method study was carried out, consisting of a literature-based comparison of 11 purposively sampled national genomics initiatives (Belgium, Denmark, Estonia, Finland, Germany, Iceland, Qatar, Saudi Arabia, Taiwan, United Kingdom (UK), and United States (USA)), and five semi-structured interviews with experts (Denmark, Estonia, Finland, UK, USA). It was analyzed to what extent and how public health benefit was pursued and then operationalized in each phase of an adapted public health policy cycle: agenda setting, governance, (research) strategy towards health benefit, implementation, evaluation.

Results: Public health benefit within national genomics initiatives was pursued in all initiatives and also operationalized in all phases of the public health policy cycle. The inclusion of public health benefit in genomics initiatives seemed dependent on the outcomes of agenda setting, such as the aims and values, as well as design of governance, for example involved actors and funding. Some initiatives focus on a research-based strategy to contribute to public health, while others focus on research translation into healthcare, or a combination of both. Evaluation of public health benefits could be performed qualitatively, such as assessing improved public trust, and/or quantitatively, e.g. research output or number of new diagnoses. However, the created health benefit for the general public, both short- and long-term, appears to be difficult to determine.

Conclusion: Genomics initiatives hold the potential to deliver health promises of population-based genomics. Yet, universal tools to measure public health benefit and clarity in roles and responsibilities of collaborating stakeholders are lacking. Advancements in both aspects will help to facilitate and achieve the expected impact of genomics initiatives and enable effective research translation, implementation, and ultimately improved public health.

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1 INTRODUCTION

Public health is defined by the World Health Organization as "the art and science of preventing disease, prolonging life and promoting health through the organized efforts of society" (World Health Organization, 2022). Following this definition, organized efforts of society that act to prevent disease, prolong life and promote health are considered as advances to ultimately benefit public health. Public health outcomes are among others shaped by a range of economic, political, behavioral, and biological factors. These biological factors entail among others the field of genomics. Genomics involves not only the knowledge of a person's genetic makeup, but how health is influenced, both positively and negatively, by the complex interaction between genes and the environment. Over the past decades, rapid developments in the field of genomics have led to increasing application of public health genomics through its integration into healthcare and prevention (Brand, 2005; Brand, 2011; Molster et al., 2018). With the potential to significantly benefit public health, public health genomics has emerged as a topical research field and expectations from researchers, policy makers, healthcare professionals and the public are substantial (Bell, 2004; Etchegary et al., 2013; Friedman et al., 2017; Khoury et al., 2018; Molster et al., 2018; Rigter et al., 2020).

In a variety of countries, national genomics initiatives have been launched. By building on the previously gathered knowledge and practices of the field of public health genomics, many of the national genomics initiatives aim to pursue public health benefit (Belcher et al., 2020; Genomic Medicine Policy, 2022; Global Alliance for Genomics and Health, 2022). Examples of promises and aims that are stated by such initiatives include "to create the most advanced genomic healthcare system in the world, underpinned by the latest scientific advances, to deliver better health outcomes at lower cost" (Government UK, 2020) and "to improve human health through genetic research, and ultimately identify new therapeutic targets and diagnostics for treating numerous diseases" (FinnGen, 2022a) (**Table 1**). The former Netherlands Genomics Initiative (2003–2013) for example aimed for society and economy to benefit from the breakthroughs enabled by genomics, by concentrating talent and spawning (new) businesses (Data Archiving and Networked Services, 2022). Health was mentioned as a field to apply genomics, but at that time health benefit was not explicitly aimed for, unlike support for research and valorization. Nowadays new national genomics plans are developed in several countries often being more explicit about aiming for improved health outcomes. Summarizing, national genomics initiatives and strategies are here defined as national organized programs that aim to improve public health by (partly) using genomics knowledge and data of citizens.

From a perspective of policy development, different phases can be differentiated in programs like national genomics initiatives. The public health policy cycle offers a framework to review the different aspects of start and roll out of national genomics initiatives. Phases that are distinguished in the public health policy framework are: agenda setting, policy advice, policy decision, implementation and evaluation (Jansen et al., 2021). Although in practice this order of succession is not always followed, an initiative generally starts with interest from specific stakeholders, including policy makers, which influences its place on the political agenda. Following an assessment by experts and/or decision makers, policy advice is drafted outlining if and how to proceed with a national's genomics initiative. After a positive policy decision, the initiative embarks on implementation, for example the start of research activities, and is evaluated throughout the process and after finalizing the genomics initiative (Jansen et al., 2021).

In national genomics initiatives aiming to improve public health, the general public may be seen as a major beneficiary. Therefore, public involvement has often been regarded of high importance in shaping national genomics initiatives (Davies et al., 2017; Wagner et al., 2017; Samuel and Farsides, 2018; Holmes et al., 2019). Public involvement has shown to improve public trust and enhance the quality of the research (Brett et al., 2014; Kelty and Panofsky, 2014), as well as to ensure effective research translation and implementation (Domecq et al., 2014; Crowe et al., 2015). A recent review of public involvement in 96 national genomics programs reported public involvement (in any capacity) in only one third of them (Nunn et al., 2019). The methods (how people were involved) and tasks (what people did) of the public involvement varied considerably between initiatives and throughout the various phases. A variety of activities have been reported by Nunn et al., including but not limited to consultations, public events, formal discussions (focus groups), and surveys.

While the study of Nunn et al. (2019) found no sufficient evidence that public involvement impacted the outcome of the national genomics initiatives, Pezzullo et al. (2021) indicates that public engagement seems to lead to policy impact. More generally, according to some, it remains uncertain whether participatory and precision medicine will eventually substantially contribute to society's healthcare interests (Juengst et al., 2012). What seems evident is that public health benefit goes beyond successful engagement and involvement of the public in a national genomics initiative.

Active genomic projects worldwide share common characteristics as well as considerable diversity in aims, scope and execution. Previous research points out that these national genomics initiatives promise to increase understanding about disease etiology, risk, prevention, diagnosis and treatment in a population in order to improve personalized (precision)

TABLE 1 | Information about population within countries and genomics initiative, and aims stated by the national genomics initiatives in literature.

Country	Population size country[a]	Initiative or Strategy	Population included in initiative (%)	Participants	Aims and goals reported by the initiative
Countries included in the literature study and semi-structured interviews:					
1.United Kingdom[b]	>67 MM	100,000 Genomes	0.14%	Patients, *via* NHS patients and their families	"Make genomics part of routine healthcare by working closely with the NHS to integrate whole genome sequencing Enhance genomic healthcare research by creating the largest genomic healthcare data resource in the world Uncover answers for participants both now and in the future through genomic-level analysis of conditions" (Genomics England, 2022)
		Genome UK	7%	Different types of patients (e.g., cancer, rare and common diseases) and healthy citizens	"Our vision is to create the most advanced genomic healthcare ecosystem in the world, where government, the NHS, research and technology communities work together to embed the latest advances in patient care Our goal is that patients in the UK will benefit from world-first advances in genomic healthcare through globally leading collaborations between the government, NHS and researchers, building on already successful programmes such as the 100,000 Genomes Project, delivered by NHS England and Genomics England, and UK Biobank." (Government UK, 2020)
2. United States[c]	>330 MM	All of Us	0.30%	Citizens	"The All of Us Research Program is a historic effort to collect and study data from one million or more people living in the United States. The goal of the program is better health for all of us." (National Institutes of Health, 2022)
3. Denmark[d]	>5 MM	National strategy for personalized medicine—Danish National Genome Centre	1%	Patients, recruited in hospital upon suspicion of hereditary disorder	"Clear diagnosis Targeted treatment Strengthened research" (Danish Ministry of Health, 2017; Danish Ministry of Health, 2021)
4. Estonia[e]	>1.3 MM	Estonian Genome Project	15%	Citizens	"It is the aim of the Estonian Genome Project to establish a database which compiles phenotype and genotype data of a large part of the Estonian population. [. . .] Additionally, the project will improve Estonian's international competitiveness in high technology and have a strong educational effect on the population." (Metspalu et al., 2004)
5. Finland[f]	>5.5 MM	FinnGen	7%	Citizens	"Project aims to improve human health through genetic research, and ultimately identify new therapeutic targets and diagnostics for treating numerous diseases." (FinnGen, 2022b)
		Genomics to Healthcare	2%	Citizens	"Genomics to Healthcare (P6), coordinated by the Finnish Institute for Health and Welfare (THL), is a large-scale national initiative aiming to prepare the Finnish health care system for the clinical utilization of genetic risk information." (Finnish Institute for Health and Welfare, 2022)

(Continued on following page)

TABLE 1 | (*Continued*) Information about population within countries and genomics initiative, and aims stated by the national genomics initiatives in literature.

Country	Population size country[a]	Initiative or Strategy	Population included in initiative (%)	Participants	Aims and goals reported by the initiative
Countries included in the literature study only:					
6. Qatar[g]	>2.5 MM	Qatar Genome Programme	0.97%	Citizens	"Qatar Genome Program (QGP) is a national population-based research project that aims to study the genetic makeup of the Qatari population and generate large databases with the aim of introducing precision medicine and personalized healthcare." (Qatar Genome, 2022)
7. Saudi Arabia[h]	>32 MM	Saudi Human Genome Program	0.31%	Citizens	"This program aims at reducing and preventing genetic diseases via implementing reliable screening and detection methods, and creating the physical and legislative infrastructure for development of personalized medicine. This is a substantial medical leap aimed at detecting the genes responsible for genetic diseases in the Kingdom." (Saudi Human Genome Program, 2022)
8. Germany[j]	>83 MM	genomDE	NM	NM	"The genomDE strategy aims to give all patients access to these benefits over the long term. Along the way, ethical, regulatory and safety questions must first be clarified." (Federal Ministry of Health, 2022)
9. Belgium[j]	>11 MM	Belgian Medical Genomic Initiative (BeMGI)	NM	NM	"The aim of the BeMGI project is to (i) Understand the biology of disease by exploiting the most advanced genomic tools (ii) Predict clinical outcome from genomic information and fulfil a pilot role towards concerted integration of genomic information in clinical care in Belgium (iii) Prepare the next generation of genomics researchers, informing medical practitioners, and conducting public outreach." (Department of Economy Science & Innovation, 2022)
10. Taiwan[k]	>2 MM	G2020 Population Genomics Pilot	2%	Patients with rare diseases or cancer	"Pilot effort will sequence 10,000 genomes by end of 2020, with the goal of embedding genome sequencing in the health system by 2025." (National Health Research Institutes Communications, 2019)
11. Iceland[l]	>365 K	deCODE	32%	Citizens	"Headquartered in Reykjavik, Iceland, deCODE is a global leader in analyzing and understanding the human genome. Using our unique expertise and population resources, deCODE has discovered key genetic risk factors for dozens of common diseases ranging from cardiovascular disease to cancer." (deCODE genetics, 2022)

[a]*Numbers retrieved from World Data Bank. % Calculated percentage of population aimed to include. K, thousand; MM, million; NM, not mentioned; NHS, National Health Service; NIH, National Institutes of Health. Participants were labeled as "citizens" when called "general public/population," "individuals," "citizens," or when no specifics were mentioned about the included population.*

[b]*Sources United Kingdom: (Government UK, 2020; Genomics England, 2022).*

[c]*Sources United States: (National Institutes of Health, 2022).*

[d]*Sources Denmark: (Danish Ministry of Health, 2017; Danish Ministry of Health, 2021; Danish Ministry of Health, 2022).*

[e]*Sources Estonia: (Metspalu et al., 2004; Allik, 2013; Metspalu, 2015).*

[f]Sources Finland: (SitraFund, 2015; FinnGen, 2022a; FinnGen, 2022b; FinnGen, 2022c; Finnish Institute for Health and Welfare, 2022; Ministry of Social Affairs and Health, 2022).
[g]Sources Qatar: (Abdul Rahim et al., 2020; Qoronfleh et al., 2020; Qatar Genome, 2022).
[h]Sources Saudi Arabia: (IEEE Pulse, 2015; Kaiser, 2016; Saudi Human Genome Program, 2022; ThermoFisher, 2022).
[i]Sources Germany: (Federal Ministry of Health, 2020; Federal Ministry of Health, 2022).
[j]Sources Belgium: (Department of Economy Science & Innovation, 2022).
[k]Sources Taiwan: (National Health Research Institutes Communications, 2019; Taiwan Human Biological Database, 2021).
[l]Sources Iceland: (deCODE genetics, 2022).

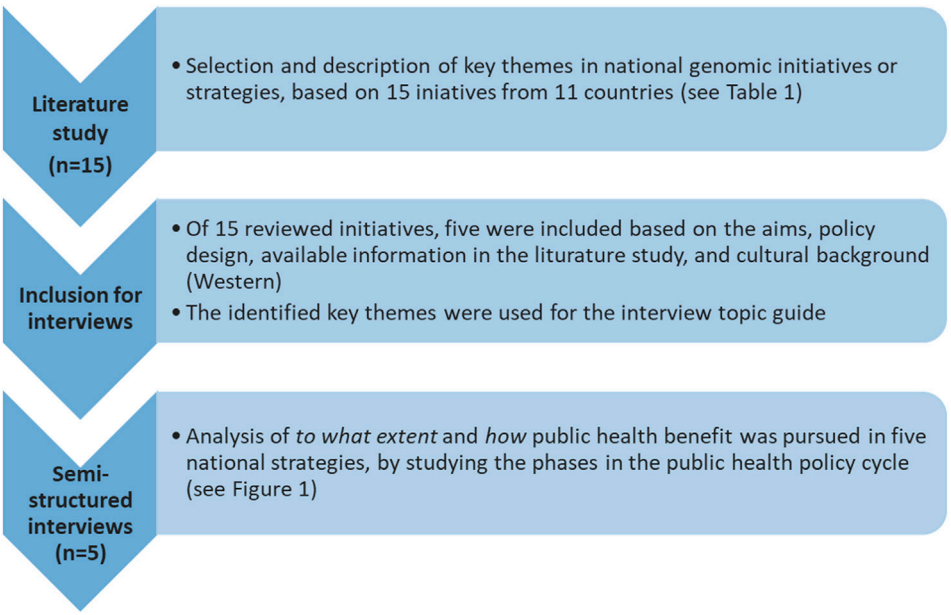

FIGURE 1 | Study design. This study consisted of two phases: 1) literature study, and 2) semi-structured interviews with experts closely involved in the selected national genomics initiatives. The key themes analyzed per genomics initiative in the literature study were: aims, population, diseases, approaches/plans/actions to improve public health, stakeholders and actors, activities to ensure a successful health benefit, as well as ethical, legal, social implications (ELSI) regarding public health benefit and public trust.

treatments and prevention, as well as support genomic technological developments and data-infrastructure (Molster et al., 2018; Stark et al., 2019; Kovanda et al., 2021). These findings suggest that a variety of policies could be followed to use population-based genomics as strategy for public health improvement. While goals regarding (progress towards) health improvement are set, creating the promised health impact requires additional steps to deliver and ensure health impact. In order to guide effective and equitable implementation of genomics knowledge into health systems, governments and policy makers seem to have a unique role to play (Molster et al., 2018). Therefore, analyzing the roll out and organization of a national genomics initiative within a policy cycle may provide key information regarding implementation towards public health benefit.

Our study aims to explore to what extent and how health benefit for the general public is being pursued and operationalized by national genomics initiatives that strive to improve public health. Using a selected set of initiatives that have a stated aim of improving public health, we assess how this objective can be included in different phases of the public health policy cycle.

2 METHODS

Key articles were used for initial data collection (Stark et al., 2019; Kovanda et al., 2021). Available catalogues from Global Alliance for Genomics and Health (GA4GH) and Genomic Medicine Policy were consulted to identify initiatives with aims that primarily focused on health (Genomic Medicine Policy, 2022; Global Alliance for Genomics and Health, 2022). To be eligible for inclusion, the initiatives had to include an aim to positively impact the health of a population or improve healthcare. Initiatives that solely aimed to increase understanding of the contribution of genetics to disease or constructing a biobank or data-infrastructure without plans to apply that knowledge for public health improvement were excluded. Furthermore, documentation of the genomics initiatives in forms of e.g., strategy reports or information provision on websites had to

be present in English to allow adequate data collation. Then, countries with national genomics initiatives were purposively sampled to represent diversity in terms of geographical location, strategies to improve public health with genomics, and different stakeholders driving the start of an initiative (e.g., government and researchers). Based on these criteria, 15 national genomics initiatives from 11 countries were selected from the available catalogues of GA4GH and Genomic Medicine Policy. For these 11 countries, a literature review was performed, followed by semi-structured interviews with experts from five purposively selected countries (**Figure 1**).

Data from this selection of national genomic initiatives were collected to give examples regarding the (interplay between the) different phases of the public health policy cycle and to illustrate how public health benefit could be pursued and operationalized. By pulling from the insights of the interviewed experts, the body of this work serves as exploration how the organization of a national genomics initiative can be viewed from a policy development perspective. Providing an elaborative and objective oversight on all the activities performed during a national genomics initiative goes beyond the objective of this study.

2.1 Data Collection and Analysis

2.1.1 Literature Review

To prepare the interviews, grey and scientific literature and public domain websites were consulted to gain insight into the landscape of national genomics initiatives (**Table 1**). Information available in English was collected and analyzed, using the following search strings: (national genomic initiative < country name>), (national genomic strategy < country name>), (national genomic program < country name>), (<name of initiative>) or (national personalized medicine program < name country>) in Google. The searches were performed from February to August 2021. Key themes were iteratively defined and analyzed, first based on the Genome UK initiative report (Government UK, 2020) due to its broad objectives, and then supplemented with themes that were identified as key aspects upon further analysis of other genomics initiatives. The key themes analyzed per genomics initiative were: aims, population, diseases, approaches/plans/actions to improve public health, stakeholders and actors, activities to ensure a successful health benefit, as well as ethical, legal, social implications (ELSI) regarding public health benefit and public trust.

2.1.2 Semi-Structured Interviews

Semi-structured interviews were conducted to gain insight in the experiences and lessons learned from experts who were closely involved in the selected genomics initiatives and have expertise in the field of genomics, healthcare, and/or policy making. A structured interview guide was developed based on the themes derived from the literature search (see **Supplementary Material S1**). In total, five semi-structured interviews were performed with one or two experts per interview from Denmark, Estonia, Finland, United Kingdom, and United States (**Figure 1**). The initiatives were selected for interviews because they reflect a variety of aims and strategies to organize a national genomics initiative and benefit public health, including improvement of patient care, embedding genomics into health services, advancement in research, and innovation in treatment. Furthermore, the organization of the initiative was taken into account to ensure that a variety of policy designs were covered in the interviews (e.g., research driven, governmentally driven). Initiatives that developed into a company were also excluded from the interviews, since a policy analysis using the public health policy cycle may not be fitting in that setting (initiative from Iceland). Furthermore, initiatives were excluded from the interviews when limited information, i.e. no public domain websites and no published reports, could be found in English (initiatives from Germany, Belgium and Taiwan). To minimize differences caused by cultural background, the authors chose to focus on initiatives from Western countries, excluding the initiatives from Qatar and Saudi Arabia.

Interviews were conducted in English. Prior to the interview, consent was collected for recording and transcribing the interview audio and archive the transcription. The recordings were deleted directly after transcription. Interviews were performed by at least two researchers, transcribed verbatim and the transcripts were checked by interviewees for accuracy.

As a theoretical framework, the public health policy cycle as described in Jansen et al. (2021) was used to extract critical aspects (**Figure 2**). From these, we explored to what extent and how public health benefit was being pursued in the genomic initiatives. During analysis, three researchers (SO, MJ, and TR) coded until reaching consensus on the coding tree based on the public health policy cycle. While analyzing the interview data according to the different phases of the policy cycle within the scope of this study, phase 2 "Policy advice" and phase 3 "Policy decision" appeared to be intertwined. Therefore, the original version of the public health policy cycle was adapted, with phase 2 becoming "(Research) strategy towards health benefit," and phase 3 becoming "Policy governance." This version was used to further analyze the results. After agreeing to the coding tree, transcripts were systematically coded by one researcher (SO). In case of doubt, researchers (SO, MJ, and TR) discussed until achieving consensus.

Specific quotes were selected (SO) if they provided relevant information about the impact on public health benefit, or discussed aspects that differed greatly from other initiatives, implying that different approaches could create public health benefit. Member checking was performed upon selection of the quotes, to check for correct interpretation and presentation of the provided information.

3 RESULTS

A total of 11 countries were included, for which 15 national genomics initiatives or strategies were identified. An overview of the included countries and key characteristics of the national initiatives or strategies is given in **Table 1**. All these initiatives and strategies aimed, upon execution or completion, to improve the health of a population or positively impact healthcare (**Table 1**).

Based on the literature review, an interview guide was developed which included questions on e.g., envisioned goals

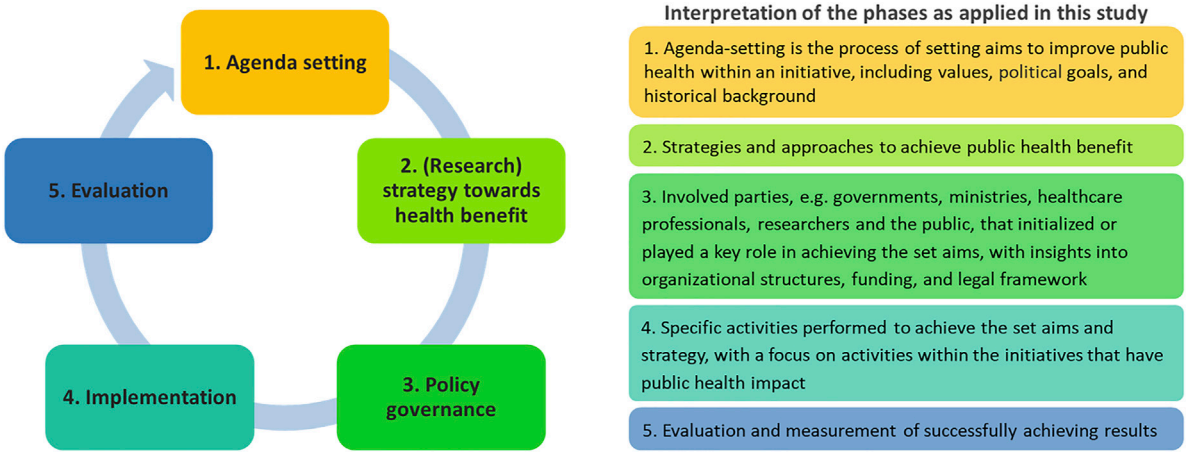

FIGURE 2 | (Adapted) Public Health Policy Cycle. The public health policy cycle consists of five phases. How activities within these phases are organized, may affect the results of a national genomics initiative. Adapted from Jansen et al. (2021), Frontiers in Pediatrics.

TABLE 2 | Exemplary of objectives and indicators to pursue public health benefit and success in national genomics initiatives mentioned in our study.

Objectives	Indicators
• Enable excellent (large-scale) genetics research	• Scientific impact or number of publications
• Identify genetic factors that increase or decrease the risk of various diseases	• 60 000 Whole Genomes Sequenced
• Determine early onset of diseases such as cardiovascular diseases or other common complex disorders	• Analyze 5.000.000 genomes from healthy populations
• Deliver benefits to the patients	• Delivered data back to 5000 people
• Develop new treatments	• Diagnostic yield (the proportion of patients of whom you have a finding)
• Advance genomics in the healthcare sector	• A private hospital that provides risk assessment on cancer
• Maintain public trust and confidence	• Building a complete infrastructure
• Kickstart the genomics industry	• Building a genome centre

within an initiative, roles and responsibilities of stakeholders, and determining whether and how an initiative will be/has been successful (**Supplementary Material S1**).

3.1 Interview Results

Interviews were performed with one policy expert and one implementation researcher from Denmark (Danish National Genome Centre), one genomics expert from Estonia (the Estonian Genome Project), one human genetics expert and one laboratory expert from Finland (FinnGen), one policy expert from the United Kingdom (100,000 Genomes), and one genomics and policy expert from the United States (All of Us).

The experts reported a variety of objectives in their national genomics initiatives (**Table 2**). Furthermore, they also shared insights in how the impact of a national genomics initiative could be assessed or ensured.

If and how public health benefit is being pursued within national genomics initiatives is the result of interplay in activities throughout the different phases of the public health policy cycle (**Figure 2**). A variety of ways to operationalize public health benefit within national genomics initiatives were found in all phases of the public health policy cycle: agenda setting, (research) strategy towards health benefit, policy governance, implementation, and evaluation.

3.1.1 Agenda Setting

The insights that the experts provided indicate that agenda setting of national genomics initiatives was influenced by the presence of strong political will or drive and demands from other stakeholders, as well as the country's history and existing societal values.

Several goals and interests of key initiators and stakeholders were identified as incentives to start a national genomics initiative. These goals fitted in the expectations that genomics can create public health benefit. Improvement in public health was reported as goal itself, combined with goals that ultimately steer towards public health benefit through organized efforts in healthcare and research:

> "The Estonian initiative was just to make a large biobank in order to be competitive. Competitive in research, and also use data in improving public health." Estonia

> "We for sure think that the patients are the most important stakeholder [. . .]. If this initiative doesn't benefit the patients, and if it doesn't gain legitimacy from the patients, then it's not really worth it." Denmark

> "This is an initiative that was initiated by researchers [. . .]. There are two main goals. The first one was to be able to produce a large enough dataset that enables excellent genetics research. And then the other goal is, of course, to utilize the data to be able to identify genetic factors that increase or decrease the risk of various diseases." Finland

Drive or demands from different stakeholders including society, key politicians, and researchers also reported the initiation of a national genomics initiative:

> "Society wants to get better medical care, and this is why we are providing the scientific base and helping medical institutions, because the university is not providing medical care itself as they just do science and teaching." Estonia

> "One person who really wanted this to happen was President Obama [. . .] he proposed it in a major announcement, and then the Congress got behind it, we got the money, and off we went." United States

In addition to the drive and demands from different stakeholders, it was often mentioned that important societal values within a country were intertwined with the agenda of a genomics initiative. These values include, for example, equity in research and health care, public trust, or transparency in research:

> "There are so many threads in here that are societal, that are about equity and some issues that are bigger than science in many ways, [. . .] so a lot of effort has always gone in 'All of Us' to think about, to study, to anticipate societal concerns around privacy, security, discrimination, and so forth." United States

Experts discussed that the history or tradition of a country could be an important factor to address societal values, and could therefore influence decisions made within a national genomics initiative:

> "Finland has this tradition of people who are very interested in research and very supportive. [. . .] Starting this kind of initiative means that we do not want to lose the trust, so that is also one of the main reasons why we are wanting to do this as transparently as possible." Finland

As stated by these experts, maintaining public trust requires additional efforts regarding transparency in research activities towards the population.

3.1.2 (Research) Strategy Towards Public Health Benefit

Although similarities in (sub)goals that lead to public health benefit could be found, the strategies to achieve these were different. Some initiatives had a rather research-based strategy to generate data, information, and knowledge to increase the understanding of population health and disease etiology.

Another strategy mentioned by the experts was a more translational strategy, focusing on bringing new or existing knowledge and developments into practice, for example by developing a citizens' support system that produces a personal health report. Within the translational strategies, the following subgoals were reported: embedding genomics in healthcare, prevention of disease, improved diagnosis, improved or personalized treatment, and development of innovative treatments or technologies. Yet, both strategies fit with the idea that national genomics initiatives benefit public health through the art and science of preventing disease, prolonging life and promoting health, as "public health" is defined by the WHO.

> "Our focus is on the patients, so the most important thing is to help the patients and to make sure that the patient gets the correct treatment." Denmark

> "We have the common goal of being able to help people and for this we need the pharma industry. We need new treatments, so we hope that the project will lead to new treatments." Finland

> "The latest strategy, [. . .] is what we call the Infinity loop. On the left-hand side, the kind of health care service works, and we support them. The data then goes to the Genomics England side and then we provide researchers access to it as secure environment. Then the findings very quickly go back into the health service in this kind of Infinity loop." United Kingdom

The Infinity loop strategy, as discussed by the experts from the United Kingdom, illustrates that advancements in genomics research and bringing these advancements into practice is an intertwined process, which requires a collaboration between research and health systems.

Some national genomics initiatives or strategies target specific areas for impact, for example, diseases that are endemic or prevalent to their country:

> "The main research focus is genetic risk factors that actually are only present in the Finnish population and that cannot be identified anywhere else because of this bottleneck population effect." Finland

The focus of this initiative illustrates an interest to improve health of the national population specifically. In comparison, a focus on specific diseases and patient groups, both in research and in implementation into health systems, was also found, including

cancer, cardiovascular diseases, pharmacogenomics, and rare diseases:

> "In 2023, we hope to have the first services for cardiovascular disease, cancer, and pharmacogenomics for the primary care providers." Estonia
>
> "The four aims of the project were to deliver 100,000 genomes from NHS patients, to identify the causes of rare diseases [and] cancer, and to provide opportunities for research and industry. [. . .] each one of them was equally important. So, to deliver benefits to patients, to provide opportunities for research, to maintain public trust and confidence, and to what we call kickstart the genomics industry." United Kingdom

Strategies to improve public health were often approached through joined forces between multiple fields within society, e.g., research, industry, public, and healthcare. Combining all these fields and formulating corresponding goals seem an important aspect within strategies to yield success.

3.1.3 Policy Governance

Different aspects that influence governance within national genomics initiatives were found to be critical in this phase. Here, we focus on drivers and funding of an initiative, legal frameworks, and the roles and responsibilities of involved stakeholders. While these aspects may not all seem to be directly linked to public health benefit, they provide insight in how the organized efforts are expected to affect the initiatives that ultimately aim to improve public health.

Firstly, drivers and ownership of the initiatives differed across our study set. Some initiatives were fully owned by the government, while others were identified as academic or public-private initiatives:

> "The National Danish Genome Centre is an agency in the ministry of Health." Denmark
>
> "We were very happy being an independent institution, who is just outside of faculties. Just under the Rector of the University. But since 2019, the Estonian Genome Center is part of the Faculty of Science and Technology of the University of Tartu." Estonia

Funding for the national genomics initiatives came from a variety of sources, including private funding, governmental financing, or funding from outside of the country. The funding source did not always affect the organizational structure. For example, the government-owned initiative in Denmark receives an annual national budget as part of a political agreement. Yet, the majority of funding was from a donation by the Novo Nordisk foundation (Novo Nordisk, 2022) (which has no decision-making role in the initiative):

> "It [the National Danish Genome Centre] is funded mainly by a private fund called Novo Nordisk foundation. This is a very big fund in Denmark, funding health research, and they have given us around 130 million euros. [. . .] That's extremely unusual in Denmark." Denmark
>
> "In the first step, we actually raised private money from the US and used very little government money at all [. . .] Since 2007, the Estonian government is the principal funder of the Estonian Genome Center. In the last five years, most of the money for the biobank is coming from the Ministry of Social Affairs. Of course, we have to apply and win research grants and attract private funding in addition to the government funds." Estonia

The legal framework of the country seems to largely influence the governance of its national genomics initiative. Often, regulations were reported to impact the organization of the initiative, including roles and responsibilities of the stakeholders regarding specific tasks, e.g. data-management and access, data protection, or recruitment of participants:

> "It was a political decision to start the initiative, that was made a political agreement. Following the agreement, they made amendments to the health law which made the construction of the national genome center possible. The political decision was based on input from researchers, clinicians, their citizens, etc." Denmark
>
> "In 2008, the US passed a law called the 'Genetic Information Non-Discrimination Act.' [. . .]When it comes to employment and health insurance, you cannot be discriminated against based on genomic information." United States

Interviewees from both Finland and Estonia stated that the existing legal framework warrants that (research into) public health benefit was ensured within the national genomics initiative:

> "The law that tells us we have to protect the data, to analyze the data and perform research, and to use the data to improve the public health. These are three things described in the law and this is why the biobank was basically created." Estonia
>
> "There are a lot of research regulations that are important for us, but the Biobank Act is the most important one. [. . .] the Biobank Act enabled broad consent. Before that, we always had to ask for consent for a specific research project, for example breast cancer research. Now the broad consent is just that the participant consents that their sample data can be used for any future medical research project that is approved by the biobank." Finland

A variety of stakeholders were identified that held leading roles and responsibilities within national genomics initiatives. This implies that different stakeholders within society were involved to translate advancements of genomics towards public health

benefit. The most frequently mentioned stakeholders were governments and politicians, national health services, researchers, biobanks, genome centers (sometimes specifically built as part of the initiative), clinicians, patients, the public, and industry. Although all parties seemed to hold important tasks, interviewees often emphasized the involvement of the government and the public as essential for the initiation and success of national genomics initiatives:

> "I guess you have to win over the government first. Otherwise, because it's so much money and the government are not supporting, there is no way to do it. [. . .] But the most important thing is you have to get people over, because finally people have to come and donate blood. The information they get is only the promise that in the future it gets better." Estonia

Remaining transparent in research and ensuring that the public participates in the initiative were mentioned as arguments to involve the general public and patients in any form. Another argument to involve the public was to ensure that the aims and activities of an initiative are in line with the public's wishes and expectations. In some settings, the patients could influence which disease groups should be looked into with the national genomics initiative:

> "We decided to include patient-citizens and obviously clinicians in deciding which groups we should look into. Therefore, we had a round where people could report to clinicians, as well as citizens who could report which groups we should look into [. . .]." Denmark

This indicates that the general public and patients may influence research translation, including how public health benefit is yielded and which policy decisions are made. To do this, the interviewed experts stated that patients and citizens fulfilled different roles affecting governance and structure within a national genomics initiative, including participation in advisory and agenda-setting committees:

> "The participants panel now has a key role in the governance of several of the big decision-making committees." United Kingdom

The perspective of participants was described as important and refreshing, since they e.g., challenged experts to rethink about common practice, and required experts to explain the choices they made within the initiatives.

3.1.4 Implementation

A variety of plans and activities to pursue public health benefit in the implementation phase were reported in all the national genomics initiatives. The operationalization of public health benefit was found to be in different stages in national genomics initiatives, as some experts discussed that the first steps towards e.g., implementation of genomics in research setting have been made, while other experts reported that these steps are still in preparation.

The diversity within the implementation phase will be illustrated below, through presentation of different activities discussed by the experts. For example, the expectations of genomics to benefit public health were translated into activities to return genetic results to participants:

> "We are running WGS now and we are actually reporting back to the patients already. Now we have five regions in Denmark. And we are reporting back to patients in two regions. The last three regions are close to getting all that data processing agreements in place." Denmark

Yet, the insights that experts provided indicate that reporting back genetic results comes with additional efforts. To maximize potential health benefits of genomic research in a comprehensive and equitable manner, recruitment of people from diverse races and ethnicities was highlighted as key:

> "It is time to have data and research that reflects the diversity of the United States population, and so [. . .] 70%–80% of the people who have been enrolled in 'All of Us' so far are from groups that have been traditionally underrepresented in biomedical research. [. . .]. A lot of them are ancestry related, [. . .] we wanted to capture people with different social economic backgrounds, rural versus urban, [. . .]. With 'All of Us,' the value is to get genomic data from ancestral groups that we do not currently have. [. . .] So, in order to really strengthen our ability to implement genomic medicine in a comprehensive way, we first need genomic data from individuals from different ancestries." United States

Additional approaches were expressed as required to understand disease etiology and health needs in underrepresented groups. Yet, the efforts to include them were faced with additional barriers:

> "I think the issue that we're still grappling with is how to get to hard-to-reach groups [. . .]. [For example] we know roughly what our census tells us about the diversity of our population, we are not so clear about what their health needs are. So, it may be one thing to have say, you know, 5% of people who are from [. . .] minority populations, but what if they have higher [or lower] health care burden in cancer, or particularly in rare diseases because of consanguinity? So, we're always keeping a very close eye on that." United Kingdom

In addition to barriers regarding recruitment of (specific groups of) participants, experts from the United Kingdom reflected on challenges to communicate results to participants:

> "Something like 80% of people would like that feedback. We haven't done it yet. It's just too complicated. Every time we think we've done the bioinformatics, a new disease association or new data comes up so that needs to be fixed, and then we have to understand how we would do that clinically for the 1% to 2% of people who are having a finding? [. . .]. So, lots of communications issues in the clinical issue." United Kingdom

Furthermore, the expert from the Estonian initiative stated to have grappled with how the results should be communicated to match this with the expectations of the participant:

> "Feedback is important. I was surprised that some people were not happy [. . .]. So, I was asking what was the problem? 'Nothing, you know they didn't tell me anything,' So, I said 'Look, that is good news, you do not have a high risk of breast cancer, or cardiovascular disease, no Parkinson, no nothing. So, you should be really happy, not just worried that you had nothing, it's good news'. And then these people started to think 'you are right.' They said, 'I'm really happy that I had no news from this thing because any news would be bad. But, in general, over 95% of people were very positive about the feedback they received and didn't regret it even 6 month later." Estonia

These insights imply that there may be tension between the expectations and true impact that can be delivered through advancement in genomic research.

In addition to returning results to participants, other efforts to improve health were reported, including translating new insights into research or healthcare, broader application of Whole Genome Sequencing (WGS) in healthcare, and implementation of polygenetic risks scores.

Many experts described the development of a data-infrastructure as key to enable genomics use within health systems:

> "Personalized medicine is often very data driven and data heavy, so that needed some change of the infrastructures and organization in the healthcare system [. . .] and so we needed somehow to be able to collect and store genomic data. That was like the first big task, and that is still the main task [. . .]." Denmark

In order to embed genomics into healthcare, multiple interviewees stated that specific attention should be paid to involving and educating the medical community:

> "So, you also have to engage the health care professionals. This is not actually just the doctors, it has to include the nurses, the pharmacists, everyone." United States

Additionally, the Danish National Genome Center highlighted that to ensure successful implementation of personalized medicine in the healthcare system, it is important to proactively secure the right expertise and workforce to perform the interpretation of WGS and other comprehensive genetic tests. For this, the development of standards for the interpretation of results and criteria for stratification of patients was necessary.

3.1.5 Evaluation

Depending on the aims and strategies, different methods to evaluate achievement of envisioned goals and success towards public health benefit were reported. A variety of elements were identified within the evaluation process that provide insight into how goals are strived to be achieved, including setting general milestones and deadlines, determining deliverables before and during execution of the initiative, and setting requirements to receive funding:

> "We have deliverables and milestones set in our consortium agreement and deadlines [. . .]. From the beginning, we have had a project start and an end date for the initiative [. . .] we have set structure for the project and set goals." Finland

The number of genomes collected was often mentioned as indicator of progress for national genomics initiative:

> "As part of the agreement with the [donation from the] Novo Nordisk foundation, we have to make 60,000 WGS by the end of 2024. You could say that's kind of the quantitative measure we have." Denmark

Additional information was collected to monitor the representation of the collected genomes, including e.g. geographic background or patient groups:

> "We used to have many complicated dashboards here, we aimed for 100,000 whole genomes [. . .] We kept a close eye on whether we had underrepresentation geographically as well as in the population mix for a long time" United Kingdom

Keeping a close on these additional characteristics implies that equity in research, a value addressed in "agenda-setting," was monitored during data collection of a national genomics initiative. Provision of samples and consent may also be an indicator for public trust, indicating that this value could also be monitored during the roll out of a national genomics initiative:

> "And that is also one important way to measure the trust, because we are assuming that if we lose the trust, people stop providing their samples, providing their consents, and it has been very stable throughout the project." Finland

As stated by the expert from the United Kingdom, achieving the aimed number of genomes was not seen as sufficient to determine success in their national genomics initiative:

> "You can't just hit the target and miss the point. You could go and get some genomes from anywhere. But if you don't have it embedded properly with the data and the data aren't high quality, or you don't have consent, then you missed it. You missed the point. This is not just a numbers game." United Kingdom

As can be seen in the reported goals, many genomics initiatives aim to improve public health, by either preventing disease, prolonging life and promoting health. Yet, the difficulty in currently assessing the public health impact was also mentioned:

> "The third criteria, which obviously takes decades to measure is: Are you making scientific discoveries that are improving human health? Are you making discoveries that are changing clinical practice? Are you making discoveries that you could point to and say that this is improving people's lives? [. . .] Science is not a sprint; it is a marathon. To really be able to measure impact on public health, you have to be willing to wait several decades." United States

While it may be too soon to determine to what extent and how public health benefit is created within a national genomics initiative, intermediate goals and indicators are often reported by interviewees. Indicators to evaluate research and technical progress include building an infrastructure that enables clinicians and researchers to use genomic technologies and data, collaborating with industry partners, and publishing novel scientific discoveries:

> "The earliest success will come from whether people are using the data. That is the earliest success. If you build something and nobody uses it, well, then you know you're failing." United States

Furthermore, indicators to evaluate progress towards public health impact were also reported, such as diagnostic yield, reporting genetic results to patients, making discoveries that change clinical practice, or developing new treatments:

> "Another metric is our diagnostic yield, as we call it, the proportion of patients where you have a finding. [. . .] And the other success metric, we're giving ourselves a hard task, is that we had an optional consent in the 100,000 Genome project for people who wanted to know additional findings." United Kingdom

> "The very important measure, and also obviously as secondary use, you could say that researchers gain access to our data and then they can actually use this to develop new treatments for patients." Denmark

The latter statement of the Danish experts indicates that, in order to ultimately prolong life, promote health and benefit public health, e.g., through developments of new treatments, efforts in research are necessary to make those improvements possible.

4 DISCUSSION

Public health genomics involves the translation of genome-based knowledge and technologies into public health (Bell, 2004; Friedman et al., 2017; Khoury et al., 2018; Molster et al., 2018; Rigter et al., 2020). This emerging field has heightened expectations for the advancement of personalized and precision medicine among researchers, healthcare professionals, policy makers and the public. In this study, we explored how public health benefit is being pursued in selected national genomics initiatives, using an adapted version of the public policy health cycle.

This study showed that the initiation and implementation of current national genomics initiatives are shaped by an interplay of aims, cultural values, history and push from various stakeholder groups. Further setup and organization of initiatives was found to depend on the governance structure as well as the chosen strategy to achieve public health impact. In general, strategies from the national genomic initiatives that we studied here are varied—ranging from more research-based strategies to translation-based strategies, or a combination of both—with a general focus on specific diseases or application areas.

In this study we found little evidence of true operationalization of public health benefit across the various public health policy cycle phases in national genomics initiatives. Therefore, as phrased by Juengst et al. (2012), there is risk that the widespread and compelling appeal of personalized genomic medicine's vision and potential virtues ultimately do not contribute to society's health care interests. Although the general aims and strategies to achieve public health impact are formulated in most national genomic initiatives, the research translation and implementation seems to be not always clearly outlined in the different aspects of the public health policy cycle.

In addition to improved public health, one of the aims or incentives that was often referenced by the interviewees was to stay ahead of competition. Yet, it was not always made clear why that is considered important. Underlying ambitions and arguments to start genomics initiatives and improve public health, such as for-profit development of technologies or treatments, may not be brought to light completely in this study. It would be interesting to study how this incentive may influence the organization and policy decisions made within a national genomics initiative, and whether and how this incentive affects the operationalization of public health benefit.

Moreover, the evaluation of actual public health benefit seems to lack well-defined indicators. Many experts stated that the amount of genomic data collected can be used to measure quantitative progress. Yet, as stated by one of the interviewed experts, "you can't just hit the target and miss the point," suggesting that the success of a national genomics initiatives aiming towards public health benefit should not only be measured by a set amount of genomic data. Experts in this study pointed to other indicators to assess progress and

effective roll out of a national genomics initiative, including data-infrastructure that enables clinicians to improve treatment, diagnostic yield, or the development of novel treatments.

Generally, research-based strategies are not primarily pursuing direct impact on public health, yet their strategy may be seen as efforts to prepare the delivery of public health benefit. Translational strategies varied, and were more directed at delivering (meaningful) results to patients and citizens. Implementation of strategies is often accompanied by public involvement and recruitment, designing and building data-infrastructure, as well as several strategy-tailored activities, including education of healthcare professionals and establishment of a (national) biobank. Approaches and activities to pursue public health benefit differed. In some initiatives, for example, patients were involved in deciding which diseases should receive priority attention from the genomic programs, while in other initiatives this decision making role was set aside for experts.

As shown by the challenges faced by e.g., Estonia and the UK regarding reporting results back to participants, it seems pertinent to pay attention to how public health benefit is operationalized and what additional activities and corresponding policy decisions are necessary to ensure this. Examples include, but are not limited to, effective communication with the patients, educational support for healthcare professionals, clarity about the meaning of complex genetic test results, and guidelines about follow-up treatment.

Generally, advancements in science that are translated into healthcare should be accompanied by careful ethical and social evaluation. National genomic initiatives are no exceptions, and also require clarity in aims and transparency in research. Dialogues involving all stakeholder during the various phases of the policy cycle can also promote responsible implementation and public trust.

Public trust in science, which was expressed by many experts as an important goal in their initiative, seems to demand transparency. Therefore, the aims of national genomics initiatives should be clear from the beginning or, in case of change due to advancements, adapted in a transparent way. The achievement of these aims are in this study shown to be evaluated as follows: scientific insights are assessed as publications and patents; infrastructures for data storage and future research assessed as infrastructural capacity achieved; and public health benefit assessed as new diagnoses for unsolved genetic diseases, pre-symptomatic diagnoses made allowing for early interventions, and health gain through timely prevention or risk management. Because many initiatives are still ongoing, the full impact of genomics on public health may not be realized for decades. The development of tools and methodologies to realize and determine effects are still evolving. Yet, we argue it is not too early to evaluate the effectiveness of activities meant to measure the progress in public health benefit.

The policy cycle framework is designed as a learning system, to enable adjusting policy to relevant developments. By feeding back outcomes of evaluation to the initial phases of the cycle, strategies are ensured to maintain relevancy. To achieve a true feedback-loop in the policy cycle of national genomic initiatives, initiators should not only set clearly-defined goals, but also pre-determined milestones and indicators that can be used to measure the progress of the chosen strategy towards health improvement. As stated by the interviewed expert from the United States, long-term effects and results of initiating and executing a national genomics initiative, including public health impact, seem difficult to determine at this early stage. To ensure that public health benefit can be measured effectively, both short and long term, it is important that pre-determined (sub)goals with accompanying requirements are set. This should include how goals are aimed to be implemented, and what data needs to be gathered in order to determine whether a national genomics initiative has been successful in improving public health.

Beskow et al. (2001) proposed a blueprint to integrate genomics into public health, consisting of research inquiries that require attention. Applying this blueprint may provide a way to effectively integrate genomics into public health throughout the different phases of the public health policy cycle that can be found in a national genomics initiative. Khoury et al. 2018 also called for specific attention regarding system management, acknowledging that public health infrastructure has a vital role as both support for and a conduit between research and practice. This call seems to be partly met by the majority of the included national genomics initiatives, as many experts expressed the importance of a data-infrastructure for the collection, analysis, and reporting of genomic results. Additionally, the UK's Infinity loop-strategy demonstrates a seemingly ideal interplay and data flow between health care services and researchers, promoting simultaneous utilization of genomics. In strategies like these, which other experts also referred to as a learning health care system (Wouters et al., 2020), system management could play an essential role in integrating genomics into public health practice, when accompanied by ongoing evaluation and subsequent refinement of the requirements and policies that ensure beneficial impact and responsible implementation.

General benefits and risks of (aspects of) national genomics initiatives can perhaps be distilled from similar implementation processes. For example, experience gained from implementing clinical decision support systems could be translated to setting up a data-infrastructure embedding genomics into health care (Sutton et al., 2020). Proposed efforts by Sutton et al. to ensure benefits overcome potential risks of setting up these infrastructures include prioritizing evidence-based genomics-disease interactions and adequate training for users of the support system (e.g., health care providers).

In a recent commentary, the WHO and member states acknowledge that to accelerate and amplify impact on population health, utilization of digital interventions, tools and systems to deliver clinical, public health, and data recommendations offer potential (Mehl et al., 2021). However, it was discussed that interoperability, continuity of care, optimized data use and accountability in health data systems is hindered due to limited translation, operationalization, and incorporation of health and data recommendations and lack of guidance on both technology and content level. Their proposed guidelines may serve as a basis for an effective approach for national genomics initiatives towards systematic, transparent, and testable data-infrastructure development with digital systems at the country level.

As stated by multiple experts, involvement and support of both the public and the government are crucial to a successful start and execution of a national genomics initiative. However, based on this study and the study of Nunn et al. 2019, it is not clear how involvement of the public impacts the envisioned goals of a national genomics initiative beyond retaining public trust. Different approaches to inform and involve the public exist. Avard et al. (2008) have distinguished indirect and direct public involvement activities. They described indirect public involvement as a one-way communication, such as surveys or consultations. Direct public involvement was described as a two-way communication process, with activities including citizen workshops, dialogues, and deliberative and consensus conferences. These approaches and activities may prove suitable for different objectives, e.g., informing about vs. co-designing research. Additionally, management of public expectations is important to avoid erosion of public trust, due to uncertainties in the delivery time and form of potential health benefits (e.g., improved diagnosis of hereditary disorders or personalized medical treatments).

Furthermore, other stakeholder groups may hold crucial roles in a successful roll out of a national genomics initiative, including but not limited to health care providers, pharmacists, or policy makers. In order to deliver the promised goals regarding public health benefit, policy makers and governments have a unique role to play (Molster et al., 2018). The complex interplay between multiple stakeholder groups with their own roles and responsibilities should be acknowledged and receive further attention. Complex structures of multi-organizational collaborative approaches can be found in national genomics initiatives. Gil-Garcia et al. (2019) called for clarity in roles and responsibilities in government inter-organizational collaboration and information sharing initiatives, and conclude that this is a critical factor for success. In light of the current study, the roles and responsibilities of stakeholders should be assessed and clarified for each of the different phases of the public health policy cycle and corresponding milestones or indicators. In this, specific attention should be paid to the parties responsible for evaluating the impact of a national genomics initiative on the envisioned goals and public health impact in the long run.

5 LIMITATIONS

This study faces several limitations. The literature review was restricted to information about national genomics initiatives available in the English language. Therefore, some national genomics initiatives may have been overlooked, e.g., due to absence or difficult to find information, while others may have been partially reviewed. Yet, the main findings within this study were collected during the interviews. The national genomics initiatives that were subject of the interviews reflect the diverse landscape of national genomics initiatives. Therefore, we expect that combining the explorative literature review and interviews from different perspectives has sufficiently enabled us to illustrate possible operationalization of public health benefit in national genomics initiatives.

The information obtained by the authors was gathered during interviews with experts who are involved in their countries' initiative, likely resulting in a limited and perhaps biased view on all aspects. As the execution of a national genomics initiative requires collaboration from multiple stakeholder groups, it would have been insightful to also have included other experts representing different stakeholder groups per country. In doing so, we could have included varying perspectives about the pursuit and operationalization of public health benefit within the different phases of the public policy health cycle, and which indicators were evaluated. However, the interviewed experts were all closely involved in their countries' national genomics initiatives, and were therefore able to provide important insights in the different phases of the public policy health cycle.

6 CONCLUSION

National genomics initiatives hold the potential to benefit to public health. This study showcases several different policies that currently pursue public health benefit through national genomic initiatives. Sometimes, public health benefit is directly pursued within national genomics initiatives, with goals set to improve prevention, diagnosis, and interventions, while in other initiatives, public health benefit is seen as a future goal of current research activities that are aimed at generating data and knowledge. To date, the development of international and standardized tools, methods, and data sharing is necessary to operationalize the anticipated beneficial impact of genomics initiatives on public health. Furthermore, evaluation of actual public health benefit can benefit from well-defined indicators, also to compare between countries and draw on lessons learned. In order to achieve the envisioned goals of national genomics initiatives, the indicators should not only be operationalized, but it should also be clear who has what role and responsibility throughout the different phases of the public health policy cycle, especially regarding evaluation of the public health benefit within a national genomics initiative.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because participants only gave consent to publication of the data included in the article. Raw data cannot be anonymized because statements can be traceable, to specific experts/expertise. Requests to access the datasets should be directed to suzanne.onstwedder@rivm.nl.

ETHICS STATEMENT

This study was executed according to Dutch national legislation. The Medical Research Involving Medical Subjects Act (WMO) does not apply to this study and therefore official approval is not required. Prior to the interview, consent was collected for recording and transcribing the interview audio and archive the transcription.

AUTHOR CONTRIBUTIONS

MC, MJ, SO, and TR contributed to conception and design of the study. TA contributed to the initial data collection. SO organized the database, analyzed the data, and wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.865799/full#supplementary-material

REFERENCES

Abdul Rahim, H. F., Ismail, S. I., Hassan, A., Fadl, T., Khaled, S. M., Shockley, B., et al. (2020). Willingness to Participate in Genome Testing: a Survey of Public Attitudes from Qatar. *J. Hum. Genet.* 65 (12), 1067–1073. doi:10.1038/s10038-020-0806-y

Allik, A. (2013). 14.05.09 35 000th Gene Donor in the Estonian Genome Project! [Online]. Available: https://genomics.ut.ee/en/content/140509-35-000th-gene-donor-estonian-genome-project (Accessed April 9, 2022).

Avard, D., Grégoire, G., and Jean, S. M. (2008). Involving the Public in Public Health Genomics: a Review of Guidelines and Policy Statements. *GenEdit* 6 (1), 1–9.

Belcher, A., Ginsburg, G. S., and Ward, R. (2020). Global Approaches to Genomic Medicine Implementation. *Sci. Transl. Med.* 12 (563), 1–2. doi:10.1126/scitranslmed.aax0911

Bell, J. (2004). Predicting Disease Using Genomics. *Nature* 429, 453–456. doi:10.1038/nature02624

Beskow, L. M., Khoury, M. J., Baker, T. G., and Thrasher, J. F. (2001). The Integration of Genomics into Public Health Research, Policy and Practice in the United States. *Public Health Genomics* 4 (1), 2–11. doi:10.1159/000051150

Brand, A. (2011). Public Health Genomics-- Public Health Goes Personalized? *Eur. J. Public Health* 21 (1), 2–3. doi:10.1093/eurpub/ckq197

Brand, H. (2005). Public Health Genetics-Potential for Public Health? *Eur. J. Public Health* 15 (2), 112. doi:10.1093/eurpub/cki089

Brett, J., Staniszewska, S., Mockford, C., Herron-Marx, S., Hughes, J., Tysall, C., et al. (2014). Mapping the Impact of Patient and Public Involvement on Health and Social Care Research: a Systematic Review. *Health Expect.* 17 (5), 637–650. doi:10.1111/j.1369-7625.2012.00795.x

Crowe, S., Fenton, M., Hall, M., Cowan, K., and Chalmers, I. (2015). Patients', Clinicians' and the Research Communities' Priorities for Treatment Research: There Is an Important Mismatch. *Res. Involv Engagem.* 1 (2), 2–10. doi:10.1186/s40900-015-0003-x

Danish Ministry of Health (2022). Danish National Genome Center. [Online]. Available: https://eng.ngc.dk/(Accessed March 5, 2022).

Danish Ministry of Health (2017). Personalised Medicine for the Benefits of Patients - National Strategy for Personalised Medicine 2017-2020. [Online]. Available: https://eng.ngc.dk/(Accessed January 25, 2022).

Danish Ministry of Health (2021). Personalised Medicine for the Benefits of Patients - National Strategy for Personalised Medicine 2021-2022. [Online]. Available: https://eng.ngc.dk/(Accessed January 25, 2022).

Data Archiving and Networked Services (2022). *Netherlands Genomics Initiative* [Online]. Available: https://www.narcis.nl/organisation/RecordID/ORG1242296/Language/nl (Accessed March 6, 2022).

Davies, Sally. (2017). Annual Report of the Chief Medical Officer 2016 "Generation Genome". [Online]. Available: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/624628/CMO_annual_report_generation_genome.pdf (Accessed January 25, 2022).

deCODE genetics (2022). deCODE Genetics. [Online]. Available: https://www.decode.com/(Accessed March 30, 2022).

Department of Economy Science & Innovation (2022). Belgian Medical Genomics Initiative (BeMGI). [Online]. Available: https://researchportal.be/en/project/belgian-medical-genomics-initiative-bemgi-0 (Accessed March 30, 2022).

Domecq, J. P., Prutsky, G., Elraiyah, T., Wang, Z., Nabhan, M., Shippee, N., et al. (2014). Patient Engagement in Research: a Systematic Review. *BMC Health Serv. Res.* 14 (1), 89–9. doi:10.1186/1472-6963-14-89

Etchegary, H., Green, J., Dicks, E., Pullman, D., Street, C., and Parfrey, P. (2013). Consulting the Community: Public Expectations and Attitudes about Genetics Research. *Eur. J. Hum. Genet.* 21 (12), 1338–1343. doi:10.1038/ejhg.2013.64

Federal Ministry of Health (2020). genomDE - National and European Initiatives Conference. [Online]. Available: https://www.eu2020.de/eu2020-en/events/-/2343352 (Accessed April 9, 2022).

Federal Ministry of Health (2022). genomeDE – National Strategy for Genomic Medicine. [Online]. Available: https://www.bundesgesundheitsministerium.de/en/en/international/european-health-policy/genomde-en.html (Accessed March 30, 2022).

FinnGen (2022a). FinnGen - about Us. [Online]. Available: https://www.finngen.fi/en/about (Accessed March 29, 2022).

FinnGen (2022b). FinnGen - Purpose and Goals. [Online]. Available: https://www.finngen.fi/en/purpose_and_goals (Accessed March 30, 2022).

FinnGen (2022c). FinnGen Research Project Is an Expedition to the Frontier of Genomics and Medicine. [Online]. Available: https://www.finngen.fi/en (Accessed April 9, 2022).

Finnish Institute for Health and Welfare (2022). P6 - Genomics to Healthcare. [Online]. Available: https://thl.fi/en/web/thlfi-en/research-and-development/research-and-projects/p6-genomics-to-healthcare (Accessed March 30, 2022).

Friedman, J. M., Cornel, M. C., Cornel, M. C., Goldenberg, A. J., Lister, K. J., Sénécal, K., et al. (2017). Genomic Newborn Screening: Public Health Policy Considerations and Recommendations. *BMC Med. Genomics* 10 (9), 1–13. doi:10.1186/s12920-017-0247-4

Genomic Medicine Policy (2022). Global Implementation of Genomic Medicine. [Online]. Available: https://www.genomicspolicy.org/(Accessed January 25, 2022).

Genomics England (2022). *100,000 Genomes Project*. [Online]. Available: https://www.genomicsengland.co.uk/initiatives/100000-genomes-project (Accessed March 30, 2022).

Gil-Garcia, R. J., Guler, A., Pardo, T. A., and Burke, G. B. (2019). Characterizing the Importance of Clarity of Roles and Responsibilities in Government Inter-organizational Collaboration and Information Sharing Initiatives. *Gov. Inf. Quaterly* 36 (4), 101393. doi:10.1016/j.giq.2019.101393

Global Alliance for Genomics and Health (2022). Enabling Responsible Genomic Data Sharing for the Benefit of Human Health. [Online]. Available: https://www.ga4gh.org/(Accessed January 25, 2022).

Government UK (2020). Genome UK - the Future of Healthcare. [Online]. Available: https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare (Accessed March 30, 2020).

Holmes, L., Cresswell, K., Williams, S., Parsons, S., Keane, A., Wilson, C., et al. (2019). Innovating Public Engagement and Patient Involvement through Strategic Collaboration and Practice. *Res. Involv Engagem.* 5 (30), 30–12. doi:10.1186/s40900-019-0160-4

IEEE Pulse (2015). The Saudi Human Genome Program. [Online]. Available: https://www.embs.org/pulse/articles/the-saudi-human-genome-program/ (Accessed April 9, 2022).

Jansen, M. E., Klein, A. W., Buitenhuis, E. C., Rodenburg, W., and Cornel, M. C. (2021). Expanded Neonatal Bloodspot Screening Programmes: An Evaluation Framework to Discuss New Conditions with Stakeholders. *Front. Pediatr.* 9 (635353), 1–7. doi:10.3389/fped.2021.635353

Juengst, E. T., Flatt, M. A., and Settersten, R. A. (2012). Personalized Genomic Medicine and the Rhetoric of Empowerment. *Hastings Cent. Rep.* 42 (5), 34–40. doi:10.1002/hast.65

Kaiser, J. (2016). Saudi Gene Hunters Comb Country's DNA to Prevent Rare Diseases. [Online]. Available: https://www.science.org/content/article/saudi-gene-hunters-comb-countrys-dna-prevent-rare-diseases (Accessed April 9, 2022). doi:10.1126/science.aal0473

Kelty, C., and Panofsky, A. (2014). Disentangling Public Participation in Science and Biomedicine. *Genome Med.* 6 (8), 8–14. doi:10.1186/gm525

Khoury, M. J., Bowen, M. S., Clyne, M., Dotson, W. D., Gwinn, M. L., Green, R. F., et al. (2018). From Public Health Genomics to Precision Public Health: a 20-year Journey. *Genet. Med.* 20 (6), 574–582. doi:10.1038/gim.2017.211

Kovanda, A., Zimani, A. N., and Peterlin, B. (2021). How to Design a National Genomic Project-A Systematic Review of Active Projects. *Hum. Genomics* 15 (20), 1–13. doi:10.1186/s40246-021-00315-6

Mehl, G., Tunçalp, Ö., Ratanaprayul, N., Tamrat, T., Barreix, M., Lowrance, D., et al. (2021). WHO SMART Guidelines: Optimising Country-Level Use of Guideline Recommendations in the Digital Age. *Lancet Digital Health* 3 (4), e213–e216. doi:10.1016/S2589-7500(21)00038-8

Metspalu, A. (2015). Estonian Genome Center—16 Years of Achievement. [Online]. Available: https://icds.ee/en/estonian-genome-center16-years-of-achievement/(Accessed April 9, 2022).

Metspalu, A., Köhler, F., Laschinski, G., Ganten, D., and Roots, I. (2004). Das estnische Genomprojekt im Kontext der europäischen Genomforschung. *Dtsch. Med. Wochenschr* 129, S25–S28. doi:10.1055/s-2004-824840

Ministry of Social Affairs and Health (2022). National Genome Centre. [Online]. Available: https://stm.fi/en/genome-center (Accessed April 9, 2022).

Molster, C. M., Bowman, F. L., Bilkey, G. A., Cho, A. S., Burns, B. L., Nowak, K. J., et al. (2018). The Evolution of Public Health Genomics: Exploring its Past, Present, and Future. *Front. Public Health* 6 (247), 1–11. doi:10.3389/fpubh.2018.00247

National Health Research Institutes Communications (2019). NHRI Taiwan Launches G2020 Population Genomics Pilot, Partnering with Illumina on an Operational Architecture for Population Genomics.

National Institutes of Health (2022). *All of Us*. [Online]. Available: https://allofus.nih.gov/about (Accessed March 30, 2022).

Novo Nordisk (2022). The Novo Nordisk Foundation. [Online]. Available: https://www.novonordisk.com/about/corporate-governance/the-novo-nordisk-foundation.html (Accessed January 25, 2022).

Nunn, J. S., Tiller, J., Fransquet, P., and Lacaze, P. (2019). Public Involvement in Global Genomics Research: a Scoping Review. *Front. Public Health* 7 (79), 1–10. doi:10.3389/fpubh.2019.00079

Pezzullo, A. M., Sassano, M., Hoxhaj, I., Pastorino, R., and Boccia, S. (2021). Citizen Engagement Initiatives in Precision Health in the European Union Member States: a Scoping Review. *BMJ Open* 11 (e045846), e045846–10. doi:10.1136/bmjopen-2020-045846

Qatar Genome (2022). About Qatar Genome. [Online]. Available: https://www.qatargenome.org.qa/about-qgp/qatar-genome/about-qatar-genome (Accessed March 30, 2022).

Qoronfleh, M. W., Chouchane, L., Mifsud, B., Al Emadi, M., and Ismail, S. (2020). The Future of Medicine, Healthcare Innovation through Precision Medicine: Policy Case Study of Qatar. *Life Sci. Soc. Policy* 16 (1), 12. doi:10.1186/s40504-020-00107-1

Rigter, T., Jansen, M. E., Groot, J. M. d., Janssen, S. W. J., Rodenburg, W., and Cornel, M. C. (2020). Implementation of Pharmacogenetics in Primary Care: a Multi-Stakeholder Perspective. *Front. Genet.* 11 (10), 1–12. doi:10.3389/fgene.2020.00010

Samuel, G. N., and Farsides, B. (2018). Genomics England's Implementation of its Public Engagement Strategy: Blurred Boundaries between Engagement for the United Kingdom's 100,000 Genomes Project and the Need for Public Support. *Public Underst. Sci.* 27 (3), 352–364. doi:10.1177/0963662517747200

Saudi Human Genome Program (2022). Saudi Human Genome Program. [Online]. Available: https://shgp.kacst.edu.sa/index.en.html#introduction (Accessed March 30, 2022).

SitraFund (2015). Finland's Genome Strategy. [Online]. Available: https://issuu.com/sitrafund/docs/finland_genomestrategy (Accessed April 9, 2022).

Stark, Z., Dolman, L., Manolio, T. A., Ozenberger, B., Hill, S. L., Caulfied, M. J., et al. (2019). Integrating Genomics into Healthcare: A Global Responsibility. *Am. J. Hum. Genet.* 104 (1), 13–20. doi:10.1016/j.ajhg.2018.11.014

Sutton, R. T., Pincock, D., Baumgart, D. C., Sadowski, D. C., Fedorak, R. N., and Kroeker, K. I. (2020). An Overview of Clinical Decision Support Systems: Benefits, Risks, and Strategies for Success. *npj Digit. Med.* 3 (17), 1–10. doi:10.1038/s41746-020-0221-y

Taiwan Human Biological Database (2021). Biobanking for a Healthier Future. [Online]. Available: https://www.twbiobank.org.tw/(Accessed April 9, 2022).

ThermoFisher (2022). The Saudi Human Genome Program: Bringing Genetic Testing to Routine Clinical Care. [Online]. Available: https://www.thermofisher.com/nl/en/home/clinical/precision-medicine/precision-medicine-learning-center/precision-medicine-resource-library/precision-medicine-articles/saudi-human-genome-program.html (Accessed April 9, 2022).

Wagner, J. K., Peltz-Rauchman, C., Rahm, A. K., and Johnson, C. C. (2017). Precision Engagement: the PMI's Success Will Depend on More Than Genomes and Big Data. *Genet. Med.* 19 (6), 620–624. doi:10.1038/gim.2016.165

World Health Organization (2022). Public Health Services. [Online]. Available: https://www.euro.who.int/en/health-topics/Health-systems/public-health-services/public-health-services (Accessed January 25, 2022).

Wouters, R. H. P., Graaf, R., Voest, E. E., and Bredenoord, A. L. (2020). Learning Health Care Systems: Highly Needed but Challenging. *Learn Health Sys* 4 (e10211), 1–6. doi:10.1002/lrh2.10211

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A RE-AIM Framework Analysis of DNA-Based Population Screening: Using Implementation Science to Translate Research Into Practice in a Healthcare System

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Introduction: DNA-based population screening has been proposed as a public health solution to identify individuals at risk for serious health conditions who otherwise may not present for medical care. The clinical utility and public health impact of DNA-based population screening is a subject of active investigation. Geisinger, an integrated healthcare delivery system, was one of the first healthcare systems to implement DNA screening programs (MyCode Community Health Initiative (MyCode) and clinical DNA screening pilot) that leverage exome data to identify individuals at risk for developing conditions with potential clinical actionability. Here, we demonstrate the use of an implementation science framework, RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance), to conduct a post-hoc evaluation and report outcomes from these two programs to inform the potential impact of DNA-based population screening.

Methods: Reach and Effectiveness outcomes were determined from the MyCode research program, while Adoption and Implementation outcomes were measured using the clinical DNA screening pilot. Reach was defined as the number of patients who were offered and consented to participate in MyCode. Effectiveness of DNA screening was measured by reviewing MyCode program publications and synthesizing findings from themes. Adoption was measured by the total number of DNA screening tests ordered by clinicians at the clinical pilot sites. Implementation was assessed by interviewing a subset of clinical pilot clinicians about the deployment of and recommended adaptations to the pilot that could inform future program dissemination.

Results: *Reach*: As of August 2020, 68% (215,078/316,612) of individuals approached to participate in the MyCode program consented. Effectiveness: Published evidence reported from MyCode demonstrates that DNA screening identifies at-risk individuals

more comprehensively than clinical ascertainment based on phenotypes or personal/family history. *Adoption*: From July 2018 to June 2021, a total of 1,026 clinical DNA screening tests were ordered by 60 clinicians across the three pilot clinic sites. *Implementation*: Interviews with 14 clinicians practicing at the pilot clinic sites revealed motivation to provide patients with DNA screening results and yielded future implementation strategies.

Conclusion: The RE-AIM framework offers a pragmatic solution to organize, analyze, and report outcomes across differently resourced and designed precision health programs that include genomic sequencing and return of clinically actionable genomic information.

Keywords: DNA-based population screening, implementation science, healthcare system, RE-AIM, genetics, MyCode

INTRODUCTION

DNA-based population screening of unselected individuals for disease-causing genomic variants has been proposed as a method for ascertaining those at risk for serious health conditions who may not otherwise be identified. This distinction of unselected individuals is critical to exploring DNA-based population screening as it refers to the system-wide selection or screening of individuals without regard to underlying risk, clinical features, or family history that may indicate hereditary risk or disease (indication-based identification) (Carey et al., 2016; Abul-Husn et al., 2019; Abul-Husn et al., 2021). Such screening has the benefit of identifying individuals with actionable genetic changes (Kalia et al., 2017) prior to diagnosis based on symptoms; symptoms which are typically the impetus for indication-based genetic testing. By identifying individuals earlier, appropriate medical action for treatment and prevention can be taken. Another benefit is the potential to overcome inequities and health disparities currently seen in indication-based identification and testing (Jakuboski et al., 2022). Several healthcare systems have initiated DNA-based population screening programs that may consist of research biobanks and/or DNA screening pilot programs (Williams, 2022). Early results from these programs demonstrate effectiveness in ascertaining individuals carrying genomic risk variants by improving risk management and facilitating early diagnoses of severe diseases (Grzymski et al., 2020; Williams, 2022). However, a key issue limiting the implementation of these DNA-based population screening programs into routine clinical care is the critical need for additional evidence demonstrating clinical utility (Murray et al., 2019).

Ongoing evidence gaps recognized in DNA-based population screening include questions about which genes—and variants within those genes—to screen, best practices for disclosing results to individuals and clinicians, short- and long-term outcomes of returning genomic information, when to perform screening, settings and care models for screening, costs and cost-effectiveness of screening, and whether screening mitigates or exacerbates health disparities. Many of these gaps relate to clinical utility, defined by the Centers for Disease Control and Prevention (CDC) as "whether genetic testing results in measurable improvement in health or improves management of patients" (Haddow et al., 2004; Murray et al., 2019; Office of Science, 2021).

In the traditional research model, evidence gaps are addressed through studies of efficacy and effectiveness conducted in narrowly defined populations or organizational contexts (Chambers et al., 2016). This has led to the general observation that it takes an average of 17 years to translate a fraction of such research into clinical care (Balas and Boren, 2000). The field of implementation science has evolved to help shorten the time to implementation of effective interventions by understanding the multi-level, complex issues inherent in the implementation, adoption, and maintenance of research evidence in health care policy and practice (Holtrop et al., 2018a; Chambers, 2018). Implementation science focuses on evaluating use and effectiveness under typical (real-world, non-controlled) conditions (Holtrop et al., 2018a) by leveraging theories, models, and frameworks for program planning, implementation, evaluation, and maintenance (Nilsen, 2015; Brownson, 2017). Due to the rapid generation of data and the need to expediate the translation of learnings from multiple contexts such as observational studies, clinical trials, and pilot programs, calls for incorporation of implementation science methodologies into the fields of genomics and precision health have been made (Chambers, 2018; Ginsburg et al., 2021; Sperber et al., 2021).

The RE-AIM framework (Reach, Effectiveness, Adoption, Implementation, and Maintenance) is an implementation science framework that addresses the research-practice gap by including evaluation of outcomes beyond efficacy and effectiveness to better identify translation potential and public health impact (Glasgow et al., 1999; Glasgow et al., 2019). RE-AIM emphasizes both internal and external validity by evaluating outcomes associated with the five dimensions in the framework acronym. RE-AIM is ideal for pragmatic contexts and facilitates evaluation of impact at the individual (reach/effectiveness) and institutional (adoption/implementation) levels simultaneously, since multi-level impact is critical for both translation and broader public health benefit (Glasgow et al., 1999; Nilsen, 2015; Brownson, 2017; Glasgow and Estabrooks, 2018; Glasgow et al., 2019). Over the last two decades, RE-AIM has been used extensively in other contexts, yet it is only beginning to be applied to precision health (Glasgow et al., 2019; Jones et al., 2021b; Blazer et al., 2021; Kim et al., 2021; Miller et al., 2021;

TABLE 1 | Key characteristics of two Geisinger DNA screening programs.

Characteristics	MyCode® community health initiative (research)	Clinical DNA screening pilot
Purpose	Return clinically actionable confirmed findings from research exome sequences to MyCode participants	Return subset of clinically actionable findings from clinically generated exome sequences to unselected patients at participating clinics
Implementation context	Geisinger population and MyCode participants	Patients receiving care at specific ambulatory clinics (primary and specialty care)
Who offers/delivers the program	Precision health associates (consenters), GCs, genetic counseling assistants funded through the GSC program	Clinicians at select sites as part of clinical practice
Screening model	Opportunistic	Proactive
Genes screened	ACMG SF v2.0 + *HFE* (c.845G > A, p.C282Y homozygotes)	ACMG SF v2.0
Who discloses results	GSC GCs	• GCs modeling the GSC disclosure process (positive results) • Ordering clinician *via* letter (negative results)
Timeline to result return	6 months–2 years based on sample batch size	6–8 weeks

ACMG, American College of Medical Genetics and Genomics; GC, genetic counselor; GSC, genomic screening and counseling.

Sperber et al., 2021). In this study, we demonstrate the use of RE-AIM to conduct a post-hoc evaluation and report outcomes from two DNA screening programs at Geisinger with the goal of generating evidence needed for systematic implementation of DNA-based population screening.

MATERIALS AND METHODS

Study Setting

Geisinger, an integrated health system serving over two million individuals in rural Pennsylvania, is an innovator in exploring DNA-based population screening approaches (Carey et al., 2016; Schwartz et al., 2018; Schmidlen et al., 2019; Savatt et al., 2020). Approximately one-third of individuals receiving care in the system are also insured by the Geisinger Health Plan, creating the ideal environment for piloting innovations in care delivery to improve health outcomes (Steele and Feinberg, 2017). Two of Geisinger's precision health programs are described above with key aspects of each program highlighted in **Table 1**.

MyCode Community Health Initiative (MyCode)

In-depth descriptions of Geisinger's MyCode program have been published elsewhere (Carey et al., 2016; Schwartz et al., 2018; Williams, 2019; Williams et al., 2018b; Kelly et al., 2021; Dewey et al., 2016; MyCode scorecard [Online], n.a). Relevant to the analyses presented here, Geisinger launched MyCode in 2007 to create a biobank of serum, blood, and DNA samples for health discovery research (Carey et al., 2016). The overall aim is to develop methods that will enable identification of individuals' unique biological, environmental, and social influences on health and promote care tailored to individual health risks (Williams et al., 2018b; Williams, 2019). In 2014, MyCode initiated exome sequencing and SNP genotyping using DNA samples through the DiscovEHR collaboration with the Regeneron Genetics Center to uncover novel genetic associations with disease and therapeutic targets (Dewey et al., 2016; Kelly et al., 2021). In anticipation of exome sequencing, MyCode amended its consent in 2013 to allow disclosure of clinically actionable findings to participants (Carey et al., 2016; Kelly et al., 2021). Any Geisinger patient is eligible to participate in MyCode and can consent in-person when they present for care or *via* the patient portal in the electronic health record (EHR). Consent documents are currently available in English and Spanish. MyCode participants who consented prior to 2013 are contacted by study staff to re-consent for DNA screening and potential return of information. As of February 2022, >300,000 Geisinger patients have consented to MyCode, >207,000 have provided samples, >184,000 have had exome sequencing and genotyping completed, and >3,100 have received a clinically actionable genetic result (MyCode scorecard [Online], n.a).

The MyCode Genomic Screening and Counseling (GSC) program was added in 2015 to identify and clinically confirm actionable genomic risk results for disclosure to patient-participants and their clinicians (Williams et al., 2018b; Schwartz et al., 2018). When MyCode exome sequence data reveals a pathogenic or likely pathogenic (P/LP) variant in a gene returned through MyCode, a clinically collected sample retained in the MyCode CLIA-certified repository is sent for clinical confirmation and reporting of the variant in a CLIA-certified genetics laboratory. The list of genes included for DNA screening through MyCode was developed based on several resources including to the American College of Medical Genetics and Genomics (ACMG) secondary findings list, as previously described, and is regularly reviewed and updated by research and clinical stakeholders based on current evidence (Schwartz et al., 2018; Kelly et al., 2021). The current list of genes includes those on the ACMG secondary findings v2.0 list (Kalia et al., 2017) in addition to biallelic variants in the *HFE* gene leading to the C282Y amino acid substitution (Kelly et al., 2021). Benign/likely benign variants and variants of uncertain significance (VUS) are not reported to MyCode participants. After CLIA confirmation of the result, the GSC program process includes 1) depositing the laboratory report with genetic test results into the patient-participant's EHR, 2) notifying the patient-participant's primary care clinician through the EHR (for Geisinger clinicians) or *via* alternative methods for external clinicians, 3) three phone call/patient portal attempts to disclose the result and recommend a complimentary genetic counseling visit, and 4) mailing of a packet with the result to the patient-participant (Schwartz et al., 2018).

Clinical DNA Screening Pilot Program

In 2018, Geisinger launched a clinical DNA screening pilot program in select ambulatory care settings to evaluate the integration of DNA

TABLE 2 | RE-AIM dimensions with standard definitions, adapted definitions, associated Geisinger DNA screening programs, and data sources.

Dimensions	Definition	DNA-based population screening definition	Program	Data sources
Reach	The absolute number, proportion, and representativeness of individuals willing to participate in a program	The number, proportion, and representativeness of individuals willing to participate in a DNA-based population program that returns genomic information	MyCode (research)	MyCode consent database
Effectiveness	The impact of an intervention on important individual outcomes, including potential negative effects, and broader impact including quality of life and economic outcomes; and variability across subgroups (generalizability or heterogeneity of effects)	The impact of returning clinically relevant genetic results to individuals on medical outcomes, psychological and quality of life outcomes, and economic outcomes, including negative effects. Variability across subgroups and including health disparities	MyCode (research)	Review of published MyCode literature
Adoption	The absolute number, proportion, and representativeness of people who deliver the program and who are willing to initiate a program	The number of clinical genomic screening tests ordered at pilot sites	Clinical DNA screening pilot	EHR
Implementation	Any adaptations made to interventions and implementation strategies	Suggested adaptations to the current clinical pilot to inform future program dissemination	Clinical DNA screening pilot	Semi-structured interviews with clinicians
Maintenance	(setting level) the extent to which a program or policy becomes institutionalized or part of the routine organizational practices and policies, and adaptations made to achieve maintenance	(setting level) extent to which MyCode and clinical pilot programs become routine/institutionalized	Not yet assessed	Not applicable
		(individual level) long term impact (e.g., longitudinal effectiveness, adherence to guidelines) of returning clinically relevant genetic information on individual health outcomes		
	(individual level) the long-term effects of a program on outcomes after a program is completed			

screening into routine healthcare (Geisinger, 2018). The clinical DNA screening test uses an exome sequencing backbone to screen for P/LP variants in the genes on the ACMG secondary findings version 2.0 list (Kalia et al., 2017). Positive screen results (P/LP variants) are disclosed to patients by a genetic counselor utilizing a modified version of the MyCode GSC program disclosure protocols; negative results are disclosed by a letter to the patient. Given the pivotal role that primary care providers play in preventive care, the clinical DNA screening pilot program was initiated to engage primary care in delivering genomic screening as a part of routine primary care practice.

The program is a system initiative that was initially implemented as a pragmatic proof-of-concept clinical pilot at 3 clinics selected based on location (one clinic per service region: central, northeast, west) and clinical interest. Clinical tools (EHR-based ordering and documenting templates) and educational information developed in collaboration with clinical partners were provided to each pilot clinic site upon program implementation at the site. All clinicians at the three clinical pilot sites can order the clinical DNA screening test for any adult individual seen irrespective of disease indications.

Study Design

We conducted a post-hoc program evaluation of data generated from the MyCode research program and the clinical DNA-screening pilot program using mixed-methods and the RE-AIM framework as adapted based on guidance in Glasgow & Estabrooks for the pragmatic gathering of data and evaluation of relevant outcomes (Glasgow and Estabrooks, 2018). This evaluation was deemed not research by the Geisinger Institutional Review Board.

Table 2 describes how the two programs inform the potential for implementation of population-based DNA screening by RE-AIM dimension and the data/method utilized to inform results. The MyCode research program provides the context most similar to real-world conditions for patient interest in and effectiveness of broad-scale population screening were it to be made available to all individuals in a health system. Therefore, Reach and Effectiveness were evaluated through the MyCode research program using MyCode consent database (Reach) and publication review (Effectiveness) to understand the potential willingness of individuals to participate in a research program that discloses health-related genomic results to participants and the impact of returning genomic information to individuals on health outcomes. As a system initiative based in primary care, the clinical DNA screening pilot program demonstrates how such a program might look in clinical practice and created an ideal natural experiment to measure Adoption and Implementation of DNA-based population screening by eligible clinicians under real-world conditions. EHR data (Adoption) and qualitative interviews (Implementation) were conducted to understand adoption variability and clinician views of offering and ordering a DNA screening test as part of routine healthcare. Maintenance was not assessed in this evaluation but guidance for how this dimension may be measured is included in **Table 2**.

Definition, Data Collection, and Outcomes Analysis Methods Per RE-AIM Dimension

Reach

Reach was defined as the number of individuals who consented or re-consented to MyCode after 2013 (when updates to consenting

allowed for disclosure of results) over the number of individuals approached to participate in the program. Representativeness (a critical component of Reach) of the population reached by MyCode was also explored. Representativeness of MyCode patient-participants was compared to non-participants (individuals who have declined or withdrawn participation or have not yet re-consented) and compared to the system's general patient population (inclusive of all individuals who have received care at Geisinger regardless of whether they are insured by Geisinger or have a Geisinger primary care clinician).

MyCode consent data is stored in a MyCode consent database. Information from this database from February 2007 to August 2020 were reviewed for individuals approached to participate in MyCode. Demographic data available from the EHR included current age, sex, race, ethnicity, 3-digit level zip code, primary care clinician (Geisinger or non-Geisinger), comorbidity index, and health insurance type. Descriptive characteristics were reported using means and medians and comparisons of categorical variables between groups were performed by Chi-squared test or Z-test for proportions. Non-normal continuous variables were compared using Wilcoxon rank sum test. All statistical analysis was performed in R (Vienna, Version 4.0.2).

Effectiveness

Effectiveness was defined as the clinical impact of returning clinically relevant genetic results to individuals. Since multiple analyses have already been conducted and published, effectiveness was evaluated by conducting a review of this published MyCode literature. Thirteen peer-reviewed publications have reported MyCode outcomes related to Effectiveness of DNA-based population screening from program initiation (2007) to 2021. Data extracted from these studies included genetic condition, study sample size, and key findings. Studies were organized and coded for the following thematic outcomes determined by the study team to represent Effectiveness: screen positive detection rate (proportion of eligible participants with a clinically confirmed P/LP variant in a gene of interest), ascertainment of at-risk individuals *via* DNA screening compared to clinical ascertainment, rate of relevant genetic disease, impact of genetic results disclosure on medical management, post-disclosure disease diagnoses attributed to DNA screening, and costs and cost-effectiveness. Coding was conducted by two raters, with discrepancies reviewed and resolved by the senior author. A brief description of each thematic area and relevance to population-based DNA screening is described below:

- Screen positive detection rate of actionable genomic variants in unselected populations: Demonstrating the P/LP variant rate related to a condition in an unselected population is an important indicator of how many at-risk individuals in a population remain unidentified or undiagnosed without DNA-based population screening.
- Ascertainment of at-risk individuals *via* DNA screening compared to clinical ascertainment: Comparing the number of individuals with P/LP variants, but unrecognized prior to DNA screening, to clinical ascertainment as a key indicator of programmatic effectiveness.
- Rate of relevant genetic disease: Understanding the rate of relevant disease among unselected individuals found to have an actionable variant can inform recommendations for managing their disease risks.
- Impact of disclosure on medical management: For population DNA screening to have the intended public health benefit, clinicians and patients must adhere to recommended medical management intended to reduce condition-specific morbidity and mortality. Identification of multilevel barriers to and facilitators of recommended management can inform interventions to improve management.
- New clinical diagnoses post-disclosure: A goal of population-based DNA screening is to impact the condition-related health outcomes of the individual identified with a P/LP variant for the condition.
- Cost and cost-effectiveness: Cost-burden on a healthcare system or patients and cost-effectiveness of population-based DNA screening is a reported barrier to implementation and an important factor for sustainability.

Adoption

For this post hoc evaluation of DNA-based population screening, Adoption was defined as the number of the clinical DNA screening tests ordered by clinicians at the clinical pilot sites, as determined by review of programmatic data. Provider type (attending, resident, Fellow, etc.) was collected to describe representativeness. Due to the clinical pilot program implementation that made the test available to all clinicians in the pilot clinic and because of the fluctuation in attending clinicians and trainees in pilot sites over time, the percentage of clinicians ordering the clinical DNA screening test (proportion/percent adopted) could not be accurately determined.

Implementation

Implementation was assessed by conducting semi-structured interviews among a subset of clinical pilot clinicians about the deployment of and recommended adaptations to the pilot that could inform future program improvement and dissemination.

Clinicians, including physicians (attendings, residents, and fellows), nurse practitioners, and physician assistants were invited to participate in the interviews. Clinicians were recruited through email using a purposive sampling strategy based on clinic and number of clinical DNA screening tests ordered during the pilot implementation (including clinicians that did not order the test) to ensure representation across pilot clinics (location-central, northeast, or west) and adoption (no tests ordered, 1–10 tests ordered, 11–20 tests ordered, 21–30 tests ordered, over 100 tests ordered). All interviews were conducted using a semi-structured interview guide to explore implementation aspects of the pilot clinical DNA screening program and inform future program dissemination. Questions were designed to explore attitudes towards clinical DNA screening in primary care, why or for whom they ordered testing for and experience with testing and results (if ordered), fit with clinical workflow, confidence in understanding and using

TABLE 3 | Characteristics of MyCode participants and general Geisinger population.

	MyCode participants who consented or re-consented after 2013 (*N* = 2,15,078)	MyCode participants who declined or withdrew or have not reconsented after 2013 (*N* = 1,00,314)	*p*-value[a]	General Geisinger population (*N* = 20,72,639)	*p*-value[b]
Age, median [IQR]	55 [38, 68]	57 [39, 71]	$p < 2.2 \times 10^{-16}$	40 [20, 62]	$p < 2.2 \times 10^{-16}$
Sex, n (%)					
Female	1,28,149 (59.6)	60,456 (60.3)	$p < 0.0001$	10,79,082 (52.1)	$p < 2.2 \times 10^{-16}$
Male	86,928 (40.4)	39,850 (39.7)		9,93,557 (47.9)	
Unknown	1 (0.0)	8 (0.0)			
Race, n (%)					
White/European ancestry	2,06,102 (95.8)	94,487 (94.2)	$p < 2.2 \times 10^{-16}$	18,76,010 (90.5)	$p < 2.2 \times 10^{-16}$
Black/African ancestry	5,771 (2.7)	3,795 (3.8)		1,09,164 (5.3)	
Native American	278 (0.1)	132 (0.1)		2,995 (0.1)	
Asian or Pacific Islander	1,516 (0.7)	1,515 (1.5)		36,894 (1.8)	
Unknown/other	1,411 (0.7)	385 (0.4)		47,576 (2.3)	
Ethnicity, n (%)					
Hispanic/Latinx	6,284 (2.9)	3,572 (3.6)	$p < 2.2 \times 10^{-16}$	1,07,788 (5.2)	$p < 2.2 \times 10^{-16}$
Not Hispanic/Latinx	2,06,776 (96.1)	94,725 (94.4)		—	
Unknown	2018 (0.9)	2017 (2.0)		—	
Have a Geisinger PCP, n (%)	1,32,652 (61.7)	60,428 (60.2)	$p < 0.0001$	5,94,847 (28.7)	$p < 2.2 \times 10^{-16}$
Insured with GHP, n (%)	82,926 (38.6)	34,240 (34.1)	$p < 2.2 \times 10^{-16}$	4,51,835 (21.8)	$p < 2.2 \times 10^{-16}$
CCI, median [IQR]	2 [0, 4]	2 [0, 4]	$p < 2.2 \times 10^{-16}$	0	$p < 2.2 \times 10^{-16}$

PCP, primary care provider; GHP, Geisinger health plan; CCI, Charlson comorbidity index; IQR, interquartile range.

[a]Comparison between MyCode screening population and control population. Chi-squared test was performed for categorical variables with multiple levels (Sex, Race, and Ethnicity). Z-test for two proportions was used for categorical variables with two levels (%Geisinger PCP, %GHP). Two-sample Wilcoxon test was used for comparing the medians for continuous variables (Age and CCI).

[b]Comparison between MyCode screening population and Geisinger population. Chi-squared test was performed for categorical variables with multiple levels (Sex and Race). Z-test for one proportion was used for logistical variables or categorical variables with two levels (Sex, % Hispanic/Latinx, %Geisinger PCP, %GHP). One-sample Wilcoxon test was used for non-normal continuous variables (Age and CCI), treating the medians of the general Geisinger population as the population median.

the test information, experience with and opinion of EHR tools provided, and recommendations to improve the program and processes (See **Supplementary Material S1** for interview guide).

A rapid qualitative analysis using a framework method was employed (Bryman and Burgess, 1994; Gale et al., 2013). Two research staff members reviewed interview summaries and full transcripts under the guidance of the first author to define emergent themes and identify supportive quotations. Emergent themes were finalized through discussion with the first author and coding accuracy was achieved through constant comparison with the first author (Beebe, 2001). Discrepancies and uncertainties with themes identified and coded quotations were resolved by additional expert consultation with the senior author. Prior to finalizing, all results were reviewed with clinical screening pilot program staff and other study team members.

RESULTS

Reach

Approximately two million individuals receive care within the Geisinger system. All have the potential to participate in MyCode by enrolling through the patient portal or when receiving care in a Geisinger facility. Of the 316,612 individuals approached to participate in the MyCode research program, 215,078 individuals had consented or re-consented after 2013 (when updates to consenting allowed for disclosure of results) as of August 2020 (68% participation rate). To evaluate the representativeness of MyCode participants, we compared those consented to receive results to individuals who actively declined to participate (78,372), withdrew consent (3,577) or have not yet re-consented to receive results (18,355) and to the general Geisinger population (2,072,639) (**Table 3**). There were statistically significant differences in demographic characteristics between individuals on a return-eligible consent (willing to participate) compared to those who were not eligible to receive results (declined, withdrew, or have not yet updated their consent) and to the general Geisinger population. Individuals who consented to receive results were younger than those not eligible to receive results, but were older than the overall Geisinger population ($p < 2.2 \times 10^{-16}$). They were also more likely to be female ($p < 0.0001$), White ($p < 2.2 \times 10^{-16}$), non-Hispanic ($p < 2.2 \times 10^{-16}$), have a Geisinger primary care physician (PCP) ($p < 0.0001$), have Geisinger Health Plan insurance ($p < 2.2 \times 10^{-16}$), and have a higher Charlson Comorbidity Index ($p < 2.2 \times 10^{-16}$) than both comparator populations.

Effectiveness

Table 4 provides detail on the multiple levels (population, individual, system) addressed by each identified thematic area relevant population-based DNA screening and the number of

TABLE 4 | Program review effectiveness construct results reported by clinical utility-associated thematic purpose.

Effectiveness-related themes	Level	Definition	Example	Number of publications to date	References
Screen positive detection rate of actionable genetic variants in unselected populations	Population	Defining the number with P/LP genetic variants	Reporting within the population on the number of individuals with P/LP genetic variants	5	(Kelly et al., 2021; Abul-Husn et al., 2016; Manickam et al., 2018; Carruth et al., 2021; Carruth et al., 2019)
Ascertainment of at-risk individuals *via* DNA screening compared to clinical ascertainment	Individual patient	Defining the number of individuals with P/LP variants and clinical phenotype that has not been previously identified	Have phenotype but were unrecognized to have the condition until receipt of the genetic information	5	(Buchanan et al., 2020; Buchanan et al., 2018; Manickam et al., 2018; Jones et al., 2021a)
Rate of relevant genetic disease	Individual patient	Comparing phenotypes of individuals with P/LP for the condition with individuals with only a clinical diagnosis	Clinical vs. genetic diagnosis of a condition	5	(Buchanan et al., 2020; Abul-Husn et al., 2016; Manickam et al., 2018; Carruth et al., 2019; Carruth et al., 2021)
Impact of disclosure on medical management	Individual patient	Reported on data congruency with desired outcome or guideline-based recommendation	Reporting on number of participants who would have been picked up on family history screening Number of participant adherent to guideline-based recommendations after receiving results	5	(Buchanan et al., 2018; Buchanan et al., 2020; Hao et al., 2020; Jones LK et al., 2018; Jones et al., 2020)
New clinical diagnoses post-disclosure	Individual patient	Medical follow-up prompted by the knowledge/return of the genomic information led directly to a diagnosis related to the variant (e.g., an ovarian cancer diagnosed) or a clinical manifestation of the diseases (e.g., aortic dilation identified after a Marfan variant returned)	Case reports or counts of new diagnoses reported post return of genetic result that can be linked to the return of the genomic information to the individual (e.g., are a direct result of medical follow-up specifically attributed to the result returned)	4	(Buchanan et al., 2020; Buchanan et al., 2018; Jones LK et al., 2018; Carruth et al., 2021)
Cost and cost effectiveness	Population or system	Reporting on costs per patients of genetic sequencing in a population	Quality adjusted life years of a genetic sequencing program (usually modeling papers)	3	(Hao et al., 2020; Guzauskas et al., 2020; Guzauskas GF et al., 2022)

P/LP, pathogenic or likely pathogenic.

publications relevant to each theme at the time of this analysis. Outcomes related to themes of interest were extracted and summarized (**Supplementary Material S2**). Overall, our published results thus far indicate that DNA screening identifies at-risk individuals more comprehensively than clinical ascertainment based on phenotypes or personal/family history, that disclosing this information can have positive impact on individual medical management and diagnostic outcomes, and that costs and cost-effectiveness in different contexts are important to assess.

Screen Positive Detection Rate of Actionable Genomic Variants in Unselected Populations

We found an overall detection rate of 2.6% for P/LP variants in the 60 genes screened by MyCode from 130,048 exomes screened at that time (Kelly et al., 2021). Thus far, MyCode data have reported P/LP variant detection rates in unselected individuals for familial hypercholesterolemia (FH)-related variants (1 in 222) (Abul-Husn et al., 2016) and hereditary breast and ovarian cancer (HBOC)-related variants (1 in 180) (Manickam et al., 2018). For arrhythmogenic cardiomyopathy (ACM), an inherited heart condition associated with sudden cardiac death, particularly in the young, MyCode data indicate a P/LP variant rate between 1 in 435 (Carruth et al., 2021) and 1 in 714 (Carruth et al., 2019), depending on the review criteria applied.

Ascertainment Of At-Risk Individuals *Via* DNA Screening Compared To Clinical Ascertainment

Based on EHR review, only 14%–20% of MyCode patient-participants had a clinical laboratory report documenting their genomic variant prior to identification through MyCode (Kelly et al., 2021). During the period under study, three genetic conditions were recognized by the CDC as having evidence for potential reduction in morbidity and mortality when identified through population DNA screening (Centers for Disease Control and Prevention, 2014). These conditions—HBOC syndrome (associated with *BRCA1* and *BRCA2* genes), Lynch syndrome (LS) (associated with *MLH1, MSH2, MSH6,* and *PMS2* genes), and FH (associated with *APOB* and *LDLR* genes)—are collectively identified as "Tier 1" conditions. For CDC Tier 1 conditions returned through MyCode, 87% (305/351) of patient-participants were unaware of their molecular diagnosis at the time of the genomic result (Buchanan et al., 2020). In another report, only 13% (7/55) of individuals with a *BRCA1/2* variant returned through MyCode had previously received clinical genetic testing that identified their molecular diagnosis

(Buchanan et al., 2018). Among individuals with a *BRCA1/2* variant returned through MyCode, 51% (45/89 individuals) met National Comprehensive Cancer Network (NCCN) criteria for clinical testing, yet had no documentation of genetic testing or referral to genetic counseling (Manickam et al., 2018). For FH, none of the individuals meeting the clinical criteria for "definite" or "probable" FH diagnosis had previously undergone genetic testing (Buchanan et al., 2020). Importantly, not all these individuals with FH would have been identified using clinical screening criteria (Jones et al., 2021a).

Rate of Relevant Genetic Disease

In MyCode, 65% of individuals identified with a P/LP variant in one of the CDC Tier 1 conditions had a personal or family history relevant to the condition (Buchanan et al., 2020). Individuals identified with an FH variant had significantly increased odds of having general (odds ratio, 2.6) and premature coronary artery disease (odds ratio, 3.7) compared to individuals with high cholesterol but without a genomic variant (Abul-Husn et al., 2016). MyCode participants with a P/LP *BRCA1/2* variant were significantly more likely than participants without a *BRCA1/2* variant to have a history of breast cancer (odds ratio, 5.95) or ovarian cancer (odds ratio, 18.3) (Manickam et al., 2018). For ACM, although some of the 140 individuals with a P/LP variant were found to have a relevant clinical feature, the prevalence of EHR-recorded cardiac findings did not differ compared to matched controls without a P/LP variant (Carruth et al., 2019). Further phenotyping among 59 individuals with a P/LP ACM variant found that only 1 (2%) met a strict definition of a clinical diagnosis of ACM, though an additional 20 (34%) satisfied at least one ACM diagnostic criterion (Carruth et al., 2021).

Impact of Disclosure on Medical Management

Across CDC Tier 1 conditions, 70% of individuals eligible for condition-specific risk management engaged in at least one risk management procedure 1–3 years post-disclosure. However, uptake was highly variable between conditions and management procedures (Buchanan et al., 2020). For females without any prior cancer diagnosis who received a *BRCA1/2* result from MyCode, mammogram or breast MRI uptake was between 50%–92% and 11%–31% had a risk reducing salpingo-oophorectomy, depending on when the analysis was performed (Buchanan et al., 2018; Buchanan et al., 2020; Hao et al., 2020). Among individuals who received a P/LP result related to FH, nearly all had lipid testing post-disclosure, 51%–83% discussed their FH result with a clinician, and 38% had important changes to their treatment regimen (Jones LK et al., 2018). Specific to FH, we also reported an increase in adherence to important lipid lowering therapy from 64 to 77% post-disclosure and in another study reported on 3 individuals above the lipid control goal (LDL-C < 100 mg/dl) pre-disclosure who met goal after disclosure which prompted following appropriate risk management specific to FH (Jones LK et al., 2018). For clinicians, disclosure of an FH result through MyCode led to ordering of lipid testing and referral for evaluation in nearly all identified individuals (Jones LK et al., 2018).

FH is the only condition in which we have reported on multi-level barriers and facilitators to guideline-recommended care (Jones et al., 2020). Patients reported multiple barriers, including experiencing care gaps due to changing evidence, lack of insurance coverage for treatment, side effects related to treatments and other family or health demands that impeded them from managing their FH. They noted having an informed medical team facilitated their care (Jones et al., 2020). Medical management barriers reported by clinicians included lack of awareness of FH, busy clinics, and difficulty convincing patients to adhere to prescribed treatment plans. Having clear diagnostic criteria was identified as a facilitator of medical management for FH (Jones et al., 2020). These results have been used to guide implementation strategy development for programs to improve medical management and inform further research (NHLBI-funded grant R61HL161775) for FH in identified individuals.

New Clinical Diagnoses Post-Disclosure

Among 305 MyCode participants found to have a molecular diagnosis of a CDC Tier 1 condition, 41 (13%) were found to have a post-disclosure cancer diagnosis or diagnosis of FH-related features within 22 months from disclosure (Buchanan et al., 2020). Twenty-five (61%) of these diagnoses were determined to be attributed to the result being returned *via* MyCode (Buchanan et al., 2020). An early case series reported on three cases with *BRCA1/2* variants whose personal and family history did not meet genetic testing referral guidelines but were found to have early-stage *BRCA1/2*-related cancers after risk management prompted by disclosure of the genetic result (Buchanan et al., 2018). In studies of FH, none of the individuals with an FH variant detected through MyCode had a clinical diagnosis of FH recorded in the EHR prior to disclosure. After disclosure of a genetic risk result for FH, only 29% had the clinical diagnosis code for FH added to their problem list in their EHR (Jones LK et al., 2018). Of 59 individuals with follow-up for ACM, two individuals received new cardiomyopathy diagnoses and had implantable defibrillators for primary prevention placed (Carruth et al., 2021).

Cost and Cost-Effectiveness

In a study of cost-burden to the healthcare system, no statistically significant differences in healthcare utilization and average total costs of care between one-year pre- and post-disclosure of a *BRCA1/2* variant in MyCode patient-participants were found ($18,821 vs. $19,359, $p = 0.76$) (Hao et al., 2020). Modeling studies demonstrate that population-based DNA screening for HBOC in unselected women at age 30 is likely to be cost-effective (incremental cost-effectiveness ratio was $87,700/quality-adjusted life year) (Guzauskas et al., 2020), and cascade testing of first-degree relatives modestly improves clinical and economic value. In contrast, population-based DNA screening for LS may be cost-effective in younger patient populations, but the plausible range of cost-effectiveness was higher than that for HBOC, and depended to some degree on lower test and intervention costs (Guzauskas GF et al., 2022).

Adoption

From July 2018 to June 2021, a total of 1,026 clinical DNA screening tests were ordered by 60 clinicians across the three pilot clinic sites in the clinical DNA screening pilot program. Of the 60 clinicians who ordered the DNA screening test at least once, 29 (48.3%) were attending physicians, 28 (46.7%) were medical fellows or residents, and 3 (5%) were advanced health practitioners (including certified nurse practitioners and physician assistants). Attending physicians generally ordered more tests than other types of clinicians (median [range]: 8 [1–532] tests ordered compared to 1 [1–21] ordered by medical residents or fellows, and 6 [1–17] ordered by advanced health practitioners).

Implementation

Clinicians practicing at the pilot clinic sites were invited to participate in interviews about their early experience with the clinical DNA screening pilot program. Among the 14 interviewed clinicians, eight (57%) were male, and nine (64%) were attending physicians. Attending physicians who completed interviews had practiced medicine for an average of 17 years, with 11.8 of those years at Geisinger. Residents and fellows who completed interviews practiced medicine an average of 2.4 years, all of them at Geisinger. Interviewed clinicians had a range of experience with ordering the clinical DNA screening tests; seven (50%) had never ordered the test. These preliminary interviews provided insights into the ordering practices of the DNA screening test by clinicians at pilot clinic sites under the initial implementation conditions:

Motivation to Order Test

Clinicians who ordered the clinical DNA screening test communicated their motivation to empower and partner with patients and families to manage their health as "giving them that power to be able to make those decisions and walk them through that is very important" (ID14; 1 test ordered).

Test Utility

One clinician indicated not ordering the test for older patients due to perception of limited medical utility in that age demographic, stating "with my 90-year-olds … they're really past the point where if they had the disease, you would know about it by now" (ID34; 18 tests ordered). Other low adopters expressed beliefs that DNA screening lacks evidence to support use compared to other routine screening tests.

> "My impression, at this point, is it is [the yield of DNA screening] less than the screening test that we have for, you know, breast cancer and screening for colon cancer, things of that nature, but like I said, I'm not sure what the actual yield is, because I know a majority of my patients who were screened had no abnormalities" (ID53; 11 tests ordered).

Conversely, high-adopters compared the DNA screening test to other screening tests (e.g., mammograms and colonoscopy) saying, "I offer this test just the same way as I would a colonoscopy or emphasize the importance of any of the immunizations which may be age-appropriate for them. So, it is just part of the whole package that I talk about. . ." (ID23; >100 tests ordered).

Understanding Test Application

Some interviewed clinicians reported only ordering the DNA screening test when they suspected a genetic condition or if they desired a result for the patient more quickly than through research avenues, such as MyCode. This suggests some clinicians may have an unclear understanding of the purpose of using a screening test (the DNA screening test) in clinical practice and the purpose of diagnostic testing (the traditional indication-based testing process where patients could be referred to genetics clinic).

Implementation in Primary Care

All interviewed clinicians expressed favorable views about the process for ordering the clinical DNA screening test. They also endorsed the result disclosure model of having a genetic counselor disclose positive results using the MyCode GSC program processes and expressed the importance of providing patients with access to genetics professionals to explain result implications.

Some clinicians expressed questions related to who would cover costs for downstream testing or cascade testing of family members if a patient was found to have an actionable variant when discussing implementation in primary care. Logistics around time and clinic workflows in primary care were also noted stating "There's alot of stuff that happens within a short 15–20 min visit, . . . a lot of physicians are already time crunched . . . this is just another one of those things that we need to do on top of that" (ID44; 2 tests ordered).

Finally, some interviewees recalled attending informational sessions for the pilot program while others reported learning about the test and how to order it only from other clinicians at their site. Therefore, future implementation strategies suggested by interviewees include standardized workflows for test ordering and results reporting, additional informational material for clinicians and patients, and recurring clinician training.

DISCUSSION

DNA-based population screening shows promise for improving population health but new methodologies, such as implementation science, are needed to understand its clinical utility from the rapidly growing evidence base and to facilitate the translation of effective DNA-based screening practices into clinical care (Murray et al., 2019; Williams, 2022). A key strength for this analysis is Geisinger's commitment to innovation in exploring precision health approaches through the existence of multiple programs currently generating evidence (Carey et al., 2016; Schwartz et al., 2018; Schmidlen et al., 2019; Savatt et al., 2020). This study demonstrates a pragmatic analysis of outcomes derived from two DNA screening programs implemented at Geisinger for different

purposes. We applied the RE-AIM implementation science framework to collectively analyze and report outcomes (Glasgow and Estabrooks, 2018). As more DNA-based population programs are being launched (Williams, 2022), this approach highlights the use of the RE-AIM framework to conduct a pragmatic program evaluation and demonstrates how the fields of genomics and precision health can utilize implementation science methods to capitalize on data generated from research and non-research programs implemented under real-world circumstances (Feero et al., 2018; Khoury et al., 2018; All of Us Research Program Investigators, 2019; Grzymski et al., 2020).

Results from the post-hoc Reach and Effectiveness evaluation of MyCode suggest most individuals at Geisinger approached are willing to participate in a research program that discloses health-related genomic information, and that DNA screening in this manner can positively impact the identification of genes and diseases tested when offered to unselected individuals. Results from the Adoption and Implementation evaluation of Geisinger's pilot clinical DNA screening program suggest that clinicians will order the test for their patients and that broader implementation should include ongoing education opportunities and be aligned with current clinical workflows.

Evaluation of MyCode's Reach as of August 2020 identified a reasonably high participation rate (68%), but also a need to better engage potential participants who reflect the full spectrum of diversity within the Geisinger population. While the population of central Pennsylvania is of primarily Northern European, non-Hispanic descent, MyCode participants have less diversity than the general Geisinger population. Potential opportunities for expanding the reach of MyCode include translation of consent into other relevant languages (English and Spanish currently available) and targeted engagement with underrepresented populations in our catchment area. Exploration of the barriers and needs of these populations is also an important next step to further ensure equitable access to precision care as these research programs are translated into the clinic. MyCode participants are also significantly more likely to have a Geisinger primary care provider and/or Geisinger health insurance coverage, suggesting that the Reach of a DNA-based population program could be greatest in a health system among those with an established patient-clinician relationship or where there are multiple opportunities to gain access to such screening throughout a system.

Evaluation of MyCode Effectiveness outcomes emphasized the potential for a research-based DNA screening program to improve health outcomes and highlighted Effectiveness gaps that remain to be studied. Further study of the clinical utility of screening for P/LP variants in the genes screened by MyCode other than those associated with HBOC, Lynch syndrome, FH, and ACM is indicated. Effectiveness studies from MyCode data are in process for several non-Tier 1 conditions, such as hereditary hemochromatosis, endocrine tumor syndromes, Long QT syndrome, and malignant hyperthermia, which should enrich our understanding of DNA screening in these conditions. Qualitative and quantitative evaluation of individual-level reactions to receiving genomic information in and across these conditions will further define the clinical and personal utility of DNA screening, as will studies addressing multi-level barriers and facilitators of post-disclosure medical management (clinician and system utilization of the result).

Additional cost-effectiveness analyses are underway for FH (Spencer et al., 2019) and continued modeling of integrated screening for all CDC Tier 1 conditions will inform decision making on reimbursement of DNA screening. We expect additional condition-specific gaps and cost analyses to be addressed as research capacity is increased to include individuals focused on other conditions and at different levels of the translational spectrum. To date, we have not reported on long-term health outcomes or improving adherence to recommended risk management at the individual-, clinician-, or system-level. Geisinger has only been disclosing results from MyCode since 2015 and the clinical DNA screening pilot program was formalized in 2018, therefore health outcomes and adherence data is currently limited and studies of interventions to impact adherence are just beginning. As MyCode continues to return results over the coming years, maintenance outcomes at the patient level related to DNA screening will be possible to analyze and report.

The clinical DNA screening program was used to assess early Adoption and Implementation outcomes, with more than 1,000 tests ordered as part of the clinical pilot. Qualitative interviews with clinicians who ordered and did not order the test identified a general acceptance of population DNA screening, with adopters finding the test ordering and result disclosure processes acceptable as currently implemented. Longitudinal data collection (both qualitative and quantitative) on adoption and implementation will be necessary to explore and demonstrate maintenance outcomes at the clinician and system level in the future.

Published literature demonstrates the importance of utilizing qualitative inquiry when reporting RE-AIM outcomes (Holtrop et al., 2018b). Our qualitative data on Implementation identified reasons clinicians interviewed did not order the test and several implementation strategies for iterative improvement in the clinical DNA screening pilot program. Ongoing education and other strategies to ensure clinician awareness and knowledge of processes could be instituted and evaluated to determine incremental improvement in test ordering and program implementation. Our early data from this pragmatic use of RE-AIM is providing guidance for implementation of a DNA screening program that fits the context of ambulatory care, thereby enabling sustainability, and is guiding the data collection approach and analyses that will inform precision health impact within the virtuous cycle of a learning healthcare system (Glasgow and Estabrooks, 2018; Glasgow et al., 2019).

The number of programs exploring the utility of DNA screening is growing rapidly (Williams, 2022), generating calls for harmonization of effectiveness data across programs and studies to improve the value of outcomes reported (Williams et al., 2018a). A few cross-program assessments of barriers and learnings have been reported from the funded IGNITE and eMERGE networks (Zebrowski et al., 2019; Wiesner et al., 2020; Sperber et al., 2021; Leppig et al., 2022). Similar cross-program evaluations could be conducted utilizing RE-AIM or

other implementation science frameworks in combination to synthesize evidence (Reilly et al., 2020) from the myriad of other programs (Williams, 2022) being conducted in both research and non-research contexts but not connected to these large networks. Our work provides a blueprint for moving beyond the traditional reporting of intervention effectiveness alone by utilizing implementation science and the RE-AIM framework to report on additional framework outcomes of Reach, Adoption, Implementation, and Maintenance across multiple DNA screening programs designed for different purposes. This approach could accelerate learnings and reduce the research-to-practice gap in DNA-based population screening and have a broader public health impact. Furthermore, a harmonized approach will facilitate evaluation of key differences in programs, including funding sources, information returned, process of consent and return, and implementation processes and costs. This data will be critical if we are to rapidly learn from the growing number of research and clinical DNA screening programs and provide the evidence needed for broad implementation to ultimately realize the public health impact of DNA screening.

The harmonized assessment of RE-AIM domains can also help prevent DNA screening programs from creating unintended adverse consequences or exacerbating health disparities. Over 90% of the participants in MyCode were of self-reported non-Hispanic, European ancestry (Buchanan et al., 2020). Similarly, over 70% of the participants in the eMERGE III cohort, a large NIH-sponsored network researching genomic screening, were also self-reported (eMERGE Consortium, 2019). This lack of diversity in genomics research impedes our understanding of potential differences in outcomes across, and how to best tailor DNA screening for, diverse populations. Therefore, it is critical that the multiple precision health programs currently working to improve engagement with under-represented populations include assessment of implementation outcomes (Williams, 2022). To further address disparities and facilitate equity, recent recommendations include consideration of health equity through integration of other existing frameworks with RE-AIM evaluations to address this important contextual factor (Shelton et al., 2020). The Reach dimension includes assessment of representativeness, but more recent guidance specifically calls for assessment across subgroups involved, such as social determinants, rural or racial/ethnic populations, healthcare setting resources (high or low resourced), or literacy, to demonstrate who the program benefits and where inequities may continue to exist (Shelton et al., 2020).

Limitations

While the existence of multiple precision health programs at Geisinger enabled these analyses, it is important to acknowledge the limitations inherent in collecting data within a single healthcare system. First, while not a limitation to our study, but one which could influence broader adoption, is Geisinger's ability to implement a clinical DNA screening pilot program based on the pre-existing acceptance of the MyCode research initiative within the system. The broad recognition of the successes of this research program across our system may have facilitated clinician interviewees' general acceptance of the program, regardless of whether they had ordered the test or not. Adoption and Implementation outcomes may be different in contexts where DNA screening is less salient to clinicians or in health systems naïve to genomics at the scale of MyCode. Secondly, our genomics programs were impacted by the COVID-19 pandemic. MyCode suspended all in-person consenting from March–December 2020, and while individuals could still consent to MyCode through electronic means, this mode currently does not yield a significant number of consents. Therefore, it is possible we would have demonstrated a higher participation rate if not for the pandemic. The COVID-19 pandemic also impacted additional implementation strategies for the clinical DNA screening pilot, in that all efforts to provide additional education and support for clinicians were suspended in pilot sites. Furthermore, while not specifically stated by the clinicians interviewed, the switch to virtual care in the ambulatory care setting under the stress of the pandemic may have limited the overall ordering of tests by clinicians. Therefore, results related to Adoption and Implementation must be interpreted within this specific context. Finally, this evaluation was based on the post-hoc, pragmatic use of RE-AIM, and as such, data collection/availability was limited to that which is accurate and practicable to extract from available program and clinical sources. The strength of this approach is that the results provide insight into outcomes under real-world conditions and identify areas where resources might be directed to either improve existing clinical data availability or to provide for resource-intensive data collection and analyses. As more programs for population-based genomic screening are piloted (Williams, 2022), studies could be prospectively designed and resourced to enable the evaluation of all RE-AIM dimensions from one or multiple genomic screening programs. Studies may also be designed to use RE-AIM in combination with other implementation science frameworks as appropriate (Reilly et al., 2020; Shelton et al., 2020).

CONCLUSION

We applied the RE-AIM implementation science framework to conduct a pragmatic program evaluation to assess what two research and DNA screening pilot programs reveal that can inform future uptake of DNA-based population screening. We provide important evidence for such screening and through this approach of utilizing data from different programs relevant to each RE-AIM domain we identify remaining gaps necessary to address clinical utility, adoption, and implementation of programs in health care systems. This pragmatic approach of utilizing data from different programs most informative for each RE-AIM dimension will be important as more hospitals and health systems begin piloting their own DNA-based population screening programs.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

LJ conceived and designed the analysis, collected the data, performed the analysis, wrote the initial draft and approved the final manuscript. NS conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. EC collected the data, performed the analysis, reviewed and approved the final manuscript. JC collected the data, performed the analysis, reviewed and approved the final manuscript. GR collected the data, performed the analysis, reviewed and approved the final manuscript. CZM conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. MH conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. JS conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. HR conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. MW conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. AS conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. AB conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. RG conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. CLM conceived and designed the analysis, collected the data, performed the analysis, reviewed and approved the final manuscript. ARconceived and designed the analysis, collected the data, performed the analysis, wrote the initial draft and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.883073/full#supplementary-material

REFERENCES

Abul-Husn, N. S., Manickam, K., Jones, L. K., Wright, E. A., Hartzel, D. N., Gonzaga-Jauregui, C., et al. (2016). Genetic Identification of Familial Hypercholesterolemia within a Single U.S. Health Care System. *Science* 354, aaf7000. doi:10.1126/science.aaf7000

Abul-Husn, N. S., Soper, E. R., Braganza, G. T., Rodriguez, J. E., Zeid, N., Cullina, S., et al. (2021). Implementing Genomic Screening in Diverse Populations. *Genome Med.* 13, 17. doi:10.1186/s13073-021-00832-y

Abul-Husn, N. S., Soper, E. R., Soper, E. R., Odgis, J. A., Cullina, S., Bobo, D., et al. (2019). Exome Sequencing Reveals a High Prevalence of BRCA1 and BRCA2 Founder Variants in a Diverse Population-Based Biobank. *Genome Med.* 12, 2. doi:10.1186/s13073-019-0691-1

All of US Research Program Investigators (2019). The "All of Us" Research Program. *N. Engl. J. Med.* 381, 668–676. doi:10.1056/NEJMsr1809937

Balas, E. A., and Boren, S. A. (2000). Managing Clinical Knowledge for Health Care Improvement. *Yearb. Med. Inf.* 9, 65–70. doi:10.1055/s-0038-1637943

Beebe, J. (2001). *Rapid Assessment Process: An Introduction*. Altamira: Rowman.

Blazer, K. R., Chavarri-Guerra, Y., Villarreal Garza, C., Nehoray, B., Mohar, A., Daneri-Navarro, A., et al. (2021). Development and Pilot Implementation of the Genomic Risk Assessment for Cancer Implementation and Sustainment (GRACIAS) Intervention in Mexico. *JCO Glob. Oncol.* 7, 992–1002. doi:10.1200/go.20.00587

Brownson, R. C. (2017). *Dissemination and Implementation Research in Health: Translating Science to Practice*. Oxford University Press.

Bryman, A., and Burgess, R. G. (1994). *Analyzing Qualitative Data*. London: Routledge.

Buchanan, A. H., Lester Kirchner, H., Schwartz, M. L. B., Kelly, M. A., Schmidlen, T., Jones, L. K., et al. (2020). Clinical Outcomes of a Genomic Screening Program for Actionable Genetic Conditions. *Genet. Med.* 22, 1874–1882. doi:10.1038/s41436-020-0876-4

Buchanan, A. H., Manickam, K., Meyer, M. N., Wagner, J. K., Hallquist, M. L. G., Williams, J. L., et al. (2018). Early Cancer Diagnoses through BRCA1/2 Screening of Unselected Adult Biobank Participants. *Genet. Med.* 20, 554–558. doi:10.1038/gim.2017.145

Carey, D. J., Fetterolf, S. N., Davis, F. D., Faucett, W. A., Kirchner, H. L., Mirshahi, U., et al. (2016). The Geisinger MyCode Community Health Initiative: an Electronic Health Record-Linked Biobank for Precision Medicine Research. *Genet. Med.* 18, 906–913. doi:10.1038/gim.2015.187

Carruth, E. D., Beer, D., Alsaid, A., Schwartz, M. L. B., Mcminn, M., Kelly, M. A., et al. (2021). Clinical Findings and Diagnostic Yield of Arrhythmogenic Cardiomyopathy through Genomic Screening of Pathogenic or Likely Pathogenic Desmosome Gene Variants. *Circ. Genom Precis. Med.* 14, e003302. doi:10.1161/CIRCGEN.120.003302

Carruth, E. D., Young, W., Beer, D., James, C. A., Calkins, H., Jing, L., et al. (2019). Prevalence and Electronic Health Record-Based Phenotype of Loss-Of-Function Genetic Variants in Arrhythmogenic Right Ventricular Cardiomyopathy-Associated Genes. *Circ. Genom Precis. Med.* 12, e002579. doi:10.1161/CIRCGEN.119.002579

Centers for Disease Control and Prevention (2014). *Tier 1 Genomics Applications and Their Importance to Public Health [Online]*. Available: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm (Accessed January 10, 2021).

Chambers, D. A. (2018). Commentary: Increasing the Connectivity between Implementation Science and Public Health: Advancing Methodology,

Evidence Integration, and Sustainability. *Annu. Rev. public health* 39, 1–4. doi:10.1146/annurev-publhealth-110717-045850

Chambers, D. A., Feero, W. G., and Khoury, M. J. (2016). Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System: A New Model for Biomedical Research. *Jama* 315, 1941–1942. doi:10.1001/jama.2016.3867

Dewey, F. E., Murray, M. F., Overton, J. D., Habegger, L., Leader, J. B., Fetterolf, S. N., et al. (2016). Distribution and Clinical Impact of Functional Variants in 50,726 Whole-Exome Sequences from the DiscovEHR Study. *Science* 354, aaf6814. doi:10.1126/science.aaf6814

eMERGE Consortium (2019). Harmonizing Clinical Sequencing and Interpretation for the eMERGE III Network. *Am. J. Hum. Genet.* 105, 588–605. doi:10.1016/j.ajhg.2019.07.018

Feero, W. G., Wicklund, C. A., and Veenstra, D. (2018). Precision Medicine, Genome Sequencing, and Improved Population Health. *Jama* 319, 1979–1980. doi:10.1001/jama.2018.2925

Gale, N. K., Heath, G., Cameron, E., Rashid, S., and Redwood, S. (2013). Using the Framework Method for the Analysis of Qualitative Data in Multi-Disciplinary Health Research. *BMC Med. Res. Methodol.* 13, 117. doi:10.1186/1471-2288-13-117

Geisinger (2018). *DNA Sequencing to Become Part of Geisinger's Routine Clinical Care [Online]*. Available: https://www.geisinger.org/about-geisinger/news-and-media/news-releases/2018/05/07/12/18/dna-sequencing-to-become-part-of-geisingers-routine-clinical-care (Accessed February 2, 2022).

Ginsburg, G. S., Cavallari, L. H., Chakraborty, H., Cooper-Dehoff, R. M., Dexter, P. R., Eadon, M. T., et al. (2021). Establishing the Value of Genomics in Medicine: the IGNITE Pragmatic Trials Network. *Genet. Med.* 23, 1185–1191. doi:10.1038/s41436-021-01118-9

Glasgow, R. E., and Estabrooks, P. E. (2018). Pragmatic Applications of RE-AIM for Health Care Initiatives in Community and Clinical Settings. *Prev. Chronic Dis.* 15, E02. doi:10.5888/pcd15.170271

Glasgow, R. E., Harden, S. M., Gaglio, B., Rabin, B., Smith, M. L., Porter, G. C., et al. (2019). RE-AIM Planning and Evaluation Framework: Adapting to New Science and Practice with a 20-Year Review. *Front. Public Health* 7, 64. doi:10.3389/fpubh.2019.00064

Glasgow, R. E., Vogt, T. M., and Boles, S. M. 1999. Evaluating the Public Health Impact of Health Promotion Interventions: the RE-AIM Framework. *Am. J. Public Health*. 89. 1322–1327. doi:10.2105/ajph.89.9.1322

Grzymski, J. J., Elhanan, G., Morales Rosado, J. A., Smith, E., Schlauch, K. A., Read, R., et al. (2020). Population Genetic Screening Efficiently Identifies Carriers of Autosomal Dominant Diseases. *Nat. Med.* 26, 1235–1239. doi:10.1038/s41591-020-0982-5

Guzauskas Gf, J. S., Garbett, S., Zhou, Z., Spencer, S. J., Snyder, S. R., Graves, J. A., et al. (2022). Cost-effectiveness of Population-wide Genomic Screening for Lynch Syndrome in the United States. *Genet. Med.* 3 (10), e2022874. doi:10.1016/j.gim.2022.01.017

Guzauskas, G. F., Garbett, S., Zhou, Z., Spencer, S. J., Smith, H. S., Hao, J., et al. (2020). Cost-effectiveness of Population-wide Genomic Screening for Hereditary Breast and Ovarian Cancer in the United States. *JAMA Netw. Open* 3, e2022874. doi:10.1001/jamanetworkopen.2020.22874

Haddow, J. E., Palomaki, G. E., and Khoury, M. (2004). "ACCE: a Model Process for Evaluating Data on Emerging Genetic Tests," in *Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease* (Oxford, United Kingdom: CDC), 217–233.

Hao, J., Hassen, D., Manickam, K., Murray, M. F., Hartzel, D. N., Hu, Y., et al. (2020). Healthcare Utilization and Costs after Receiving a Positive BRCA1/2 Result from a Genomic Screening Program. *J. personalized Med.* 10, 7. doi:10.3390/jpm10010007

Holtrop, J. S., Rabin, B. A., and Glasgow, R. E. (2018a). Dissemination and Implementation Science in Primary Care Research and Practice: Contributions and Opportunities. *J. Am. Board Fam. Med.* 31, 466–478. doi:10.3122/jabfm.2018.03.170259

Holtrop, J. S., Rabin, B. A., and Glasgow, R. E. (2018b). Qualitative Approaches to Use of the RE-AIM Framework: Rationale and Methods. *BMC Health Serv. Res.* 18, 177. doi:10.1186/s12913-018-2938-8

Jakuboski, S. H., Mcdonald, J. A., and Terry, M. B. (2022). Do current Family History-Based Genetic Testing Guidelines Contribute to Breast Cancer Health Inequities? *npj Breast Cancer* 8, 36. doi:10.1038/s41523-022-00391-4

Jones Lk, R. A., Manickam, K., Butry, L., Lazzeri, A., et al. (2018). Healthcare Utilization and Patients' Perspectives after Receiving a Positive Genetic Test for Familial Hypercholesterolemia: A Pilot Study. *Circ. Genom Precis. Med.* 11, e002146. doi:10.1161/CIRCGEN.118.002146

Jones, L. K., Jefferson, C. R., Chen, N., and Murray, M. F. (2021a). Genetic Screening for Familial Hypercholesterolemia Identifies Patients Not Meeting Cholesterol Treatment Guidelines. *Coron. Artery Dis.* 32, 588–589. doi:10.1097/mca.0000000000000998

Jones, L. K., Mcminn, M., Kann, D., Lesko, M., Sturm, A. C., Walters, N., et al. (2021b). Evaluation of a Multidisciplinary Lipid Clinic to Improve the Care of Individuals with Severe Lipid Conditions: a RE-AIM Framework Analysis. *Implement Sci. Commun.* 2, 32. doi:10.1186/s43058-021-00135-8

Jones, L. K., Sturm, A. C., Seaton, T. L., Gregor, C., Gidding, S. S., Williams, M. S., et al. (2020). Barriers, Facilitators, and Solutions to Familial Hypercholesterolemia Treatment. *PLoS One* 15, e0244193. doi:10.1371/journal.pone.0244193

Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., et al. (2017). Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): a Policy Statement of the American College of Medical Genetics and Genomics. *Genet. Med.* 19, 249–255. doi:10.1038/gim.2016.190

Kelly, M. A., Leader, J. B., Wain, K. E., Bodian, D., Oetjens, M. T., Ledbetter, D. H., et al. (2021). Leveraging Population-Based Exome Screening to Impact Clinical Care: The Evolution of Variant Assessment in the Geisinger MyCode Research Project. *Am. J. Med. Genet. C Semin. Med. Genet.* 187, 83–94. doi:10.1002/ajmg.c.31887

Khoury, M. J., Bowen, M. S., Clyne, M., Dotson, W. D., Gwinn, M. L., Green, R. F., et al. (2018). From Public Health Genomics to Precision Public Health: a 20-year Journey. *Genet. Med.* 20, 574–582. doi:10.1038/gim.2017.211

Kim, S., Aceti, M., Baroutsou, V., Bürki, N., Caiata-Zufferey, M., Cattaneo, M., et al. (2021). Using a Tailored Digital Health Intervention for Family Communication and Cascade Genetic Testing in Swiss and Korean Families with Hereditary Breast and Ovarian Cancer: Protocol for the DIALOGUE Study. *JMIR Res. Protoc.* 10, e26264. doi:10.2196/26264

Leppig, K. A., Kulchak Rahm, A., Appelbaum, P., Aufox, S., Bland, S. T., Buchanan, A., et al. (2022). The Reckoning: The Return of Genomic Results to 1444 Participants across the eMERGE3 Network. *Genet. Med.* 24 (5), 1130–1138. doi:10.1016/j.gim.2022.01.015

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome Sequencing-Based Screening for BRCA1/2 Expected Pathogenic Variants Among Adult Biobank Participants. *JAMA Netw. Open* 1, e182140. doi:10.1001/jamanetworkopen.2018.2140

Miller, D. M., Gaviglio, A., and Zierhut, H. A. (2021). Development of an Implementation Framework for Overcoming Underdiagnoses of Familial Hypercholesterolemia in the USA. *Public Health Genomics* 24, 110–122. doi:10.1159/000513872

MyCode scorecard [Online] (n. a). Available at: https://www.geisinger.org/-/media/OneGeisinger/pdfs/ghs/research/mycode/mycode-scorecard.pdf?la=en (Accessed February 1, 2022)

Murray, M. F., Evans, J. P., Angrist, M., Uhlmann, W. R., Lochner Doyle, D., Fullerton, S. M., et al. (2019). A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults. *NAM Perspect.* 1, 1.

Nilsen, P. (2015). Making Sense of Implementation Theories, Models and Frameworks. *Implement Sci.* 10, 53. doi:10.1186/s13012-015-0242-0

Office of Science (Os), O. O. G. A. P. P. H. (2021). *ACCE Model Process for Evaluating Genetic Tests [Online]*. Available: https://www.cdc.gov/genomics/gtesting/acce/index.htm (Accessed January 3, 2021).

Reilly, K. L., Kennedy, S., Porter, G., and Estabrooks, P. (2020). Comparing, Contrasting, and Integrating Dissemination and Implementation Outcomes Included in the RE-AIM and Implementation Outcomes Frameworks. *Front. Public Health* 8, 430. doi:10.3389/fpubh.2020.00430

Savatt, J. M., Wagner, J. K., Joffe, S., Rahm, A. K., Williams, M. S., Bradbury, A. R., et al. (2020). Pediatric Reporting of Genomic Results Study (PROGRESS): a Mixed-Methods, Longitudinal, Observational Cohort Study Protocol to Explore Disclosure of Actionable Adult-And Pediatric-Onset Genomic Variants to Minors and Their Parents. *BMC Pediatr.* 20, 1–13. doi:10.1186/s12887-020-02070-4

Schmidlen, T., Schwartz, M., Diloreto, K., Kirchner, H. L., and Sturm, A. C. (2019). Patient Assessment of Chatbots for the Scalable Delivery of Genetic Counseling. *J. Genet. Couns.* 28, 1166–1177. doi:10.1002/jgc4.1169

Schwartz, M. L. B., Mccormick, C. Z., Lazzeri, A. L., Lindbuchler, D. M., Hallquist, M. L. G., Manickam, K., et al. (2018). A Model for Genome-First Care: Returning Secondary Genomic Findings to Participants and Their Healthcare Providers in a Large Research Cohort. *Am. J. Hum. Genet.* 103, 328–337. doi:10.1016/j.ajhg.2018.07.009

Shelton, R. C., Chambers, D. A., and Glasgow, R. E. (2020). An Extension of RE-AIM to Enhance Sustainability: Addressing Dynamic Context and Promoting Health Equity over Time. *Front. Public Health* 8, 134. doi:10.3389/fpubh.2020.00134

Spencer, S., Guzauskas, G., Williams, M., Snyder, S., Jones, L., Hao, J., et al. (2019). "Cost Effectiveness of Population-wide Genomic Screening of Familial Hypercholesterolemia: Importance of FH Patient Statin Uptake and Achieving Target LDL Levels," in 41st Annual Meeting of the Society for Medical Decision Making (Portland, ORSMDM).

Sperber, N. R., Dong, O. M., Roberts, M. C., Dexter, P., Elsey, A. R., Ginsburg, G. S., et al. (2021). Strategies to Integrate Genomic Medicine into Clinical Care: Evidence from the IGNITE Network. *J. Pers. Med.* 11, 647. doi:10.3390/jpm11070647

Steele, G. D., and Feinberg, D. T. (2017). *ProvenCare: How to Deliver Value-Based Healthcare the Geisinger Way*. NewYork, NY: McGraw Hill Professional.

Wiesner, G. L., Kulchak Rahm, A., Appelbaum, P., Aufox, S., Bland, S. T., Blout, C. L., et al. (2020). Returning Results in the Genomic Era: Initial Experiences of the eMERGE Network. *J. Pers. Med.* 10, 30. doi:10.3390/jpm10020030

Williams, J. L., Chung, W. K., Fedotov, A., Kiryluk, K., Weng, C., Connolly, J. J., et al. (2018a). Harmonizing Outcomes for Genomic Medicine: Comparison of eMERGE Outcomes to ClinGen Outcome/Intervention Pairs. *Healthc. (Basel)* 6, 83. doi:10.3390/healthcare6030083

Williams, M. S., Buchanan, A. H., Davis, F. D., Faucett, W. A., Hallquist, M. L. G., Leader, J. B., et al. (2018b). Patient-Centered Precision Health in A Learning Health Care System: Geisinger's Genomic Medicine Experience. *Health Aff. (Millwood)* 37, 757–764. doi:10.1377/hlthaff.2017.1557

Williams, M. S. (2019). Early Lessons from the Implementation of Genomic Medicine Programs. *Annu. Rev. Genomics Hum. Genet.* 20, 389–411. doi:10.1146/annurev-genom-083118-014924

Williams, M. S. (2022). Population Screening in Health Systems. *Annu. Rev. Genomics Hum. Genet.* 23. doi:10.1146/annurev-genom-111221-115239

Zebrowski, A. M., Ellis, D. E., Barg, F. K., Sperber, N. R., Bernhardt, B. A., Denny, J. C., et al. (2019). Qualitative Study of System-Level Factors Related to Genomic Implementation. *Genet. Med.* 21, 1534–1540. doi:10.1038/s41436-018-0378-9

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BRIEF RESEARCH REPORT
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Using Long-Term Follow-Up Data to Classify Genetic Variants in Newborn Screened Conditions

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With the rapid increase in publicly available sequencing data, healthcare professionals are tasked with understanding how genetic variation informs diagnosis and affects patient health outcomes. Understanding the impact of a genetic variant in disease could be used to predict susceptibility/protection and to help build a personalized medicine profile. In the United States, over 3.8 million newborns are screened for several rare genetic diseases each year, and the follow-up testing of screen-positive newborns often involves sequencing and the identification of variants. This presents the opportunity to use longitudinal health information from these newborns to inform the impact of variants identified in the course of diagnosis. To test this, we performed secondary analysis of a 10-year natural history study of individuals diagnosed with metabolic disorders included in newborn screening (NBS). We found 564 genetic variants with accompanying phenotypic data and identified that 161 of the 564 variants (29%) were not included in ClinVar. We were able to classify 139 of the 161 variants (86%) as pathogenic or likely pathogenic. This work demonstrates that secondary analysis of longitudinal data collected as part of NBS finds unreported genetic variants and the accompanying clinical information can inform the relationship between genotype and phenotype.

Keywords: newborn screening, longitudinal data, inborn errors of metabolism, newborn screening translational research network (NBSTRN), longitudinal pediatric data resource (LPDR), clinvar, variant classification, American college of medical genetics and genomics (ACMG)

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1 INTRODUCTION

From the development of Sanger Sequencing in 1977 (Sanger et al., 1977) to the advent of Next-Generation Sequencing (NGS) in 2005 (Shendure et al., 2005), the availability of low-cost genetic information has markedly expanded. As of 13 September 2021, the NCBI Reference Sequence Database (RefSeq) reported the submission of 40, 213, 945 transcript reads across 113,002 organisms (O'Leary et al., 2016). With the obstacles of high sequencing cost and intensive labor to generate data mostly overcome, genomics faces new hurdles: the interpretation and use of genetic variants to aid clinical decision-making (Krier et al., 2016). The importance of determining genotype-phenotype correlations to impact health outcomes has been reported in many publications (Trefz et al., 1993; Arnold et al., 2010; LD et al., 2016; Hsu et al., 2019) and current efforts to interpret genotype-phenotype correlations prefer to use population-specific biobanks, such as the All of Us Program (Denny et al., 2019) and the UK Biobank (Sudlow et al., 2015). The mining of these biobanks for

variant and health information is a valuable resource for informing the relationship between genotype and phenotype, and improving the treatment, management, and health outcomes in individuals with a genetic disease.

To investigate another resource for determining the clinical relevance of variants, we conducted secondary analysis of a longitudinal data set of individuals identified with a rare genetic disease through newborn screening (NBS) for information about treatment and disease course. In the United States, NBS is a multi-component system of prenatal education, neonatal screening, clinical referral and diagnosis, and long-term medical management. A federal advisory committee recommends which conditions to screen, but the composition of screening panels is determined by state based NBS programs. The majority of screened conditions are inborn errors of metabolism (IEM), and 44 IEM disorders are currently included in the Recommended Uniform Screening Panel (RUSP) (Federal Advisory Committees, 2021). Variant and health information from a completed, 10-year natural history study of IEMs, called Inborn Errors of Metabolism Collaborative (IBEMC) (Berry et al., 2010; SA et al., 2016), was analyzed to find unpublished variants and review health information. The IBEMC dataset provides the potential for variant interpretation (Pena et al., 2016) using data from subjects that have had genetic testing for their condition and information about their clinical course collected over time.

2 MATERIALS AND METHODS

2.1 Newborn Screening Translational Research Network (NBSTRN)

NBSTRN is a resource for investigators engaged in newborn screening related research led by the ACMG and is funded by a contract from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and is a key component of the NICHD Hunter Kelly Newborn Screening Research Program (U.S. Code, 2021). The NBSTRN develops data tools and resources to facilitate both primary and secondary research efforts (Lloyd-Puryear et al., 2019) (https://nbstrn.org/). This effort utilized the Longitudinal Pediatric Data Resource (LPDR), one of the NBSTRN data tools housed in a Federal Information Security Modernization Act (FISMA) moderate environment, for the secondary analysis of the IBEMC data set (IBEMC MCAD Cohort; IBEMC PKU Cohort).

2.2 Inborn Errors of Metabolism Information System (IBEM-IS)

To discover unpublished genetic variants that may be implicated in the manifestation of IEMs, data from the Inborn Errors of Metabolism Information System (IBEM-IS) were examined. The IBEM-IS data were collected and managed in the IBEM-IS at Michigan Public Health Institute. The data set included phenotypic and genotype data on individuals with one of 42 NBS screened disorders. The original study was observational, resulting in only a subset of cases reported as having a genotype based on the following three factors as reported by the IBEMC: 1) the clinical relevance of genotyping as determined by the clinician, 2) the willingness of insurance providers to cover genotyping, and 3) the desire of patients to know his/her genotype (SA et al., 2016). The IBEM-IS collects information from subjects that could be used for secondary analysis and includes data categories such as demographic information, disease presentation, clinical diagnosis, treatments and interventions (Berry et al., 2010; SA et al., 2016). At the conclusion of the 10-years study, the IBEMC dataset was deidentified and transferred to the LPDR for secondary use by the research community. We accessed the IBEM-IS via the LPDR on 10 July 2018, and successfully analyzed data from 32 diseases and 1904 subjects.

2.3 Classification Guidelines

ClinVar, a repository of genetic variants and their correlation to medically important phenotypes (MJ et al., 2018), was used as the reference database for variants. Multiple publications have noted the importance of updating ClinVar with newly discovered variants and its importance in understanding the clinical implications of human variation (Harrison et al., 2016; Danos et al., 2018; Wain et al., 2018; Wei et al., 2018) Using ClinVar as a reference for published genotypes, each gene data set was exported from ClinVar for genes associated with diseases in the IBEM-IS from November 28–29, 2018, with the exception of Citrullinemia (CIT), extracted on 14 November 2018.

According to ClinVar (National Library of Medicine, 2019), submissions must assign standard terms for clinical significance as designated by ACMG/AMP (Richards et al., 2015) and this includes assignments for the consequence of the variant as Benign, Likely Benign, of Uncertain Significance, Likely Pathogenic, or Pathogenic. Although ClinVar establishes these terms as standard formats for reporting clinical significance, ClinVar does not calculate nor verify the assignment of these terms to submitted variants (Representation of clinical significance in ClinVar and other variation resources at NCBI). ClinVar designates the task of assigning a clinical significance term to the submitter, with exceptions for submissions from OMIM and early submissions before standard terms were required. In these instances, ClinVar calculated and verified the clinical significance of submitted variants.

We used the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) variant interpretation guidelines (Richards et al., 2015), to build evidence for accurate variant classification and used the IBEM-IS data points shown in **Table 1**. The ACMG/AMP publication provided a method for ascertaining the strength of evidence for determining a variant's correlation with a disease phenotype. Points of evidence include population data, computational and predictive data, functional data, segregation data, *de novo* data, allelic data, other databases, and other data. Varying types of data and observations correlate to either pathogenic or benign criteria, which are incorporated into the final determination of significance. The classification criteria used in this analysis can be seen in **Table 2**. PS3 (functional assay) and PP4 (well-characterized phenotype)

TABLE 1 | Variant classification criteria and supporting data Source(s). The ACMG/AMP Evidence-Based Criteria (Richards et al., 2015) was used to determine supporting data sources. No supporting data was generated for the "Population Data" criteria defined by the ACMG/AMP guidelines. Supporting data for other evidence-based criteria were found using computational tools (Calabrese et al., 2009; Capriotti and Altman, 2011; Shihab et al., 2013), within in the long-term follow-up dataset (Segregation Data, De novo Data), reported by other databases (Invitae | Clinvitae, 2019), or assumed from the nature of newborn screening/the disease (Functional Data, Other Data).

ACMG/AMP evidence-based criteria	Supporting data source
Population Data	No population data was generated
Computational and Predictive Data	FATHMM(Shihab et al., 2013), SNPS&GO (Calabrese et al., 2009; Capriotti and Altman, 2011)
Functional Data	All cases confirmed by newborn screen and supplemental testing
Segregation Data	Family history
De novo Data	Family history
Allelic Data	For autosomal recessive disorders, it is assumed that reported variants were reported *in trans*
Other Database	ClinVitae (Invitae | Clinvitae, 2019)
Other Data	Analyzed disorders have been established as genetically based, supporting a distinctive phenotype for gene

TABLE 2 | Number of variants assigned a pathogenicity criterion. The ACMG/AMP guidelines have various clinical significance criteria, that when combined, result in a clinical significance classification. ACMG/AMP scoring criteria are show on the left, with the number of variants assigned that criteria shown on the right. Percentages calculated from the total number of unpublished variants (n = 161).

ACMG/AMP evidence found in LPDR	Number of variants (n = 161)
PVS1 (Null Variants)	43 (26.7%)
PS3 (Functional Studies)	150 (93.1%)
PM3 (Cis/trans confirmation)	66 (41.0%)
PM5 (Novel missense at same position as published pathogenic variant)	13 (8.1%)
PM6 (De novo)	2 (1.2%)
PP1 (Segregation Analysis)	7 (4.3%)
PP3 (Computational *in silico* data)	77 (47.8%)
PP4 (Phenotype to support variant)	150 (93.1%)
PP5 (Found in reputable database)	23 (14.3%)
BP4 (Computational *in silico* data)	1 (0.6%)
BP7 (Synonymous variants)	4 (2.5%)

criteria were assigned to 161 unpublished variants found in the IBEM-IS dataset, due to each patient in the data set having a confirmatory diagnostic test and well-known disorder. Unmapped variants were not assigned any criteria. Unpublished variants are described as variants that have not been submitted to ClinVar and unmapped variants are variants that did not map to any transcripts listed in the RefSeq database. Because all subjects enrolled in IBEMC were diagnosed using functional blood metabolite or enzyme assays through their newborn screen and confirmatory diagnostic testing, the variants for these subjects were classified as PS3. All diseases in the IBEMC study have been well-characterized and display a specific early-onset phenotype, deserving the attribution of PP4. All other criteria were determined based on the clinical information available for each variant. Mutalyzer (Lefter et al., 2021), a web-based tool for mapping variants to reference sequences, was used to validate the unpublished variants found in the IBEM-IS (**Supplementary Table S1**). ClinVitae (Invitae | Clinvitae, 2019) was used as a secondary source of published variants. ClinVitae is a database reporting variants from Clinvar, Emory Genetics Laboratory Variant Classification Catalog, Invitae, ARUP Mutation Databases, Kathleen Cunningham Foundation Consortium, and Carver Mutation Database. FATHMM (Shihab et al., 2013) and SNPS&GO (Calabrese et al., 2009; Capriotti and Altman, 2011) web-based computational prediction tools were used to predict the functional effects of variants reported. FATHMM is a web-based evolutionary conservation prediction tool that is used to predict the functional consequence of both coding and non-coding variants. SNPS&GO is a web-based protein structure/function prediction tool that assesses the functional impact of coding variations.

2.4 Pipeline Structure

To analyze the IBEM-IS data within the LPDR, a Python-based (v2.7.16) (Python, 2019) script was used to extract patient information and compare variants to ClinVar. Python is a high-level, object-oriented programming language allowing users to interact with dynamic data and interface with open-source libraries. Much of the script utilized data frames and analysis tools provided by Pandas library. Pandas is an open-source Python package used to analyze structured data and is considered a powerful data manipulation and analysis tools (pandas, 2019). The script references the IBEM-IS data set and ClinVar gene extracts through saved comma-separated values (CSV) files. The pipeline was built around essential processes, that were needed to analyze the data thoroughly and are expanded upon in the following sections.

2.4.1 Review Case Level Data

The IBEM-IS has over 8,228 subjects reporting longitudinal data distributed across 7,300 data fields. To facilitate data set analysis, the entire IBEM-IS dataset was divided into disorder category tables (amino acid disorders, fatty acid oxidation disorders, etc.) then subsequently further divided into disease-specific tables. In addition to making the data set more manageable, this process helps to confirm that a patient's diagnosis was submitted correctly. Once the data was sorted, the total number of subjects with the disease was calculated and each patient's record was checked for the submission of a variant. In IBEM-IS, variants were reported in one of two formats: 1) the selection of published genotypes and 2) a custom text submission. Variants at this stage were also checked for nonvalid variant submissions, such as "none" or "negative", to streamline comparison to ClinVar extracts. If a variant was found in the patient's record, it was saved and used for comparison.

2.4.2 Convert ClinVar Variants

ClinVar reports variants using the Human Genome Variation Society (HGVS) format, which describes the genetic variant (i.e. c.549A > C) and the resulting protein variant (i.e., p. Phe256Leu)[27]. ClinVar also requires that the variant be submitted containing the reference sequence accession code to which the variant was mapped. There was not a uniform variant reporting format in the IBEM-IS data and most submissions consisted of only a genetic or a protein variant, not including both elements of the HGVS format. When included as protein variants, most variants were reported using single-letter amino acid codes and position in the protein, i.e. F256L. The HGVS segment in the ClinVar variant was converted to the single-letter amino acid code format to reconcile the two protein reporting formats during analysis.

2.4.3 Compare Genotypes to ClinVar Database and Deduplicate

Variants found in the IBEM-IS were compared to published ClinVar variants. If the IBEM-IS variant matched a ClinVar variant, the variant was appended to the disease-specific published list. If the IBEM-IS variant did not match a ClinVar variant, the variant was appended to the disease-specific unpublished list. The records containing variants not found in ClinVar were manually re-checked and used for the next step in the pipeline.

2.4.4 Extract Clinical Data

When a variant was not found in ClinVar, the patient's record was searched for clinical data. Clinical data of interest were NBS result, family history, treatment, medical management, and allelic (*cis*/*trans* testing) data to aid in determination of recessive phenotypes. These clinical data points were selected according to the ACMG/AMP guidelines (Richards et al., 2015). If clinical data was discovered in the patient's record, it was extracted and saved.

2.4.5 Output Check and Variant Classification

To archive all results obtained from the pipeline, an output text file (.txt) was saved with information for each disease. The output text file contains the clinical data associated with each variant, the locally compiled published and unpublished list of variants, and the total number of subjects found in the disease-specific table. After the output text file is exported, a manual check of variants is needed to ensure variant comparison accuracy. After the output verification, the information was compiled for pathogenicity classification using the ACMG/AMP guidelines. Classified variants will be submitted to the ClinVar repository.

2.5 Time-Stamped Analysis

To perform a time-stamped analysis, ClinVar was searched on 1 October 2021 for the 33 genes in which the 150 variants were classified. ClinVar records were searched by gene name and all variants associated with the gene were downloaded. The 150 classified variants in this study were checked for inclusion in the updated ClinVar search. Variants that were found were analyzed for classification accuracy by comparing the ClinVar classification to the classification given in this study.

3 RESULTS

3.1 LPDR Data Summary

2,124 subjects were enrolled in the IBEM-IS when the data was transferred to the LPDR for secondary use. Of these enrolled, 1904 subjects had a diagnosis of one of the 32 diseases that were successfully analyzed to determine if genetic variants had been reported. Ten diseases were not analyzed due to either no genotype or unpublished variants reported for a patient. Genotyping was performed on 982 (51.6%) out of 1904 subjects with a diagnosis of one of 32 analyzed diseases. Of the analyzed diseases, 10 (31.3%) were categorized as amino acid disorders, 8 (25%) were fatty acid oxidation disorders, 11 (34.4%) were organic acid disorders, and 3 (9.4%) were categorized as other disorders. **Table 2** lists the number of subjects for each condition and the categorization of variants in ClinVar. These data show that data collected by observational studies and maintained by the NBSTRN contain diverse disease data.

3.2 Classification of 150 Variants With Supporting Clinical Information

Among the 982 subjects where a genetic variant was recorded in the LPDR, 564 individual variants were identified. Of those variants, 403 (71.5%) were present in ClinVar and 161 (28.5%) variants were not found in the ClinVar database. The 161 unpublished variants were reported in 29 diseases, shown in **Supplementary Table S2**. The clinical data from subjects with these 161 variants was used to build evidence for variant-disease correlation. The breakdown of the ACMG/AMP scoring criteria assigned to unpublished variants is shown in **Table 2**. While mapping variants to reference sequences, 11 variants were discovered that were reported with an incorrect reference amino acid at the submitted protein residue position. These incorrect submissions were confirmed with FATHMM (Shihab et al., 2013) and SNPS&GO (Calabrese et al., 2009) (**Supplementary Table S3, S4**). These 11 variants were not

TABLE 3 | Classification of the 161 unpublished variants according to ACMG/AMP guidelines. By combining the criteria shown in **Table 3**, variants were assigned a clinical significance. The classification definitions are: 1) Pathogenic, a variant that is "actionable" and may affect clinical decision making regarding management, treatment, or surveillance, 2) Likely Pathogenic, meaning "greater than 90% certainty of a variant . . . being disease-causing" (Richards et al., 2015), 3) Variant of Unknown Significance (VUS), meaning the data was either conflicting or did not report information that fulfilled the ACMG/AMP criteria, and 4) Unmapped variants, referring to variants in the data set that reported incorrect reference amino acids.

ACMG/AMP classification	Number of variants (n = 161)
Pathogenic (Criteria 1a)	44 (27.3%)
Pathogenic (Criteria 3b)	4 (2.5%)
Likely Pathogenic (Criteria 2)	41 (25.5%)
Likely Pathogenic (Criteria 3)	50 (31.1%)
Variants of Unknown Significance (VUS)	11 (6.8%)
Unmapped Variants	11 (6.8%)

further analyzed nor assigned a classification. The remaining 150 variants (93.1%) mapped to reference sequences were attributed PS3 and PP4 pathogenicity criteria due to the nature of the disease dataset being studied (**Supplementary Table S5**). Ninety-one variants were classified as Likely Pathogenic and were assigned using the "Likely Pathogenic 2" (one strong and one to two moderate) and "Likely Pathogenic 3" (one strong and more than two supporting) combination criteria. 41 variants were classified according to "Likely Pathogenic 2" and 50 were classified according to "Likely Pathogenic 3". Moderate and supporting classification criteria were obtained from computational prediction (PM5 and PP3), discovery in other databases (PP5), segregation (PP1), *de novo* (PM6), and allelic (PM3) data. The distribution of variants assigned these criteria can also be found in **Table 3**. During analysis, 11 variants discovered did not have enough clinical information to assign a classification. These 11 variants were attributed with PS3 and PP4 classification criteria but did not have additional information necessary to determine a classification, thus, they remain as Variants of Uncertain Significance (VUS). These data show that the LPDR contains undescribed variants and the clinical data needed to classify them.

Forty-eight of the 161 variants were found to have evidence supporting classification as Pathogenic. A total of 44 predicted null variants were discovered across 20 diseases, which were attributed with PVS1 pathogenicity criteria. PVS1 and PS3 attributed variants satisfied the "Pathogenic 1a" combination requirements for classifying the variant as Pathogenic. Four variants were classified as Pathogenic according to combination criteria for "Pathogenic 3b", using two moderate (PM1-6) classification criteria and two supporting (PP1-PP5) criteria. These data show that the LPDR contains substantial numbers of pathogenic variants that have remained undescribed.

3.3 Time-Stamp Analysis Demonstrates the Continual Expansion of ClinVar

To determine whether our novel variants had been submitted to ClinVar since the original analysis, we performed an updated search of ClinVar (Methods) for variants in the 33 genes from our analysis. The updated search returned an additional 7,469 variants, resulting in a total of 14,556 variants (original plus updated). Of the 150 novel variants we classified in the original analysis, eight had since been submitted to ClinVar (Hypergeometric test; p = 1.61e-05). We compared the pathogenicity classification in ClinVar for the eight variants (**Table 4**). Four of the eight variants (*GCDH*:c.776C > T (p.Ser259Leu), *GCDH*:c.880C > T (p.Arg294Trp), *GALT*:c.601C > T (p.Arg201Cys), *ASL*:c.1366C > T (p.Arg456Trp)) were classified as Pathogenic or Likely Pathogenic in ClinVar and are additionally supported by the classification in this study. The remaining four of eight variants are classified as Uncertain Significance or Conflicting Interpretations of Pathogenicity in ClinVar. The time-stamp analysis demonstrates that ClinVar is a continually changing resource of genotype-phenotype characterizations and that data collections like the IBEM-IS contribute to this ongoing effort.

4 DISCUSSION

This study is the first to use secondary analysis of health information from a NBS longitudinal dataset housed in the LPDR to classify variants. In addition to collecting variant data used in the diagnosis of individuals, longitudinal databases also capture follow-up visits describing the treatment plan and additional clinical testing data. By analyzing these databases, we have the opportunity to expand our knowledge of genotype-phenotype correlations, determine the clinical relevance of variants, and reduce the number of VUSs complicating interpretation of variants in reference variant databases.

This work demonstrates that longitudinal data contained in resources like the NBSTRN LPDR should be considered of high value to the research and clinical communities. The LPDR offers a unique ability to access both NBS and clinical data of subjects with a confirmed diagnosis. The LPDR also offers another unique advantage to understanding genotype-phenotype correlations: subjects are followed from the neonatal period over an extended period with clinical data medical management over the lifespan of diagnosed individuals. This method of continuous data capture can be used to determine if patient genotypes are relevant to disease outcomes or could help direct clinical care based on past findings. The LPDR should, therefore, be useful in translating genetic variant findings into clinical action. While our effort focused on the secondary analysis of IEMs, the NBS community is beginning to accelerate efforts to capture long-term follow-up (LTFU) data on all NBS conditions. Methods and approaches like the one described here, can be applied to these new efforts to enhance broad understanding of clinical relevance of variant data captured in newborns and further inform public policy regarding the utility of genome sequencing in newborn screening.

Of note, the IBEM-IS did not mandate the use of HGVS variant in data capture and did not recommend any standardization of formatting. The lack of uniformity between variant submissions was a difficult task to overcome in this

TABLE 4 | Classifications of eight variants identified in time-stamp analysis. Eight variants classified in this study were submitted to ClinVar since the original search for submissions. The classifications assigned to the eight variants in ClinVar, as well as the review status, and in this study are shown. One star and two-star review statuses correspond to variants having criteria provided by a single submitter and criteria provided by multiple submitters without conflicting interpretations, respectively.

Variant	ClinVar classification	Study classification
NM_000159.4 (GCDH):c.776C > T (p.Ser259Leu)	Likely Pathogenic (Review Status: 1 star)	Likely Pathogenic
NM_000159.4 (GCDH):c.880C > T (p.Arg294Trp)	Pathogenic (Review Status: 1 star)	Likely Pathogenic
NM_000155.4 (GALT):c.601C > T (p.Arg201Cys)	Pathogenic (Review Status: 2 star)	Likely Pathogenic
NM_004453.4 (ETFDH):c.731T > C (p.Phe244Ser)	Uncertain Significance (Review Status: 1 star)	Likely Pathogenic
NM_000016.6 (ACADM):c.92G > A (p.Arg31His)	Uncertain Significance (Review Status: 2 star)	Uncertain Significance
NM_000018.4 (ACADVL):c.1019G > A (p.Gly340Glu)	Uncertain Significance (Review Status: 1 star)	Likely Pathogenic
NM_000018.4 (ACADVL):c.1838G > A (p.Arg613Gln)	Conflicting Interpretations of Pathogenicity (Review Status: 1 star)	Likely Pathogenic
NM_000048.4 (ASL):c.1366C > T (p.Arg456Trp)	Pathogenic (Review Status: 1 star)	Likely Pathogenic

analysis. As more projects are completed and transferred to the NBSTRN for secondary research, the issue of non-interoperable variant submissions will worsen unless uniform requirements for data entry are promoted. As such, it is recommended that data tools like the LPDR work to educate researchers about standardized formats, such as the HGVS. Using a standardized format will allow researchers to spend less time cleaning data and help ensure the integrity of data within. As the amount of genetic variant data available continues to grow, researchers and clinicians will need data tools like the LPDR to determine the best care for individuals with a variant, offering detailed phenotypic correlations and presenting a valuable opportunity for corroboration of the clinical relevance of each genotype.

DATA AVAILABILITY STATEMENT

The IBEMC dataset can be accessed through the Longitudinal Pediatric Data Resource (LPDR) hosted by the Newborn Screening Translational Research Network (NBSTRN) (NBSTRN, 2021a; NBSTRN, 2021b). The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

Conceptualization: AB; Data curation: MH, IBEMC; Formal Analysis: KW; Funding Acquisition: AB, SB, ME; Investigation: KW; Methodology: KW; Project administration: AB, SB, ME; Resources: AB, SB, ME; Software: KW; Supervision: AB; Validation: KW; Visualization: KW; Writing-original draft: KW; Writing-review and editing; AB, SB, ME, MH.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.859837/full#supplementary-material

Supplementary Table S1 | Results of Sequence Variant Nomenclature according to the Human Genome Variation Society from Mutalyzer (Wildeman et al., 2008).

Supplementary Table S2 | For each disorder, the number of subjects reporting a genotype are shown. Unique variants not found in ClinVar were assigned clinical significance and shown in the number of variants classified as Pathogenic, Likely Pathogenic, or remain as Variants of Uncertain Significance. Variants were assigned a clinical significance using data shown in **Table 1**.

Supplementary Table S3 | Variant pathogenicity predictions provided by FATHMM (Shihab et al., 2013).

Supplementary Table S4 | Variant pathogenicity predictions provided by SNPS&GO (Calabrese et al., 2009; Capriotti and Altman, 2011).

Supplementary Table S5 | Detailed scoring assessment for each unpublished variant identified from the IBEMC.

REFERENCES

Arnold, G. L., Saavedra-Matiz, C. A., Galvin-Parton, P. A., Erbe, R., DeVincentis, E., Kronn, D., et al. (2010). Lack of Genotype-Phenotype Correlations and Outcome in MCAD Deficiency Diagnosed by Newborn Screening in New York State. *Mol. Genet. Metabolism* 99, 263–268. doi:10.1016/J.YMGME.2009.10.188

Berry, S. A., Jurek, A. M., Anderson, C., and Bentler, K. (2010). The Inborn Errors of Metabolism Information System: A Project of the Region 4 Genetics Collaborative Priority 2 Workgroup. *Genet. Med.* 12, S215–S219. doi:10.1097/GIM.0b013e3181fe5d23

Berry, S. A., Leslie, N. D., Edick, M. J., Hiner, S., Justice, K., and Cameron, C. (2016). Inborn Errors of Metabolism Collaborative: Large-Scale Collection of Data on Long-Term Follow-Up for Newborn-Screened Conditions. *Genet. Med.* 18, 1276–1281. doi:10.1038/GIM.2016.57

Calabrese, R., Capriotti, E., Fariselli, P., Martelli, P. L., and Casadio, R. (2009). Functional Annotations Improve the Predictive Score of Human Disease-Related Mutations in Proteins. *Hum. Mutat.* 30, 1237–1244. doi:10.1002/humu.21047

Capriotti, E., and Altman, R. B. (2011). Improving the Prediction of Disease-Related Variants Using Protein Three-Dimensional Structure. *BMC Bioinforma.* 12, S4. doi:10.1186/1471-2105-12-S4-S3

Clinvitae (2019). Invitae Clinvitae genetic variant search. Available at: https://www.invitae.com/en/clinvitae/(Accessed December 18, 2019).

Danos, A. M., Ritter, D. I., Wagner, A. H., Krysiak, K., Sonkin, D., Micheel, C., et al. (2018). Adapting Crowdsourced Clinical Cancer Curation in CIViC to the ClinGen Minimum Variant Level Data Community-driven Standards. *Hum. Mutat.* 39, 1721–1732. doi:10.1002/humu.23651

Denny, J. C., Rutter, J., and Goldstein, D. B. (2019). The "All of Us" Research Program. *N. Engl. J. Med.* 381, 668–676. doi:10.1056/nejmsr1809937

Federal Advisory Committees (2021). Recommended Uniform Screening Panel Official web site of the U.S. Health Resources & Services Administration, Available at: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html (Accessed May 24, 2021).

Harrison, S. M., Riggs, E. R., Maglott, D. R., Lee, J. M., Azzariti, D. R., Niehaus, A., et al. (2016). Using ClinVar as a Resource to Support Variant Interpretation. *Curr. Protoc. Hum. Genet.* 89 (16), 1–8. doi:10.1002/0471142905.hg0816s89

Hsu, R.-H., Chien, Y.-H., Hwu, W.-L., Chang, I.-F., Ho, H.-C., Chou, S.-P., et al. (2019). Genotypic and Phenotypic Correlations of Biotinidase Deficiency in the Chinese Population. *Orphanet J. Rare Dis.* 14, 992. doi:10.1186/S13023-018-0992-2

Krier, J. B., Kalia, S. S., and Green, R. C. (2016). Genomic Sequencing in Clinical Practice: Applications, Challenges, and Opportunities. *Dialogues Clin. Neurosci.* 18, 299–312. doi:10.31887/dcns.2016.18.3/jkrier

Landrum, M. J., Lee, J. M. B., Brown, G. R., Chao, C., Chitipiralla, S., et al. (2018). ClinVar: Improving Access to Variant Interpretations and Supporting Evidence. *Nucleic Acids Res.* 46, D1062–D1067. doi:10.1093/NAR/GKX1153

Lefter, M., Vis, J. K., Vermaat, M., den Dunnen, J. T., Taschner, P. E. M., and Laros, J. F. J. (2021). Mutalyzer 2: Next Generation HGVS Nomenclature Checker. *Bioinformatics* 37, 2811–2817. doi:10.1093/bioinformatics/btab051

Lloyd-Puryear, M., Brower, A., Berry, S. A., Brosco, J. P., Bowdish, B., and Watson, M. S. (2019). Foundation of the Newborn Screening Translational Research Network and its Tools for Research. *Genet. Med.* 21, 1271–1279. doi:10.1038/s41436-018-0334-8

O'Leary, N. A., Wright, M. W., Brister, J. R., Ciufo, S., Haddad, D., McVeigh, R., et al. (2016). Reference Sequence (RefSeq) Database at NCBI: Current Status, Taxonomic Expansion, and Functional Annotation. *Nucleic Acids Res.* 44, D733–D745. doi:10.1093/nar/gkv1189

National Library of Medicine (2019). Representation of clinical significance in ClinVar and other variation resources at NCBI, Available at: https://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/(Accessed December 18, 2019).

NBSTRN (2021a). IBEMC MCAD Cohort. Available at: https://nbstrn.org/tools/lpdr/ibemc-mcad (Accessed June 13, 2021)

NBSTRN (2021b). IBEMC PKU Cohort. Available at: https://nbstrn.org/tools/lpdr/ibemc-pku (Accessed June 12, 2021).

Pandas (2019). pandas PyPI, Available at: https://pypi.org/project/pandas/ (Accessed December 18, 2019).

Pena, L. D. M., Hansenvan Calcar, J., Edick, M. J., Walsh Vockley, C., Leslie, N., et al. (2016). Outcomes and Genotype-Phenotype Correlations in 52 Individuals with VLCAD Deficiency Diagnosed by NBS and Enrolled in the IBEM-IS Database. *Mol. Genet. Metabolism* 118, 272–281. doi:10.1016/J.YMGME.2016.05.007

Pena, L. D. M., van Calcar, S. C., Hansen, J., Edick, M. J., Walsh Vockley, C., Leslie, N., et al. (2016). Outcomes and Genotype-Phenotype Correlations in 52 Individuals with VLCAD Deficiency Diagnosed by NBS and Enrolled in the IBEM-IS Database. *Mol. Genet. Metabolism* 118, 272–281. doi:10.1016/j.ymgme.2016.05.007

Python (2019). Python 2.7.17 documentation, Available at: https://docs.python.org/2/index.html (Accessed December 18, 2019).

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al. (2015). Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. Med.* 17, 405–424. doi:10.1038/gim.2015.30

Sanger, F., Nicklen, S., and Coulson, A. R. (1977). DNA Sequencing with Chain-Terminating Inhibitors. *Proc. Natl. Acad. Sci. U.S.A.* 74, 5463–5467. doi:10.1073/pnas.74.12.5463

Shendure, J., Porreca, G. J., Reppas, N. B., Lin, X., McCutcheon, J. P., Rosenbaum, A. M., et al. (2005). Accurate Multiplex Polony Sequencing of an Evolved Bacterial Genome. *Science* 309, 1728–1732. doi:10.1126/science.1117389

Shihab, H. A., Gough, J., Cooper, D. N., Stenson, P. D., Barker, G. L. A., Edwards, K. J., et al. (2013). Predicting the Functional, Molecular, and Phenotypic Consequences of Amino Acid Substitutions Using Hidden Markov Models. *Hum. Mutat.* 34, 57–65. doi:10.1002/humu.22225

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., et al. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Med.* 12, e1001779. doi:10.1371/journal.pmed.1001779

Trefz, F. K., Burgard, P., König, T., Goebel-Schreiner, B., Lichter-Konecki, U., Konecki, D., et al. (1993). Genotype-phenotype Correlations in Phenylketonuria. *Clin. Chim. Acta* 217, 15–21. doi:10.1016/0009-8981(93)90233-T

U. S Code (2021). 42 USC 300b-15: Hunter Kelly Research Program. Available at: https://uscode.house.gov/view.xhtml?req=(title:42 section:300b-15 edition: prelim (Accessed September 17, 2021).

Wain, K. E., Palen, E., Savatt, J. M., Shuman, D., Finucane, B., Seeley, A., et al. (2018). The Value of Genomic Variant ClinVar Submissions from Clinical Providers: Beyond the Addition of Novel Variants. *Hum. Mutat.* 39, 1660–1667. doi:10.1002/humu.23607

Wei, C.-H., Phan, L., Feltz, J., Maiti, R., Hefferon, T., and Lu, Z. (2018). TmVar 2.0: Integrating Genomic Variant Information from Literature with dbSNP and ClinVar for Precision Medicine. *Bioinformatics* 34, 80–87. doi:10.1093/bioinformatics/btx541

Wildeman, M., van Ophuizen, E., den Dunnen, J. T., and Taschner, P. E. M. (2008). Improving Sequence Variant Descriptions in Mutation Databases and Literature Using the Mutalyzer Sequence Variation Nomenclature Checker. *Hum. Mutat.* 29, 6–13. doi:10.1002/humu.20654

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Developing a National Newborn Genomes Program: An Approach Driven by Ethics, Engagement and Co-design

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The transformative potential of whole genome sequencing (WGS) as a diagnostic tool in healthcare has been demonstrated by initiatives including the 100,000 Genomes Project and is now offered to certain patients in the National Health Service (NHS) in England. Building on these foundations, the utility of WGS in the newborn period can now be explored. Genomics England is working in partnership with NHS England and NHS Improvement and other healthcare, patient and public interest groups to design a research program embedded in the NHS to explore the potential challenges and implications of offering WGS in all newborns. The program will aim to: 1) evaluate the feasibility, utility and impact on the NHS of screening for childhood-onset rare actionable genetic conditions; 2) understand how, with consent, genomic and healthcare data could be used to enable research to develop new diagnostics and treatments; and 3) explore the implications of storing an individual's genome for use over their lifetime. Recognizing the important practical, scientific and ethical questions that we must explore in dialogue with the public and experts, we are taking a collaborative, evidence-based and ethically deliberate approach to designing the program. An iterative co-design process including a nationwide public dialogue has identified emergent themes and ethical considerations which are the focus of the program's design. These themes will be further developed through continued engagement with healthcare professionals, researchers, ethics experts, patient groups and the public, with an ongoing commitment to embedding ongoing ethics research and co-design into the delivery of the program.

Keywords: newborn screening, whole genome sequencing, rare diseases, public health, ethics, public engagement, co-design

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INTRODUCTION

The United Kingdom (UK) has consistently taken the lead to introduce genomic technologies into healthcare and research, particularly whole genome sequencing (WGS). Initiatives such as the 100,000 Genomes Project and the National Health Service (NHS) Genomic Medicine Service in England have demonstrated the potential of WGS to increase the diagnostic yield for a range of rare

conditions and its role in cancer (Turnbull et al., 2018; Smedley et al., 2021). In the UK, newborn screening is provided by the NHS on the basis of recommendations from the UK National Screening Committee and consists of a physical examination, hearing screen and a blood spot test. The blood spot test directly screens for nine rare conditions, for which there is substantial evidence that early identification and treatment can improve health outcomes (NHS, 2022). Parental consent is required, and there is high uptake with 95–99% of newborns screened (GOV.UK, 2022). The UK tests for fewer conditions than other high-income countries, and there is growing recognition of the potential of early and pre-symptomatic detection of a larger number of conditions to provide benefits to the child and their family, particularly highlighted by rare disease communities. This may be done through the expansion of genomic and/or other technologies, and by reviewing the evidence required to incorporate conditions in screening programs in the context of a national publicly-funded health system (Genetic Alliance UK, 2022). Other genomic population screening research initiatives have taken place or are underway internationally, and highlight the importance of equitable access, managing expectations and uncertainties, and ensuring a robust consent process (Screen4care, 2022; Holm et al., 2018; Roman et al., 2020; Downie et al., 2021). However, there remains a relative lack of empirical evidence about the benefits and harms of these programs, particularly in the long term.

The UK Chief Medical Officer emphasized the importance of providing expanded and equitable access to genomic services in her 2016 Annual Report and requested a group to investigate the benefits of genomic analysis in children including in the context of newborn screening (Department of Health and Social Care, 2017). The Genomic Analysis in Children Task and Finish Group—made up of experts from laboratory and clinical genomics, ethics and screening as well as patient and parent representatives—highlighted that WGS has the potential to add to current aspects of the newborn screening program, as well as provide additional opportunities for ongoing research and feedback of information beyond the newborn period. An initial conservative analysis of rare inherited conditions suggests that 1 in 260 live births are affected with a condition for which identification through WGS has the potential to reduce or avoid harm in early life. The group recommended the initiation of a large scale, resourced research program in the UK to gather evidence on the effectiveness, feasibility and acceptability of WGS for screening in newborns (Genomics England, 2022a).

Genomics England is working in partnership with NHS England and NHS Improvement as well as a range of healthcare, patient and public interest groups to develop this program. A recently published vision outlines three distinct but related aims of the Newborn Genomes Program (Genomics England, 2022a):

1) to identify a larger number of rare and actionable conditions than currently screened for;
2) to enable research on genomic and health data from newborns to further develop diagnostics and treatments; and
3) to explore the potential benefits, risks and broader implications of storing an individual's genome for use over their lifetime.

These aims will be explored through a research pilot aimed to start in 2023, guided by a protocol subject to research ethics approval, and crucially embedded within the NHS. This would include at least 100,000 babies, powered to provide the data required to determine the effectiveness of WGS in the newborn screening context based on modelling of likely incidence of conditions targeted and conservative estimates of sensitivity and specificity (Genomics England, 2022a). An NHS Steering Group has been established to provide advice and expertise around decisions being made about the design of the program, and ensure that any learnings can be effectively translated from research to clinical care in a nationwide health system.

WGS has increasingly demonstrated the ability to detect a broad range of genomic variants using a single technology, with costs, sequencing and analysis times decreasing to provide results where an intervention may be time-sensitive. This technology provides flexibility to analyze additional variants when new evidence about pathogenicity or treatment would support their inclusion in newborn screening, or to analyze in a diagnostic context if symptoms arise in an individual in the future, without requiring new or additional samples (Belkadi et al., 2015; Dimmock et al., 2021). WGS also provides great value for research discovery, with potential for genome-wide research to identify new diagnoses, diagnostics and treatments, and allows for a greater understanding of the relevance of particular genetic variants to health and disease. This could be supported using the successful model that Genomics England has developed in collaboration with its participants, where de-identified genomic and health data are presented in a trusted research environment to accredited researchers for agreed purposes with access controlled by participant-led governance.

Despite these advantages, the use of WGS in newborn screening at a national health system level is a novel approach and limitations remain, particularly when testing asymptomatic rather than pre-symptomatic individuals. For example, it will be important to minimize feedback of information that is uncertain or not clinically useful, and the burden this may place on families and health systems (Nuffield Council on Bioethics, 2017; Biesecker et al., 2021; Downie et al., 2021). The sensitivity, specificity, positive and negative predictive values would be expected to vary for each condition depending on its prevalence, ability to distinguish pathogenic from benign variants, and ability to detect known and unknown pathogenic variants (Hagenkord et al., 2020; Marshall et al., 2020). Changing any of these metrics could result in under or over-diagnosis of any of these conditions, or missing diagnoses. This necessitates careful thought to determine which conditions will be analyzed and fed back in the newborn period, requiring the establishment of clear pathways to additional investigations such as biochemical tests to confirm diagnoses or clarify any findings. Challenges also remain with regards to re-analysis of data over time, and how to manage initial and ongoing consent.

Taking into account different perspectives, the team are embracing a collaborative approach and ongoing commitment to openness, grounded in national dialogue and research with experts and the public. This paper will outline our approach to engagement, co-design and ethical considerations that are required to ensure a transparent and evidence-based program within a nationwide publicly funded health system.

Public Dialogue and Engagement

Research in this area—just as for any population screening program that might follow—must be premised on public acceptance and support. This is not a one-off process but one of ongoing dialogue and adaptation as expectations emerge and evidence develops. In 2020-2021, a national dialogue commissioned by Genomics England, the UK National Screening Committee and United Kingdom Research and Innovation's Sciencewise program, was carried out with members of the UK public (Van Mil, 2021). This was a novel approach to ensuring that the public's views directly impacted the initiation and design of a nationwide population screening-based research program. 133 participants reflective of the UK population each took part in a series of interviews and group workshop sessions, which were recorded and analyzed using grounded theory methodology. Participants expressed broad support for the potential use of WGS for newborn screening, whilst also raising a number of issues and principles that would need to be addressed before this could be initiated in practice (Van Mil, 2021). Further engagement with stakeholders including patients and families with rare conditions, public interest groups, policy and commissioning services, ethics experts, healthcare professionals and Royal Colleges, laboratory and diagnostic services and researchers have echoed similar considerations (Genomics England, 2022a). These and the considerations raised in the public dialogue have been grouped into six emergent themes which will be discussed further in this paper and guide the program as it continues to develop:

1) The benefits, limitations, and unknowns of WGS as a screening tool;
2) Principles for including conditions in the screening panel, co-developed with relevant stakeholders;
3) Person-centered consent across screening, research and reanalysis;
4) A supportive and inclusive experience for all families;
5) Trusted and future-proofed genomic data storage and usage; and
6) A sustainable and scalable program for the NHS, should the evidence generated from the pilot support a future clinical service.

Ethical Implications of Whole Genome Sequencing in Newborns

Alongside public dialogue and engagement, ethics will be central to the co-design of the program and an ongoing component of the research pilot itself.

The three aims of the Newborn Genomes Program each raise distinct, yet related, ethical considerations that will need to be explored prior to, throughout, and beyond, the duration of the program. Initial ethical themes which have been raised through the public dialogue and ongoing stakeholder engagement, reflecting previous research include (Botkin and Rothwell, 2016; Friedman et al., 2017; Nuffield Council on Bioethics, 2017; Sénécal et al., 2018; Goldenberg et al., 2019; Biesecker et al., 2021; Levy, 2021): consent, specifically considering the context of genomics in screening; the benefits and harms of results in a pre-symptomatic context (such as uncertainty, overmedicalization, genetic determinism, and the psycho-social impacts on parent-child relationships); data governance including storage, access and use by clinical, academic and life sciences industry partners including access requests by parents; balancing the rights and needs of the child with those of the wider family; equitable access and the potential for discrimination; resource utilization and prioritization; and broader societal implications and future unintended consequences. It will be important to identify whether there are novel ethical areas for consideration in the newborn context which will need to be included in the ethics agenda for the program.

Crucially, the program aims to incorporate ethics not only in the context of an underlying research-ethics approved protocol, but also as an inherent part of program by embedding ethics throughout the governance, design, implementation and evaluation. An initial set of foundational ethical principles and commitments are being developed and will evolve into an ethical framework including different positions for each of the three aims of the program, developed through a combination of ethics research, engagement and deliberation with experts and a diverse range of publics. Genomics England's existing Ethics Advisory Committee, Participant Panel and internal Ethics team, a dedicated newborn ethics working group, as well as external stakeholder and public engagement activities including young people and expectant parents, will offer insights to ethical matters arising in relation to the program with a focus on ensuring ongoing trustworthiness. The program provides opportunities to test these ethical and social dimensions before, during and after the pilot, to broaden our insight and foresight for the program and any related future developments. Furthermore, the program intends to facilitate and inform broader ethical debates which stretch beyond the research pilot, particularly in relation to the possibilities and challenges of using the genome as a lifetime clinical resource.

What Does it Mean to Co-design?

The principles of experience-based co-design underlie our approach to designing the program in an iterative manner (Donetto et al., 2015). In line with this approach, working groups are being developed with representation across the country from different stakeholders (including healthcare professionals, researchers, scientists, patients and members of the public) to provide advice and recommendations regarding the design of the program. Outputs from these groups would feed in to the NHS Steering Group and existing governance structures

within Genomics England to inform delivery of the pilot. Here, we provide two illustrative examples.

In contrast to other state screening programs or related research programs where criteria are typically informed exclusively by clinicians, policymakers and researchers, we have included wider views of the public, rare disease patient communities and ethics experts, reflecting our focus on the importance of public acceptability of a nationwide research program. A working group of 28 individuals reflecting these various areas of expertise has been established to develop a set of principles using consensus methodology, which will inform the conditions (and the genes and variants that cause them) that could be initially analyzed, as well as an approach to an ongoing review process where conditions may be added or removed based on new information. While there are arguably many possible answers to this question, the overarching view from the public dialogue is being used as a starting point: to broadly focus on conditions that have an impact in early childhood, and where there are intervention(s) that can cure, prevent or slow progression. Consideration must also be afforded to conditions which would demonstrate cost-effectiveness for a publicly-funded national health service, and whether the condition has an established follow-on test(s) and care pathway across the NHS with identified specialists who could provide care and follow up support. Once the principles have been established by the working group, they will be applied to genes, followed by variant curation and rigorous empirical analysis to estimate the false positive and false negative rates of the variant detections in the selected genes. There are a number of processes that have been published to generate a list of genes that will be drawn upon (Ceyhan- Birsoy et al., 2017; Milko et al., 2019; Downie et al., 2021; Bick et al 2020). These principles and the final list of conditions, genes and variants will be made available for deliberative debate for further input from professional, patient and public groups across the UK.

Another working group is focusing on the recruitment process for parents who may consider participating in the pilot through consenting on behalf of their newborn. This group includes a range of healthcare professionals including midwives, as well as parent and patient representatives with a variety of perspectives. It is critical that the pilot will be understandable and desirable to parents of all backgrounds, to enable informed decision making about taking part as well as ensuring equity of access. As such, the group meet regularly to brainstorm and share their thoughts on the recruitment materials, messages, and the process of recruitment for the pilot. The concepts developed in these group sessions are then taken out and tested with healthcare professionals and expecting parents across the UK in an iterative learning process, including a focus on traditionally underserved groups in genomic research.

Additional working groups that have or will be initiated in the coming months will focus on education and training for the workforce; consent including parents' initial decision to join the program as well as the need for young people to review their decision at 16 and the ongoing opportunity to withdraw; treatment and support pathways for families receiving results; sampling and sequencing approaches; and how the program will be evaluated.

DISCUSSION

The United Kingdom is uniquely positioned to build on the foundations of WGS in a diagnostic context and design a program to gather evidence on the effectiveness, feasibility and acceptability of WGS in newborns. This ambitious research program of genomics in newborn screening is the largest to date, with an opportunity to assess the benefits and challenges of this approach at an unprecedented scale and within a nationwide publicly funded health service. Furthermore, due to the NHS's already close integration with genomic research, experience gained throughout the program could be more seamlessly translated into clinical practice in an equitable and cost-effective manner. This is in contrast to other newborn screening initiatives involving genomics which involve distinctly separate research pathways, and one or a small number of hospital systems (Downie et al 2021). Our proposed approach involves prioritizing nationwide engagement, co-design and ethical considerations to directly feed into decisions made about the program, and as key components to ensuring that the benefits, practicalities and challenges of this program can be realized. This focusses on a commitment to involving the public and patient communities in shared decision-making about programs that will impact on population health.

There are a number of implications that will be the focus of program design in the coming months, building on the challenges and learnings from the implementation of the 100,000 Genomes Project and other national screening initiatives. As a research program where results will be fed back *via* clinical pathways in a number of hospitals and community health services across the country, there is a need to consider the time, training and resource requirements from the point of recruitment through to ongoing care, with interactions needing to be carefully monitored to ensure that the research pilot is not affecting uptake of the current newborn screening program. Sampling, sequencing and bioinformatic pipelines, laboratories and reporting systems must be capable of processing samples at scale and in a time frame that can allow for treatment to be rapidly initiated, within days for some conditions. There must be a clear plan as well as adequate support and information available for those families where a rare condition is identified. To consider the potential of this as a future national clinical service, the program would not only need to demonstrate evidence of benefit and cost-effectiveness and the ability to maintain trust and high ethical standards, but also be operationally feasible at scale within a national publicly-funded health system. In order to effectively capture and assess outcomes of this program a co-designed robust evaluation framework will be devised to ensure that technology performance, health outcomes, implementation, psychosocial and ethical issues can be monitored. This will include both qualitative and quantitative metrics, and ensure that any evidence can be independently evaluated in a formative manner to be able to adapt and improve processes throughout the course of the pilot.

Factors influencing the adoption of WGS in newborn screening will likely reflect many of those already known to

impact adoption of population-wide screening, genomic testing and other novel technologies, and will be explored throughout the course of this program alongside other emergent issues (Dheensa et al., 2019; Best et al., 2021; Sanderson et al., 2022). At a more individual level, factors include perceived relevance to one's own health or their family; prior experiences with screening and health care; time and resources available to access and understand information to make an informed choice; engagement and leadership from trusted sources; as well as cultural, religious, familial and personal values. Factors at a health systems level include organizational culture and leadership, perceived relevance to one's clinical practice, access to education and training, and ability and capacity to work with colleagues within and across specialties to make complex pathways work seamlessly. At a broader societal level, public acceptability and trustworthy systems and organizations are imperative, particularly in the context of population-wide screening in a publicly-funded national health system. Crucially, the ethically-focused and collaborative aspects of the design and development of the Newborn Genomes Program are expected to continue throughout the duration of the pilot, reflecting a commitment to transparency, trustworthiness and learning at every step.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

AP, CP, and AA contributed to conception and design of the paper. AP wrote the first draft of the manuscript. AA, DB, ML, and RS supported writing sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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REFERENCE

Belkadi, A., Bolze, A., Itan, Y., Cobat, A., Vincent, Q. B., Antipenko, A., et al. (2015). Whole-genome Sequencing Is More Powerful Than Whole-Exome Sequencing for Detecting Exome Variants. *Proc. Natl. Acad. Sci. U.S.A.* 112 (17), 5473–5478. doi:10.1073/pnas.1418631112

Best, S., Long, J. C., Gaff, C., Braithwaite, J., and Taylor, N. (2021). Investigating the Adoption of Clinical Genomics in Australia. An Implementation Science Case Study. *Genes* 12 (2), 317. doi:10.3390/genes12020317

Bick, D., Bick, S. L., Dimmock, D. P., Fowler, T. A., Caulfield, M. J., and Scott, R. H. (2020). An Online Compendium of Treatable Genetic Disorders. *Am. J. Med. Genet.* 187, 48–54. doi:10.1002/ajmg.c.31874

Biesecker, L. G., Green, E. D., Manolio, T., Solomon, B. D., and Curtis, D. (2021). Should All Babies Have Their Genome Sequenced at Birth? *BMJ* 325, 1–2. doi:10.1136/bmj.n2679

Botkin, J. R., and Rothwell, E. (2016). Whole Genome Sequencing and Newborn Screening. *Curr. Genet. Med. Rep.* 4 (1), 1–6. doi:10.1007/s40142-016-0084-3

Ceyhan-Birsoy, O., Machini, K., Lebo, M. S., Yu, T. W., Agrawal, P. B., Parad, R. B., et al. (2017). A Curated Gene List for Reporting Results of Newborn Genomic Sequencing. *Genet. Med.* 19 (7), 809–818. doi:10.1038/gim.2016.193

Department of Health and Social Care (2017). *Annual Report of the Chief Medical Officer 2016: Generation Genome.* [Internet]. Available from: https://www.gov.uk/government/publications/chief-medical-officer-annual-report-2016-generation-genome.

Dheensa, S., Lucassen, A., and Fenwick, A. (2019). Fostering Trust in Healthcare: Participants' Experiences, Views, and Concerns about the 100,000 Genomes Project. *Eur. J. Med. Genet.* 62 (5), 335–341. doi:10.1016/j.ejmg.2018.11.024

Dimmock, D., Caylor, S., Waldman, B., Benson, W., Ashburner, C., Carmichael, J. L., et al. (2021). Project Baby Bear: Rapid Precision Care Incorporating rWGS in 5 California Children's Hospitals Demonstrates Improved Clinical Outcomes and Reduced Costs of Care. *Am. J. Hum. Genet.* 108 (7), 1231–1238. doi:10.1016/j.ajhg.2021.05.008

Donetto, S., Pierri, P., Tsianakas, V., and Robert, G. (2015). Experience-based Co-design and Healthcare Improvement: Realizing Participatory Design in the Public Sector. *Des. J.* 18 (2), 227–248. doi:10.2752/175630615x14212498964312

Downie, L., Halliday, J., Lewis, S., and Amor, D. J. (2021). Principles of Genomic Newborn Screening Programs. *JAMA Netw. Open* 4 (7), e2114336. doi:10.1001/jamanetworkopen.2021.14336

Friedman, J. M., Cornel, M. C., Goldenberg, A. J., Lister, K. J., Sénécal, K., and Vears, D. F. (2017). Genomic Newborn Screening: Public Health Policy Considerations and Recommendations. *BMC Med. Genomics* 10 (1), 9. doi:10.1186/s12920-017-0247-4

Genetic Alliance Uk (2022). *Fixing the Present, Building for the Future: Newborn Screening for Rare Conditions.* [Internet]. London. Available from: https://geneticalliance.org.uk/wp-content/uploads/2020/01/Newborn-Screening-Report.pdf.

Genomics England (2022). *Newborn Genomes Programme | Genomics England.* [Internet]. London: Genomics England. [cited 25 January 2022]. Available from: https://www.genomicsengland.co.uk/newborn-sequencing/.

Genomics England (2022). *About Us: Governance | Genomics England.* [Internet]. London: Genomics England. [cited 5 April 2022]. Available from: https://www.genomicsengland.co.uk/about-us/governance.

Goldenberg, A. J., Lloyd-Puryear, M., Brosco, J. P., Therrell, B., Bush, L., Berry, S., et al. (2019). Including ELSI Research Questions in Newborn Screening Pilot Studies. *Genet. Med.* 21 (3), 525–533. doi:10.1038/s41436-018-0101-x

Gov.Uk (2022). *Newborn Blood Spot Screening Data Collection and Performance Analysis Report 1 April 2018 to 31 March 2019.* [Internet]. London: GOV.UK. [cited 25 January 2022]. Available from: https://www.gov.uk/government/publications/newborn-blood-spot-screening-data-collection-and-performance-analysis-report/newborn-blood-spot-screening-data-collection-and-performance-analysis-report-1-april-2018-to-31-march-2019.

Hagenkord, J., Funke, B., Qian, E., Hegde, M., Jacobs, K. B., Ferber, M., et al. (2020). Design and Reporting Considerations for Genetic Screening Tests. *J. Mol. Diagnostics* 22 (5), 599–609. doi:10.1016/j.jmoldx.2020.01.014

Holm, I. A., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., Frankel, L. A., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18 (1), 225. doi:10.1186/s12887-018-1200-1

Levy, H. L. (2021). Ethical and Psychosocial Implications of Genomic Newborn Screening. *Int. J. Neonatal Screen.* 7 (1), 2. doi:10.3390/ijns7010002

Marshall, C. R., Chowdhury, S., Taft, R. J., Lebo, M. S., Buchan, J. G., Harrison, S. M., et al. (2020). Best Practices for the Analytical Validation of Clinical Whole-Genome Sequencing Intended for the Diagnosis of Germline Disease. *NPJ Genom Med.* 5 (1), 47. doi:10.1038/s41525-020-00154-9

Milko, L. V., O'Daniel, J. M., DeCristo, D. M., Crowley, S. B., Foreman, A. K. M., Wallace, K. E., et al. (2019). An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screening. *J. Pediatr.* 209, 68–76. doi:10.1016/j.jpeds.2018.12.027

NHS (2022). *Newborn Screening - Overview*. [Internet]. London: nhs.uk. [cited 25 January 2022]. Available from: https://www.nhs.uk/conditions/baby/newborn-screening/overview/.

Nuffield Council on Bioethics (2017). *Whole Genome Sequencing of Babies*. [Internet]. London: Nuffield Council on Bioethics. Available from: https://www.nuffieldbioethics.org/publications/whole-genome-sequencing-of-babies.

Roman, T. S., Crowley, S. B., Roche, M. I., Foreman, A. K. M., O'Daniel, J. M., Seifert, B. A., et al. (2020). Genomic Sequencing for Newborn Screening: Results of the NC NEXUS Project. *Am. J. Hum. Genet.* 107 (4), 596–611. doi:10.1016/j.ajhg.2020.08.001

Sanderson, S. C., Lewis, C., Hill, M., Peter, M., McEntagart, M., Gale, D., et al. (2022). Decision-making, Attitudes, and Understanding Among Patients and Relatives Invited to Undergo Genome Sequencing in the 100,000 Genomes Project: A Multisite Survey Study. *Genet. Med.* 24 (1), 61–74. doi:10.1016/j.gim.2021.08.010

Screen4care (2022). *Screen4Care – Shortening the Path to Rare Disease Diagnosis by Using Newborn Genetic Screening and Digital Technologies | Screen4Care*. [Internet]. Brussels: Screen4care.eu. [cited 25 January 2022]. Available from: https://www.screen4care.eu/.

Sénécal, K., Unim, B., Unim, B., and Maria Knoppers, B. (2018). Newborn Screening Programs: Next Generation Ethical and Social Issues. *obm Genet.* 2 (3), 1. doi:10.21926/obm.genet.1803027

Smedley, D., Smith, K., Martin, A., Thomas, E., McDonagh, E., Cipriani, V., et al. (2021). 100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care — Preliminary Report. *N. Engl. J. Med.* 385 (20), 1868–1880. doi:10.1056/NEJMoa2035790

Turnbull, C., Scott, R. H., Thomas, E., Jones, L., Murugaesu, N., Pretty, F. B., et al. (2018). The 100 000 Genomes Project: Bringing Whole Genome Sequencing to the NHS. *BMJ* 361, 1–7. doi:10.1136/bmj.k1687

Van Mil, H. (2021). *Implications of Whole Genome Sequencing for Newborn Screening: A Public Dialogue*. [Internet]. London: Hopkins Van Mil. Available from: https://www.genomicsengland.co.uk/wp-content/uploads/2021/07/public-dialogue-wgs-for-nbs-final-report.pdf.

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BRIEF RESEARCH REPORT
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Using a Participatory Approach to Develop Research Priorities for Future Leaders in Cancer-Related Precision Public Health

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Precision public health is an emerging discipline combining principles and frameworks of precision health with the goal of improving population health. The development of research priorities drawing on the strengths of precision and public health is critical to facilitate the growth of the discipline to improve health outcomes. We held an interactive workshop during a virtual conference bringing together early-career researchers across public health disciplines to identify research priorities in precision public health. The workshop participants discussed and voted to identify three priority areas for future research and capacity building including 1) enhancing equity and access to precision public health research and resources, 2) improving tools and metrics for evaluation and 3) applying principles of implementation science to support sustainable practices. Participants also developed future objectives for achieving each priority. Future efforts by working groups will continue the process of identifying, revising, and advancing critical research priorities to grow the impact of precision public health.

Keywords: precision public health, research priorities, cancer, conference, transdisciplinary research, equity, implementation science, evaluation

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1 INTRODUCTION

Genomic information can personalize prevention and treatment strategies across many therapeutic areas, leading to better clinical and population health outcomes. Genomics is a cornerstone of precision medicine, which can be used along with other individual-level behaviors and environmental factors to deliver the right care to the right *patient* at the right time. Expanding these approaches to improve population health has been termed "precision public health," the goal of which is to ensure that prevention and control strategies are delivered to the right *populations* at the right time (Khoury et al., 2016).

Numerous applications of precision public health provide opportunities to improve care. For example, newborn testing for rare diseases offers the opportunity to intervene early for treatable conditions. The use of polygenic risk scores allows precision medicine approaches for cardiovascular disease prevention. Genomic sequencing in COVID-19 surveillance enables professionals to track

variants of public health concern and respond with targeted testing and vaccination in populations of greatest need (Khoury and Holt, 2021).

A key opportunity for precision public health lies in the application of genomic information to enhance cancer prevention and treatment. Despite evidence in favor of integrating genomics into population-level cancer prevention and control approaches through the use of precision public health strategies, there has been limited translation of this approach into public health and clinical practice (Roberts et al., 2019, 2017). Prior works have identified a need for research prioritization in this emerging discipline that draws from the respective strengths of precision medicine and public health to capitalize on opportunities to improve population health (Allen et al., 2019a, 2019b; Roberts et al., 2021).

Given that the field of precision public health is still emerging, there are limited opportunities for investigators to come together to form collaborations and develop much needed transdisciplinary research priorities. Instead, researchers are often siloed in their specific institution or department and may need to attend a variety of disciplinary conferences that are only tangentially related to their research agendas to learn about precision public health. To address this need, we convened an international transdisciplinary conference on October 14–15, 2021 for leaders and early-stage investigators who work in precision public health to develop and support capacity building in precision public health research, with a broad focus on oncology. During the conference, we held a workshop for participants from across different precision public health disciplines to identify transdisciplinary research priorities for precision public health in oncology.

2 METHODS

2.1 Conference

The Transdisciplinary Conference for Future Leaders in Precision Public Health was held on October 14–15, 2021 virtually (PharmSci, 2021). Participants included international, early career researchers and practitioners as well as others interested in the topic of precision public health. The conference was advertised through social media (Twitter, San Francisco, CA), listservs, emails and all speaker and planning member networks to invite a wide audience working in diverse areas of precision public health. The conference included several key components 1) talks from a keynote speaker and six additional leaders across areas of precision public health such as environmental health, biostatistical modeling, healthy policy and health behavior, 2) networking sessions, 3) a virtual poster session held *via* Twitter and conference website (PharmSci, 2021), and 4) a workshop to identify priorities for precision public health research, which is the focus of this paper. A visual diagram of the conference proceedings is found in **Supplementary Figure S1**.

2.2 The Workshop

The conference workshop was designed to meet the following goals: 1) generate and facilitate the development of research priorities that address the challenges of and gaps in precision public health research, 2) achieve consensus about broad research priority areas, and 3) develop transdisciplinary networks. There were three workshop sessions, with a total duration of 4.5 h, distributed over the 2 days of the conference. These sessions included 1) *An "Envisioning Success" brainstorming process to identify research priority ideas*, 2) Voting by participants *on the research priority ideas to generate research priorities*, and 3) *Small group meetings to develop and draft objectives for the identified research priorities*. A professional facilitator led the sessions using the Zoom functionalities of Chat and Breakout Rooms to engage the virtual participants (Zoom Video Communications, San Jose CA). Each session began with a participant self-introduction and sharing responses to a Networking question.

It's October 2025. You are at the 5th Annual Transdisciplinary Conference for Future Leaders in Precision Public Health. Dr. Francis Collins, whose legacy includes the leadership of the international Human Genome Project, is the keynote speaker. As he takes the podium, your heart races in anticipation of the inclusion of your work being cited in his talk: "Perspectives from the Field: Translation of Cancer Genetics to Population Screening." Dr. Collins shares stories and testimonies about lives being saved and extended. He attributes the success to the very transdisciplinary work described in the Research Priorities setting for the Precision Public Health field at this Conference just four years ago. Noting how former skeptics of precision public health now agree that there is significant benefit to integrating the two fields, he emphasizes that it is no easy task to work across disciplines and internationally. He acknowledges the commitment of this group of "future leaders" in identifying opportunities to equitably implement precision-based approaches and embracing the complexity inherent in Precision Public Health approaches. Given the progress in addressing the challenges of "the right intervention to the right population at the right time", he compliments the attendees for being the current leaders of the field. You reflect on how far you have come since this Conference was launched in October 2021 and your role in it."

FIGURE 1 | Envisioning success scenario from workshop session 1.

2.2.1 Session 1

An appreciative-inquiry approach (Cooperrider and Whitney, 2005) was adopted to engage the participants in envisioning future success. The following "Envisioning Success" scenario was provided to stimulate the discussion (**Figure 1**).

Participants were then invited to individually reflect on two questions related to this success scenario and enter their responses in the Zoom chat:

1) What key research challenges did we address in defining our research priorities?
2) How did we collectively pursue these priorities?

The participants were then distributed to Zoom breakout rooms to brainstorm and identify research priorities to move the field of precision public health forward. This process involved two discussion periods in sequence, each lasting 45 min. The output from breakout discussion was the input for consideration during a larger group discussion.

The breakout session was designed to be discipline specific, to initiate the discussion among participants with a common perspective. Breakout rooms were defined for five specific public health disciplines (Health Behavior, Epidemiology, Health Policy, Biostatistics, and Environmental Health). The participants were directed to select the option that best represents their work.

The second discussion period was a full group discussion during which the output from the breakout discussions was reported to the

TABLE 1 | Conference participant characteristics.

Characteristic	All registrants *N* (%)	Conference attendees *N* (%)	Workshop attendees *N* (%)
Geography			
Asia	1 (0.89%)	1 (1.92%)	0 (0%)
Australia	11 (9.82%)	4 (7.69%)	2 (13.33%)
Europe	1 (0.89%)	0 (0%)	0 (0%)
North America	97 (86.61%)	45 (86.54%)	12 (80.00%)
South America	2 (1.79%)	2 (3.85%)	1 (6.67%)
Public health discipline[a]			
Health Behavior	36 (32.14%)	15 (28.85%)	5 (33.33%)
Epidemiology	30 (26.79%)	17 (32.69%)	5 (33.33%)
Health Policy	43 (38.39%)	15 (28.85%)	5 (33.33%)
Biostatistics	14 (12.50%)	7 (13.46%)	2 (13.33%)
Environmental Health	9 (8.04%)	7 (13.46%)	0 (0%)
Total	112 (100%)	52 (46.43%)	15 (13.39%)

[a]*Public Health Discipline was self-reported by participants and more than one discipline could be selected.*

Conference Planning Team and discussed as a larger group. The purpose of the second discussion period was to bring participants across disciplines together to develop transdisciplinary priorities.

Priorities identified in the workshop were analyzed by the Conference Planning Team immediately following session 1. Overarching concepts were developed from the priorities that had been identified by conference participants and mapped to research directions previously published by the authors (Roberts et al., 2021). These common concepts were used to categorize all research priorities and generate a list of 10 emergent research priorities based on frequency of concepts.

2.2.2 Session 2

The 10 emergent research priorities were presented to all participants, who were given the opportunity to vote for their top three priorities *via* a link to an online Poll Everywhere survey (Poll Everywhere, San Francisco, CA). The survey remained open for all conference attendees and speakers to complete until four hours prior to Session 3 to accommodate participants in different time zones. We reported the percent of individuals who voted for each theme, and the top three research priorities were the basis for Session 3.

2.2.3 Session 3

In this session, participants were charged with developing draft objectives to accomplish the top-three ranked research priorities.

Zoom breakout rooms were defined for each of these research priorities and the participants were asked to join the Breakout Room which best aligned with their interests. A template was provided to support the development of objectives, specifying content expectations for SMART Objectives: Specific, Measurable, Action-oriented, Realistic, Time-bound (Doran, 1981). These SMART objectives will be the foundation for ongoing research priority working groups consisting of and led by workshop participants.

3 RESULTS

3.1 Participants

In total, 112 participants registered for the conference and 52 individuals participated during live sessions (**Table 1**). We advertised the availability of recorded speaker sessions for viewing on-demand at later times, so some individuals registered to receive access to recorded sessions without planning to attend live sessions. Among the 52 attendees, 15 participated in the interactive workshop sessions. All fields of public health were represented except for environmental health. Workshop participants came from Australia, South America and North America.

3.2 Sessions 1 and 2: Research Priority Areas

The research priority ideas generated in Session 1 as most important to move the field of precision public health forward and build capacity for precision public health included equity and access, evaluation, research capacity, infrastructure, implementation research, workforce preparation, stakeholder engagement, public education, collaboration and ethical considerations (**Table 2**). Equity and access, evaluation and implementation science were ranked as the top three priorities for precision public health.

3.3 Session 3: Objectives for Research Priority Areas

Due to time constraints participants were not able to fully develop SMART Objectives. Here we report draft objectives that will continue to be developed into SMART objectives.

3.3.1 Equity and Access

The overarching aim of this priority area, as discussed in Sessions 1 and 2, was *to increase the diversity, equity, and inclusion of participants in precision public health research so that everyone has access to it*. During Session 3, the subgroup discussed a need to think critically about diversity, including how it is defined and suggested working from the definition of underrepresented populations used in The *All of Us* Research Program (Mapes et al., 2020). The group proposed that additional work may be needed to identify gaps in health equity related to precision public health in order to ensure that true equity, not simply diverse

TABLE 2 | Precision public health research priorities: themes from breakout session one.

Research priority	Description	% votes *n* = 28
Equity and access	Increase the diversity of participants included in precision public health research so that everyone has access to it	19
Evaluation	Standardize evaluation of precision public health interventions and research (e.g. clinical utility, cost-effectiveness, and patient-reported outcomes)	21
Research capacity	Advance training, mentorship and opportunities for researchers at all levels (particularly early career) in precision public health	8
Infrastructure	Identify data sources, leverage existing databases and improvements in how to store, access and link data from multiple sources	9
Implementation research	Support delivery and long-term sustainability of precision public health research initiatives and interventions	15
Workforce preparation	Prepare health professionals to deliver precision public health interventions, including appropriate training and education	8
Stakeholder engagement	Involve stakeholders (e.g., communities, payers etc.) at all stages of precision public health research	10
Public education	Increase public understanding of precision public health, genetic and genomic risk communication	5
Collaboration	Advance transdisciplinary and cross-industry partnerships in tackling precision public health challenges	4
Ethical considerations	Advance understanding about key ethical considerations in precision public health	1

TABLE 3 | Objectives by priority.

Top three research priority areas	Preliminary objectives
Equity and Access	
	Conduct a scoping review to understand barriers for the inclusion of under-represented populations in precision public health/precision medicine research across the translational spectrum (using NIH All of US definition of under-represented populations)
	Develop a framework for evaluating whether health equity has been adequately integrated into precision public health research and interventions
	Develop a justice-based model for identifying potential harms and unintended consequences in precision public health
	Identify/implement mechanisms for promoting a diverse workforce in precision public health practice and research
Evaluation	
	Consolidate and develop tools to evaluate the effectiveness of precision public health approaches, including: an objective list of quality measures/criteria, collaborative efforts with grant review criteria, predictive measures for evaluated expected value and impact on health outcomes, identification of which predictive strategies/approaches to use, modified existing frameworks in cost-effectiveness and public health evaluation programs, evaluation tools that incorporate qualitative/mixed methods, and quantitative approaches; ways to track precision public health programs to identify where/when evaluation is needed
	Develop competencies to guide training initiatives in precision public health
	Evaluate new precision public health approaches and applications in comparison to more traditional approaches used within the field of public health (e.g., cost-effectiveness)
	Link with implementation scientists to undertake dissemination of best practices related to precision public health
	Develop metrics to evaluate the success of evaluations in guiding research and practice directions
Implementation Science	
	Promote stakeholder (e.g., community, patient, clinician, policymakers, payers) engagement and use of measures of feasibility and acceptability (ideally common measures) during pre-implementation phases of precision public health programs
	Apply implementation science to address technical needs (e.g., electronic health records) for precision public health research and practice
	Design for dissemination, develop research programs that have sustainability and spread plans (e.g., model after National Center for Advancing Translational Sciences RFA or after how Patient Centered Outcomes Research Institute mandates specific things on community engagement)
	Create a repository for findings on successful implementation strategies, sharing knowledge across settings, not limited to the high burden of creating peer reviewed literature, more rapid sharing, accessible to clinicians not just researchers
	Conduct research that evaluates implementation of precision public health iteratively and includes implementation needs in cost-effectiveness/economic modeling

recruitment, is achieved. Diversity was discussed in terms of socioeconomics, race/ethnicity, geography, as well as other dimensions of diversity yet to be identified through health equity research in precision public health. In addition, the group discussed a need to consider equity and access across the translational research spectrum, including who is included in precision public health and precision medicine research. Specific objectives primarily included objectives that were foundational to better understanding and laying the groundwork for equity research in precision public health (**Table 3**). Further, it was discussed that in places where known disparities in equity and access to precision public health exist (e.g., access to genetic testing for hereditary cancer conditions), work to intervene on them should advance.

3.3.2 Evaluation

This group discussed how to evaluate whether "the right intervention is given to the right population at the right time" (Khoury et al., 2016). The general aim of this priority area was *to develop evaluation metrics and tools that are specific enough to be meaningful across diverse settings, and also allow for adaptation to specific settings.* Specific objectives proposed for this research priority area focused on consolidating and adapting frameworks and tools to evaluate effectiveness, develop metrics for precision public health outcomes and training initiatives that can apply to qualitative and quantitative approaches, as well as develop, evaluate, and compare new precision public health approaches to traditional methods (**Table 3**). Finally, the group also emphasized the need for developing standards by which to identify areas in precision public health where evaluation is most needed.

3.3.3 Implementation Research

A number of specific objectives were developed to *support the delivery and long-term sustainability of precision public health using the tools of implementation science.* The group discussed sub-objectives across different phases of precision public health translation including: pre-implementation (stakeholder engagement, assessment of feasibility and acceptability), implementation (e.g., attending to technical needs) and sustainability (scale and spread, sharing knowledge, iterative evaluation) (**Table 3**).

4 DISCUSSION

Our workshop participants developed three research priority areas for the field of precision public health: Equity and access, evaluation and implementation research. These priority areas are the foundation for ongoing working groups following the conference. While the third session aimed to create SMART objectives for each research priority, the participants ended up developing broader objectives given the available time. As a first charge, these groups will work to refine objectives to be SMART objectives and develop a set of group goals to begin advancing research in these priority areas.

4.1 Health Equity

Health equity has been a long-standing concern related to the field of precision public health, in particular as it relates to potential unintended consequences on existing health disparities if innovations are not accessible in an equitable manner (Korngiebel et al., 2017). At the same time, this concern for health equity has been viewed as a core reason for why precision public health research is imperative in an era of precision medicine and precision prevention. Precision public health can study issues of equity in precision public health research and practice and tailor strategies and initiatives to improve equitable access to high quality care (Roberts et al., 2021). Further, health equity must be considered not just in the implementation of precision public health, but also across the translational research pathway (Landry et al., 2018).

To date, much of the existing health equity work that has been done in precision public health has been related to issues of racial and ethnic diversity. For instance, extensive research has demonstrated racial and ethnic disparities in access to genetic testing for hereditary breast and ovarian cancer (Williams et al., 2019) as well as Lynch syndrome (Dharwadkar et al., 2022). Interventions to ameliorate these disparities must be developed with intentions to sustain and spread them across settings. Other dimensions of diversity have been less explored, for example geographic, gender, and ability diversity, and for this reason, participants in the working group believed additional work to fully understand who is at risk of falling behind in precision public health is needed.

With this knowledge in hand, justice-based frameworks and models for providing health equity in precision public health are needed. An existing framework for precision public health by Olstad and McIntyre defines precision public health as the study of how different dimensions of social position interact to shape health risk for precisely defined population groups, while also integrating relevant biological and behavioural considerations (Olstad and McIntyre, 2019). Such frameworks can serve a foundation for work by researchers and practitioners in the field of precision public health to promote health equity. Finally, a need to build capacity for precision public health research through training the next generation of precision public health researchers has been established in the literature (Allen et al., 2019a, 2019b; Pearson et al., 2020). This group called for specific attention to promoting diversity among precision public health researchers, aligning with calls for promoting diversity in genomics research more broadly (Robbins et al., 2021).

4.2 Evaluation

As the field of precision public health continues to develop, there is an urgent need to assess methods and common measures (both qualitative and quantitative) for precision public health research, including predictive analytics. Indeed, others in the field have noted the challenges of heterogeneous data measures and sources on their effective use for predictive analytics, as the field of precision public health advances (Pearson et al., 2020).

Developing common outcomes metrics to evaluate the use and effectiveness of precision public health is an area of recognized need (Doyle et al., 2018). In 2018, a team of multidisciplinary researchers developed common metrics for assessing the implementation of state public health programs aimed to improve Hereditary Breast and Ovarian Cancer and Lynch syndromes. The team, consisting of diverse stakeholders in implementation science, patient advocacy, medical genetics, health literacy, disparities and public health practitioners, developed 38 outcomes. As noted by the authors, additional efforts to test the validity of these outcomes and develop outcomes for other types of precision public health efforts are still needed, including standard metrics for evaluating the costs of precision public health interventions.

4.3 Implementation Science

Prior work has demonstrated a gap in literature and research that bridges the fields of genomic medicine and implementation science (Roberts et al., 2019, 2017). Similarly, the implementation sub-group identified a need to merge more broadly precision public health with implementation science. Other work in the field of precision public

health has recognized this need as well from translating genomics into clinical settings (Veterans Health Administration, 2021; Chambers et al., 2016; Genomics, 2020) to advancing state precision public health initiatives (Doyle et al., 2018).

4.4 Future Directions and Limitations

Cutting across these three areas was a recognized need for increased capacity building for precision public health researchers in health equity, evaluation methods, and implementation science. Additionally, areas of overlap identified between these three priorities offer opportunities for growth of the field. For example, themes of advancing research in implementation and health equity arose and have been supported in the literature (Yousefi Nooraie et al., 2020), as well as overlap between advancing evaluation of precision public health and implementation science. A recent JACC State of the Art Review reported a need to crosscut predictive analytics methods with implementation science (Pearson et al., 2020). Thus, future work across our priority areas will be essential to drive growth in precision public health research and implementation in practice. Finally, while health equity, evaluation and implementation science were prioritized, additional priority areas were identified during Session 1. Future work should further explore research priorities within these areas as well.

These research priorities lists were developed with input from 15 engaged precision public health researchers and practitioners: Given the small number of researchers who participated in this process, we are likely missing some key perspectives. Future efforts will continue to discern valuable directions for research in precision public health and engage diverse precision public health research disciplines in these efforts through working groups. We also plan to develop the Transdisciplinary Conference for Future Leaders in Precision Public Health into an annual event bringing together researchers, clinicians, and policymakers to refine continually research directions for the field. At future conferences, we will intentionally seek increased participation from an international audience. We will engage our professional networks at the CDC Office of Genomics and Precision Public Health (CDC, 2021) and the PharmAlliance network (PharmAlliance, 2022) to conduct widespread promotion to international researchers. Additionally, we plan to offer opportunities for funding support for travel to encourage diverse participation by an international audience with specific travel awards reserved for individuals from low- and middle-income countries.

5 CONCLUSION

Health equity and access, evaluation and implementation science related objectives in precision public health have been developed and continue to be refined and cross-examined by current working groups. Next steps to address objectives raised by these groups will bring us closer to advancing the field of precision public health.

DATA AVAILABILITY STATEMENT

The deidentified raw data supporting the conclusion of this article will be made available by the authors upon request, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MR, ET, AS, LL, DO, and CA contributed to the conception of the study. MR, JM, CA, LP, and ET contributed to the design, organization, and analysis of the study. MR wrote the first draft of the manuscript; ET, CA, LP, DO, LL, JM, and AS provided feedback and LP and MR revised the manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Allen, C. G., Fohner, A. E., Landry, L., Paul, J. L., Smith, S. G., Turbitt, E., et al. (2019b). Perspectives from Early Career Investigators Who Are "Staying in the Game" of Precision Public Health Research. *Am. J. Public Health* 109, 1186–1187. doi:10.2105/AJPH.2019.305199

Allen, C. G., Fohner, A. E., Landry, L., Paul, J., Smith, S. G., Turbitt, E., et al. (2019a). Early Career Investigators and Precision Public Health. *Lancet* 394, 382–383. doi:10.1016/S0140-6736(19)30498-2

CDC (2021). About Us | Genomics | CDC [WWW Document]. Available at: https://www.cdc.gov/genomics/about/index.htm (Accessed 427, 22).

Chambers, D. A., Feero, W. G., and Khoury, M. J. (2016). Convergence of Implementation Science, Precision Medicine, and the Learning Health Care System. *JAMA* 315, 1941–1942. doi:10.1001/jama.2016.3867

Cooperrider, D., and Whitney, D. (2005). *Appreciative Inquiry*. Oakland: Berrett-Koehler Publishers, 37–48.

Dharwadkar, P., Greenan, G., Stoffel, E. M., Burstein, E., Pirzadeh-Miller, S., Lahiri, S., et al. (2022). Racial and Ethnic Disparities in Germline Genetic Testing of Patients with Young-Onset Colorectal Cancer. *Clin. Gastroenterology Hepatology* 20, 353–361. doi:10.1016/j.cgh.2020.12.025

Doran, G. (1981). There's a S.M.A.R.T. Way to Write Management's Goals and Objectives. *Manag. Rev.* 70, 35–36.

Doyle, D. L., Clyne, M., Rodriguez, J. L., Cragun, D. L., Senier, L., Hurst, G., et al. (2018). Proposed Outcomes Measures for State Public Health Genomic Programs. *Genet. Med.* 20, 995–1003. doi:10.1038/gim.2017.229

Genomics (2020). Implementing Genomics in Practice (IGNITE) [WWW Document]. Available at: https://www.genome.gov/Funded-Programs-Projects/Implementing-Genomics-in-Practice-IGNITE (Accessed November 7, 2020).

Khoury, M. J., and Holt, K. E. (2021). The Impact of Genomics on Precision Public Health: Beyond the Pandemic. *Genome Med.* 13, 67. doi:10.1186/s13073-021-00886-y

Khoury, M. J., Iademarco, M. F., and Riley, W. T. (2016). Precision Public Health for the Era of Precision Medicine. *Am. J. Prev. Med.* 50, 398–401. doi:10.1016/j.amepre.2015.08.031

Korngiebel, D. M., Thummel, K. E., and Burke, W. (2017). Implementing Precision Medicine: The Ethical Challenges. *Trends Pharmacol. Sci.* 38, 8–14. doi:10.1016/j.tips.2016.11.007

Landry, L. G., Ali, N., Williams, D. R., Rehm, H. L., and Bonham, V. L. (2018). Lack of Diversity in Genomic Databases Is A Barrier to Translating Precision Medicine Research into Practice. *Health Aff.* 37, 780–785. doi:10.1377/hlthaff.2017.1595

Mapes, B. M., Foster, C. S., Kusnoor, S. V., Epelbaum, M. I., AuYoung, M., Jenkins, G., et al. (2020). Diversity and Inclusion for the All of Us Research Program: A Scoping Review. *PLOS ONE* 15, e0234962. doi:10.1371/journal.pone.0234962

Olstad, D. L., and McIntyre, L. (2019). Reconceptualising Precision Public Health. *BMJ Open* 9, e030279. doi:10.1136/bmjopen-2019-030279

Pearson, T. A., Califf, R. M., Roper, R., Engelgau, M. M., Khoury, M. J., Alcantara, C., et al. (2020). Precision Health Analytics with Predictive Analytics and Implementation Research. *J. Am. Coll. Cardiol.* 76, 306–320. doi:10.1016/j.jacc.2020.05.043

Pharmalliance (2022). About PharmAlliance – PharmAlliance. Available at: https://www.pharmalliance.org/pharmalliance-about/ (Accessed April 27, 2022).

PharmSci (2021). UNC Eshelman School of Pharmacy. Available at: https://pharmacy.unc.edu/pharmsci2021/ (Accessed 117, 22).

Robbins, S. M., Daulton, C. R., Hurle, B., and Easter, C. (2021). The NHGRI Short Course in Genomics: Energizing Genetics and Genomics Education in Classrooms Through Direct Engagement Between Educators and Scientists. *Genet. Med.* 23, 222–229. doi:10.1038/s41436-020-00962-5

Roberts, M. C., Clyne, M., Kennedy, A. E., Chambers, D. A., and Khoury, M. J. (2019). The Current State of Funded NIH Grants in Implementation Science in Genomic Medicine: A Portfolio Analysis. *Genet. Med.* 21, 1218–1223. doi:10.1038/gim.2017.180

Roberts, M. C., Fohner, A. E., Landry, L., Olstad, D. L., Smit, A. K., Turbitt, E., et al. (2021). Advancing Precision Public Health Using Human Genomics: Examples from the Field and Future Research Opportunities. *Genome Med.* 13, 97. doi:10.1186/s13073-021-00911-0

Roberts, M. C., Kennedy, A. E., Chambers, D. A., and Khoury, M. J. (2017). The Current State of Implementation Science in Genomic Medicine: Opportunities for Improvement. *Genet. Med.* 19, 858–863. doi:10.1038/gim.2016.210

Veterans Health Administration (2021). PHASER Program - National Oncology Program Office [WWW Document]. Available at: https://www.cancer.va.gov/phaser.asp (Accessed November 7, 2021).

Williams, C. D., Bullard, A. J., O'Leary, M., Thomas, R., Redding, T. S., and Goldstein, K. (2019). Racial/Ethnic Disparities in BRCA Counseling and Testing: A Narrative Review. *J. Racial Ethn. Health Disparities* 6, 570–583. doi:10.1007/s40615-018-00556-7

Yousefi Nooraie, R., Kwan, B. M., Cohn, E., AuYoung, M., Clarke Roberts, M., Adsul, P., et al. (2020). Advancing Health Equity Through CTSA Programs: Opportunities for Interaction Between Health Equity, Dissemination and Implementation, and Translational Science. *J. Clin. Trans. Sci.* 4, 168–175. doi:10.1017/cts.2020.10

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Impact of Proband Indication for Genetic Testing on the Uptake of Cascade Testing Among Relatives

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Although multiple factors can influence the uptake of cascade genetic testing, the impact of proband indication has not been studied. We performed a retrospective, cross-sectional study comparing cascade genetic testing rates among relatives of probands who received either diagnostic germline testing or non-indication-based proactive screening via next-generation sequencing (NGS)-based multigene panels for hereditary cancer syndromes (HCS) and/or familial hypercholesterolemia (FH). The proportion of probands with a medically actionable (positive) finding were calculated based on genes associated with Centers for Disease Control and Prevention (CDC) Tier 1 conditions, HCS genes, and FH genes. Among probands with a positive finding, cascade testing rates and influencing factors were assessed. A total of 270,715 probands were eligible for inclusion in the study (diagnostic n = 254,281,93.9%; proactive n = 16,434, 6.1%). A positive result in a gene associated with a CDC Tier 1 condition was identified in 10,520 diagnostic probands (4.1%) and 337 proactive probands (2.1%), leading to cascade testing among families of 3,305 diagnostic probands (31.4%) and 36 proactive probands (10.7%) ($p < 0.0001$). A positive result in an HCS gene was returned to 23,272 diagnostic probands (9.4%) and 970 proactive probands (6.1%), leading to cascade testing among families of 6,611 diagnostic probands (28.4%) and 89 proactive probands (9.2%) ($p < 0.0001$). Cascade testing due to a positive result in an HCS gene was more commonly pursued when the diagnostic proband was White, had a finding in a gene associated with a CDC Tier 1 condition, or had a personal history of cancer, or when the proactive proband was female. A positive result in an FH gene was returned to 1,647 diagnostic probands (25.3%) and 67 proactive probands (0.62%), leading to cascade testing among families of 360 diagnostic probands (21.9%) and 4 proactive probands (6.0%) ($p < 0.01$). Consistently higher rates of cascade testing among families of diagnostic probands may be due to a perceived urgency because of personal or family history of disease. Due to the proven clinical benefit of cascade testing, further research on obstacles to systematic implementation and uptake of testing for relatives of any proband with a medically actionable variant is warranted.

Keywords: cascade testing, genetic testing, diagnostic testing, proactive screening, hereditary cancer syndromes, familial hypercholesterolemia, CDC tier 1 conditions

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INTRODUCTION

Cascade testing is the process of providing genetic counseling and testing to at-risk blood relatives following the detection of a pathogenic variant in a disease-causing gene in a family member (i.e., the proband). Confirming the presence (or absence) of a pathogenic variant in at-risk relatives can inform clinical management, including both preventative measures for unaffected relatives and potential changes in treatment for affected relatives. For example, given a proband with diagnosed breast cancer and a pathogenic variant in *BRCA1*, an unaffected relative who is confirmed to have the same genetic variant may increase mammography screenings or opt for risk-reducing surgery (Daly et al., 2021). The same unaffected relative, if confirmed negative for the pathogenic *BRCA1* variant, could likely forgo escalated screenings or other preventive interventions. A recent study estimated that it would take 9.9 years to detect all carriers of a pathogenic variant in one of 18 genes associated with a hereditary cancer syndrome (HCS) in the United States (including *BRCA1*) if cascade testing were used, compared with 59.5 years if it were not (Offit et al., 2020). Further, cascade testing has the ability to inform reproductive health decisions, especially in relatives who have been identified as carriers of an autosomal recessive disease, and has been demonstrated to be a cost-effective approach for identifying at-risk individuals across many disease types, especially in young, unaffected relatives (Marks et al., 2002; Wonderling et al., 2004; Ademi et al., 2014; Grosse, 2015; Kerr et al., 2017; O'Brien et al., 2021). As a result, cascade testing has immense potential for improving the efficiency of healthcare resource utilization by reducing the burden of care for individuals and families as well as health systems.

Most studies of cascade testing have focused on the genes associated with Tier 1 conditions as established by the Centers for Disease Control and Prevention (CDC), which include hereditary breast and ovarian cancer (HBOC), Lynch syndrome, and familial hypercholesterolemia (FH) (Centers for Disease Control and Prevention, 2021). Evidence demonstrating the utility of cascade testing has led to recommendations and guidelines from professional societies and from the CDC that encourage extending testing to at-risk relatives (Nordestgaard et al., 2013; Hampel et al., 2015; Randall et al., 2017; Committee on Gynecologic Practice, 2018; Sturm et al., 2018; Daly et al., 2021).

Despite mounting evidence on the utility of cascade testing, uptake rates among at-risk relatives remain low overall, though vary across clinical settings (Cernat et al., 2021). Most studies focusing on genes associated with HCS report cascade testing uptake rates between 30 and 60% (Fehniger et al., 2013; Menko et al., 2019; Lee et al., 2021). Uptake rates have been much lower (4–12%) among families with FH in the United States (Ahmad et al., 2016; Gidding et al., 2020; Ajufo et al., 2021), but much higher (30% up to 90%) among families with FH in other Western countries (Marks et al., 2006; Ahmad et al., 2016; van den Heuvel et al., 2020). Limited data are available on cascade testing uptake for proactive or non-indication-based genetic screening, though results from the Electronic Medical Records and Genomics (eMERGE) phase III study demonstrated that only about one-third of probands who received non-indication-based screening reported sharing their test results with their relatives (Wynn et al., 2021). In the present study, we assessed differences in uptake of cascade testing between relatives of probands who received indication-based diagnostic genetic testing and relatives of probands who received proactive, non-indication-based screening for genes associated with HCS or FH.

MATERIALS AND METHODS

Study Population and Design

Two retrospective cohorts of unrelated probands unselected for sex, self-reported ancestry, or age were compiled with individuals who underwent diagnostic germline genetic testing or proactive screening at Invitae from January 2017 through March 2021.

The diagnostic proband cohort included individuals who had clinician-ordered, indication-based testing via the Invitae Common Hereditary Cancers Panel (up to 47 genes) or the Invitae Familial Hypercholesterolemia Panel (up to 4 genes). Specific clinical criteria that led to clinician-ordered testing (e.g., the individual met guidelines from professional societies for testing) were unknown and thus individuals were unselected for test indication (i.e., personally affected versus family history).

The proactive proband cohort included individuals who were referred by clinicians for screening via the Invitae Cancer Screen (up to 61 genes), the Invitae Cardio Screen (up to 77 genes), or the Invitae Genetic Health Screen (up to 147 genes). Genes for inclusion in these panels were selected based on published guidance from the American College of Medical Genetics and Genomics (ACMG) and ClinGen Working groups, in addition to clinical studies establishing personal risk for monogenic disorders (Foreman et al., 2013; Green et al., 2013; Dewey et al., 2016; Webber et al., 2018). Probands undergoing non-indication-based screening have been described previously (Haverfield et al., 2021). In brief, all probands were included in the analysis, regardless of a personal or family history of cancer or cardiovascular disease. Individuals were excluded only if a familial variant associated with a condition on the screening panel had been previously identified.

In both cohorts, if a proband harbored at least one clinically significant variant (including carrier status), then the proband's relatives were eligible for cascade testing for the identified variant(s). A clinically significant variant was defined as a pathogenic/likely pathogenic (P/LP) variant, a pathogenic-low penetrance (P[LP]) variant, or an increased risk allele (IRA). P(LP) variants are less penetrant compared to other P/LP variants in the same gene and may result in a less obvious Mendelian pattern of inheritance (e.g., *HFE* p.Cys282Tyr or p.His63Asp). IRAs are variants in genes that increase the risk for a condition and have stringent criteria (Ioannidis et al., 2008), but are not associated with a Mendelian inheritance pattern (e.g., *APC* p.Ile1307Lys). Testing was offered at no charge to the relatives for up to 90 days following the proband's test report date, though the cascade testing window was extended to 150 days after March 30, 2020, due to the COVID-19 pandemic. All blood relatives were eligible for cascade testing, and those who received testing

from January 2017 through August 2021 were included in the analysis as long as they were tested for at least one gene in which the proband had a clinically significant variant. Relatives who were tested for the purposes of reclassifying variants of uncertain significance (VUS) in probands within the diagnostic cohort were excluded from the analysis.

Review and analysis of de-identified and aggregated data were approved for waiver of authorization by the WCG Institutional Review Board (study number 1167406).

Genetic Testing

Requested genes were sequenced via a short-read next-generation sequencing (NGS) assay that used genomic DNA extracted from blood or saliva samples as reported previously (Lincoln et al., 2015; Haverfield et al., 2021). A bioinformatics pipeline aligned sequencing reads and utilized community standard and custom algorithms to identify single nucleotide variants (SNVs), small and large insertions or deletions (indels), structural variants, and exon-level copy-number variants (CNVs) (Lincoln et al., 2015, 2021; Truty et al., 2019).

Detected variants were analyzed and interpreted using Sherloc (Nykamp et al., 2017), a points-based framework that incorporates the joint consensus guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Richards et al., 2015). Based on the evidence, variants were classified as benign or likely benign (B/LB), VUS, P/LP, IRA, or P(LP). Clinically significant P/LP, IRA, and P(LP) variants that did not meet stringent NGS quality metrics were confirmed by an orthogonal assay prior to reporting (Lincoln et al., 2019). For individuals who underwent diagnostic testing, variants classified as P/LP, IRA, P(LP), and VUS were reported. For individuals who underwent proactive screening, only P/LP, IRA, and P(LP) findings were reported, as VUS are not reported as part of proactive screening (Haverfield et al., 2021). All results were returned to the ordering healthcare provider, who then oversaw results disclosure to the individual who underwent diagnostic testing or proactive screening.

Individuals were considered to have "positive" findings with medically actionable results if one clinically significant variant was found in a gene associated with an autosomal dominant disorder or two clinically significant variants were found in a gene associated with an autosomal recessive disorder. In addition, male individuals with one clinically significant variant in any gene associated with an X-linked disorder were considered to have positive findings. Female individuals with one clinically significant variant in a gene associated with an X-linked dominant disorder or two clinically significant variants in a gene associated with an X-linked recessive disorder were considered to have positive findings. A carrier finding was classified as one clinically significant variant in a gene associated with an autosomal recessive disorder in any individual or one clinically significant variant in a gene associated with an X-linked recessive disorder in female individuals. Though all results were disclosed to the ordering clinician first, individuals, regardless of result (e.g., no clinically significant result, medically actionable result), could seek post-test genetic counseling through Invitae, though this was not required.

Analysis

Medically Actionable (Positive) and Clinically Significant (Carrier) Findings in Probands

The proportion of probands with positive and carrier findings were calculated for the diagnostic and proactive cohorts. The three primary comparisons were based on genes that were analyzed in both cohorts (i.e., CDC Tier 1 conditions, HCS, and FH genes). Demographics of each of these groups were also summarized.

Eleven genes associated with CDC Tier 1 conditions (*APOB*, *BRCA1*, *BRCA2*, *EPCAM*, *LDLR*, *LDLRAP1*, *MLH1*, *MSH2*, *MSH6*, *PCSK9*, and *PMS2*) were analyzed in all probands (regardless of panel type). Forty-five HCS genes available to both cohorts were analyzed among patients who underwent diagnostic testing or proactive screening for HCS genes (**Supplementary Table S1**). Similarly, four FH genes available to both cohorts were analyzed among individuals who underwent testing or screening for FH. Proactive probands who received screening through the Invitae Genetic Health Screen were included in both the HCS and FH cohorts, as this panel included genes across both clinical areas. Diagnostic probands who had both the Invitae Common Hereditary Cancers Panel and the Invitae Familial Hypercholesterolemia Panel ordered were also included in both cohorts.

Additional genes were also analyzed if ordered for probands in either cohort. Diagnostic probands who had the Invitae Common Hereditary Cancers Panel had *CTNNA1* and *RAD50* analyzed. Proactive probands who had the Invitae Cardio Screen or the Genetic Health Screen had up to an additional 72 genes associated with other cardiology-related conditions or up to 16 genes associated with other HCS analyzed. The Invitae Genetic Health Screen also included 10 genes associated with other hereditary diseases (e.g., hereditary hemochromatosis [*HAMP*, *HFE*, *HJV*, *SLC40A1 and TFR2*] and malignant hyperthermia susceptibility [*CACNA1S and RYR1*]) that were analyzed in proactive probands only.

Cascade Testing

Among probands with a medically actionable or clinically significant finding, the proportion who had at least one relative undergo cascade testing through Invitae was calculated (i.e., cascade testing rate). Cascade testing uptake rates were compared between the diagnostic and proactive cohorts by calculating the difference in proportion for two independent samples. In addition, the number of relatives tested per proband was analyzed.

Among relatives, demographic characteristics were calculated and stratified according to the proband's result type (e.g., medically actionable result in a shared HCS gene). Concordance of findings between the relative and proband was assessed.

Demographic and Clinical Factors Associated With Cascade Testing Utilization

We also assessed whether any demographic or clinical characteristics of probands influenced the rate of cascade testing among relatives. In both diagnostic and proactive cohorts, probands with medically actionable findings and with relatives who had undergone cascade

TABLE 1 | Demographic information of probands by clinical area[a].

	HCS		FH	
	Diagnostic probands (N = 247,875)	**Proactive probands (N = 15,984)**	**Diagnostic probands (N = 6,503)**	**Proactive probands (N = 10,776)**
Sex, n (%)[b]				
Female	216,965 (87.5)	9,265 (58.0)	3,676 (56.5)	5,296 (49.1)
Male	30,908 (12.5)	6,719 (42.0)	2,827 (43.5)	5,480 (50.9)
Age, years				
Mean (SD)	55.5 (14.5)	48.4 (13.2)	45.0 (20.4)	48.1 (13.0)
Median (Q1, Q3)	55 (45, 67)	48 (37,57)	48 (31, 60)	48 (37, 57)
Self-reported ancestry, n (%)				
Ashkenazi Jewish	7,638 (3.1)	606 (3.8)	86 (1.3)	359 (3.3)
Asian	8,009 (3.2)	1,057 (6.6)	318 (4.9)	739 (6.9)
Black	16,829 (6.8)	233 (1.5)	403 (6.2)	135 (1.3)
French-Canadian	313 (0.1)	32 (0.2)	21 (0.3)	28 (0.3)
Hispanic	17,485 (7.1)	441 (2.8)	480 (7.4)	198 (1.8)
Mediterranean	664 (0.3)	148 (0.9)	43 (0.7)	115 (1.1)
Native American	534 (0.2)	10 (0.1)	15 (0.2)	5 (0.05)
Pacific Islander	350 (0.1)	15 (0.1)	16 (0.3)	7 (0.1)
Sephardic Jewish	271 (0.1)	109 (0.7)	5 (0.1)	23 (0.2)
White	160,173 (64.6)	9,700 (60.7)	3,988 (61.3)	6,696 (62.1)
Multiple ancestries	20,668 (8.3)	1,527 (9.6)	432 (6.6)	1,087 (10.1)
Other	3,889 (1.6)	716 (4.5)	162 (2.5)	373 (3.5)
Unknown	11,052 (4.5)	1,390 (8.7)	534 (8.2)	1,011 (9.4)

FH, familial hypercholesterolemia; HCS, hereditary cancer syndrome; Q, quartile; SD, standard deviation.

[a]Diagnostic probands who had both the Invitae Common Hereditary Cancers Panel and the Invitae Familial Hypercholesterolemia Panel ordered were included in both clinical areas. Proactive probands who had the Invitae Genetic Health Screen were included in the analysis of HCS, and FH, screening results.

[b]Sex was unknown for two diagnostic probands undergoing HCS testing.

testing were compared with probands who had a medically actionable finding but did not have relatives who had undergone cascade testing. These two groups were compared based on the following factors: age at time of testing, sex, self-reported ethincity, and whether the proband had a post-test genetic counseling session provided through Invitae. Two additional comparisons were made for probands who underwent diagnostic testing or proactive screening for HCS: whether the gene was associated with a CDC Tier 1 condition (diagnostic and proactive cohorts) and reported personal history of cancer (diagnostic cohort only). Differences in categorical data were assessed by comparing proportions for two independent samples; differences in age were assessed using 2-sample, 2-tailed t-tests. No comparisons were made for the proactive FH cohort due to small sample sizes.

RESULTS

Proband Characteristics

A total of 270,715 probands were eligible for inclusion in the study: 254,281 (93.9%) who received indication-based diagnostic testing and 16,434 (6.1%) who received non-indication-based proactive screening (**Supplementary Table S2**). Diagnostic testing or proactive screening for HCS genes was completed for 247,875 diagnostic probands and 15,984 proactive probands. Diagnostic testing or proactive screening for FH was completed for 6,503 diagnostic probands and 10,776 proactive probands. Of note, 97 diagnostic probands (0.04%) and 10,326 proactive probands (62.8%) had both HCS and FH genes analyzed.

Demographic information for both cohorts based on clinical area is reported in **Table 1**. Diagnostic probands undergoing genetic testing for HCS were mostly female (87.5%) with a mean age of 55.5 ± 14.5 years. Proactive probands with HCS genes included in the genetic screen were also mostly female (58.0%), with a mean age of 48.4 ± 13.2 years. In both diagnostic and proactive cohorts undergoing testing or screening for FH, approximately half of the probands were female (56.5 and 49.1%, respectively), and the mean ages were 45.0 ± 20.4 years and 48.1 ± 13.0 years, respectively.

Positive Findings and Cascade Testing Rates in Genes Associated With CDC Tier 1 Conditions

A positive result in a gene associated with a CDC Tier 1 condition was identified in 10,520 (4.1%) and 337 (2.1%) of the diagnostic and proactive probands, respectively (**Figure 1A**). The proportion of patients with positive findings varied by gene (**Figure 1B**). Significantly more diagnostic probands than proactive probands with a positive finding in a gene associated with a CDC Tier 1 condition had at least one relative pursue cascade testing (diagnostic $n = 3{,}305$, 31.4%; proactive $n = 36$, 10.7%; $p = 4.76\times10^{-16}$; **Figure 1A**). Compared to proactive probands, a higher proportion of diagnostic probands with a medically actionable finding in each gene had at least one relative pursue cascade testing, ranging from 9.1 to 48.3% (*vs.* 2.4–28.6% among proactive probands (**Figure 1B**).

A total of 7,750 relatives of diagnostic probands (2.3 relatives/proband) and 71 relatives of proactive probands (2.0 relatives/

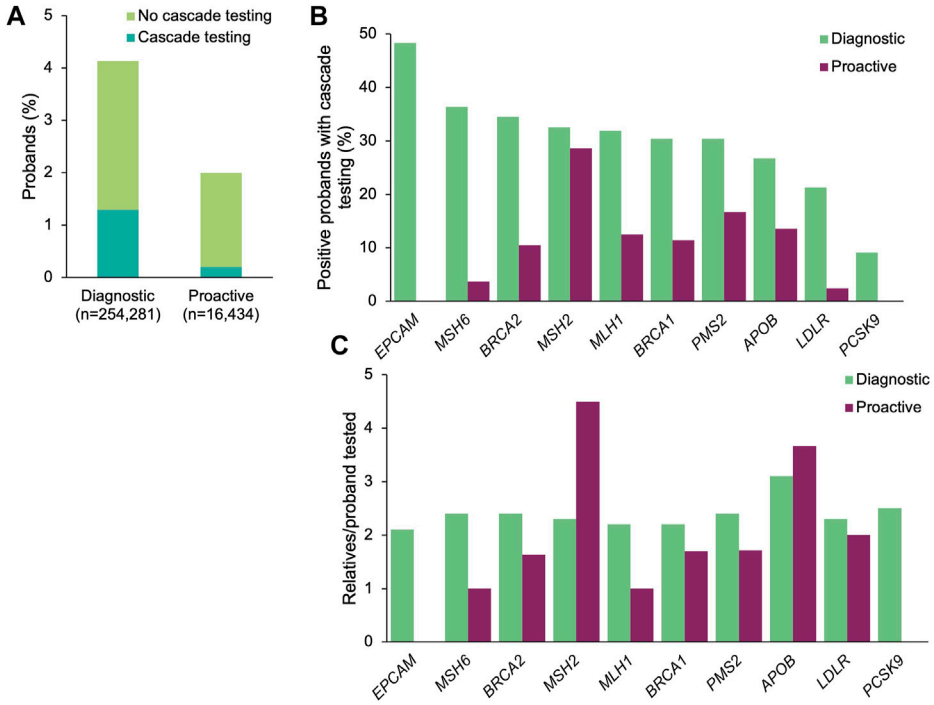

FIGURE 1 | Yield of medically actionable findings in probands among the 11 genes associated with a CDC Tier 1 condition and rates of cascade testing. **(A)** Proportion of diagnostic and proactive probands with a positive result in a gene associated with a CDC Tier 1 condition, stratified by whether cascade testing was pursued. The denominator was the total number of probands that underwent diagnostic testing (n = 254,281) or proactive screening (n = 16,434). **(B)** Proportion of probands with a medically actionable result in a gene associated with a CDC Tier 1 condition with at least one relative who pursued cascade testing. The denominator was the number of probands with a medically actionable result in each gene associated with a CDC Tier 1 condition for each cohort. Probands with a positive finding in more than one gene associated with a CDC Tier 1 condition were included in calculations for each gene. **(C)** Mean number of relatives who pursued cascade testing per proband with a positive result in a gene associated with a CDC Tier 1 condition. If cascade testing was pursued for positive findings in more than one gene detected in the proband, the relatives and probands were included in the calculations for each gene. CDC, Centers for Disease Control and Prevention.

proband) underwent cascade testing. The majority of relatives in both cohorts were first-degree relatives (diagnostic 76.1%, n = 5,896; proactive 73.2%, n = 52), with the remaining being second-degree (10.8%, n = 838; 12.7%, n = 9), third-degree (5.5%, n = 423; 12.7%, n = 9), and more distant relatives (7.7%, n = 593; 1.4%, n = 1). Genes with the most relatives per family tested were *APOB* (3.1 relatives/proband) and *PCSK9* (2.5 relatives/proband) in the diagnostic cohort and in *MSH2* (4.5 relatives/proband) and *APOB* (3.7 relatives/proband) in the proactive cohort (**Figure 1C**).

HCS Panels: Proband Results and Cascade Testing Outcomes

Among the 45 shared HCS genes, a positive result was returned to 23,272 (9.4%) of the diagnostic probands and 970 (6.1%) of the proactive probands (**Figure 2A**). The most common positive findings among diagnostic probands were in *CHEK2* (18.6% of positive findings), *BRCA2* (15.3%), *BRCA1* (11.7%), *ATM* (9.7%), and *APC* (7.3%) (**Figure 2B**). The most common positive findings among proactive probands were in *CHEK2* (24.0%), *APC* (12.6%), *BRCA2* (10.8%), *ATM* (10.6%), and *BRCA1* (9.1%). The frequencies of positive findings across all HCS genes are listed in **Supplementary Table S3**.

Cascade testing was pursued significantly more often when a positive finding in an HCS gene was returned for diagnostic probands than when it was returned for proactive probands (diagnostic n = 6,611, 28.4%; proactive n = 89, 9.2%; p = 1.01×10^{-43}) (**Figure 2A**). In general, diagnostic probands were more likely to have at least one relative pursue cascade testing across all HCS genes compared to proactive probands (**Figure 2B**, **Supplementary Table S3**). However, cascade testing rates were similar for *MSH2*, *SDHA*, *RAD51D*, *NF1*, *CDH1*, *SDHB*, *SDHC*, and *VHL*. A higher proportion of proactive probands with a medically actionable finding in *SDHD* and *TSC1* had at least one relative undergo cascade testing compared to diagnostic probands, but this difference is likely due to the absolute number of probands in each group that had a medically actionable finding in those genes.

A total of 14,590 relatives of diagnostic probands (2.0 relatives/proband) and 168 relatives of proactive probands (1.9 relatives/proband) were tested. Multigene panel testing was ordered for a minority of relatives (diagnostic n = 3,731, 25.6%; proactive n = 29, 17.3%), with the remainder having testing limited to genes with clinically significant and/or medically actionable findings in the proband. Most were first-degree relatives (diagnostic 77.2%, n = 11,261; proactive 78.0%, n = 131), with the remaining being second-degree (10.1%, n = 1469; 8.3%, n = 14), third-degree (4.7%, n = 682; 10.1%, n = 17), or more distant relatives (8.1%, n =

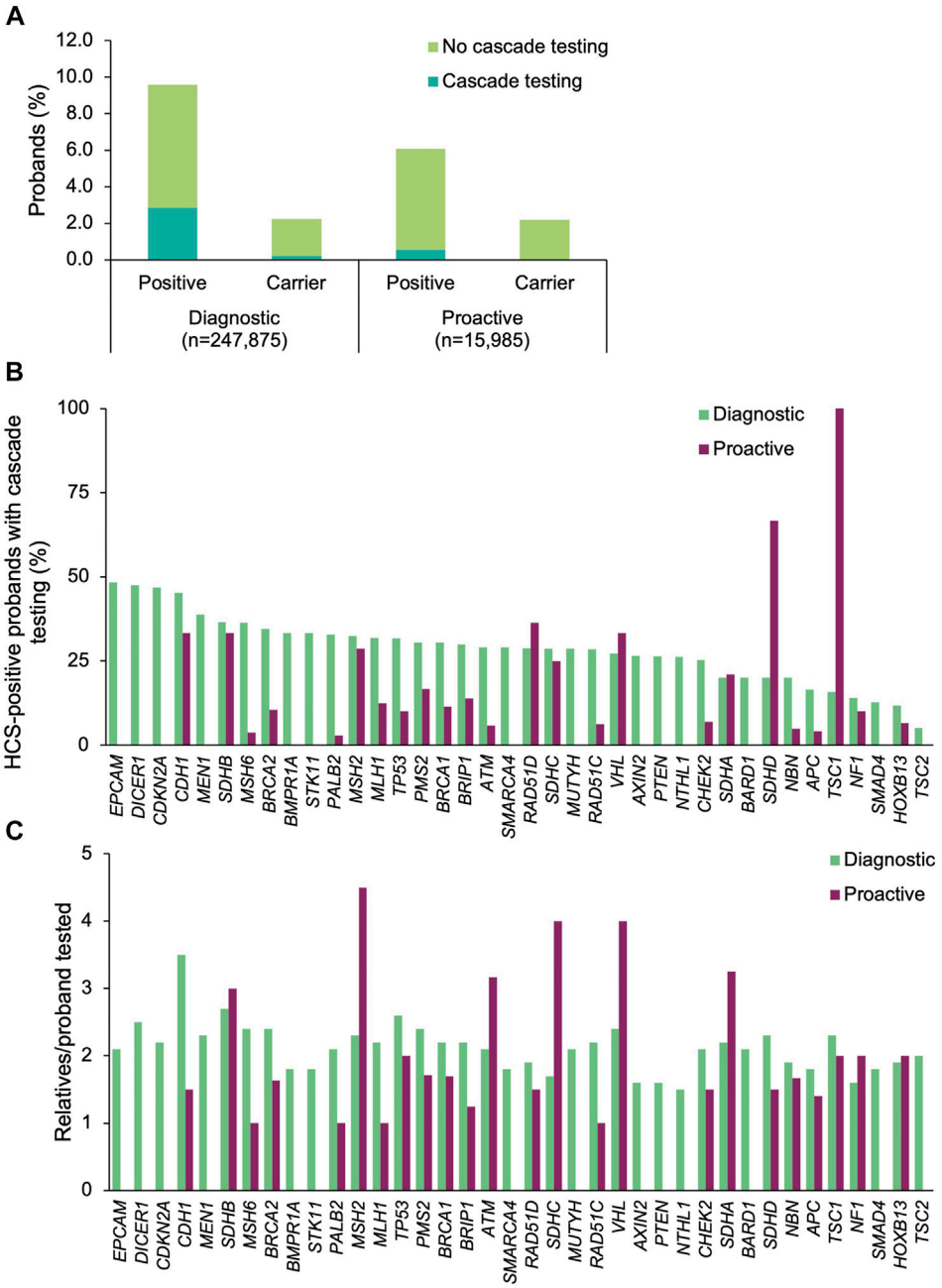

FIGURE 2 | Yield of medically actionable (positive) and clinically significant (carrier) findings in probands who underwent diagnostic testing or proactive screening for HCS genes and rates of cascade testing. **(A)** Proportion of diagnostic and proactive probands with a positive result in an HCS gene, stratified by whether cascade testing was pursued. The denominator was the total number of probands who underwent diagnostic testing (n = 247,875) or proactive screening (n = 15,985) for HCS genes. **(B)** Proportion of probands with a medically actionable result in each HCS gene common to both diagnostic and proactive panels of interest who had at least one relative undergo cascade testing. The denominator was the number of probands with a positive result in each HCS gene for each cohort. Probands with a positive finding in more than one HCS gene were included in calculations for each gene. Thirty-eight of the 45 shared HCS genes are shown. Data for the remaining seven genes can be found in **Supplementary Table S3**. **(C)** Mean number of relatives who pursued cascade testing per proband with a positive result in an HCS gene. If cascade testing was pursued for positive findings in more than one gene detected in the proband, the relatives and probands were included in the calculations for each gene. Data are shown for 38 genes; data for the remaining seven genes can be found in **Supplementary Table S3**. HCS, hereditary cancer syndrome.

1,178; 3.0%, n = 5). The number of relatives per proband that underwent cascade testing was highest for *CDH1* (3.5 relatives/proband), *SDHB* (2.7 relatives/proband), and *TP53* (2.6 relatives/proband) in the diagnostic cohort and for *MSH2* (4.5 relatives/proband), *SDHC* (4.0 relatives/proband), and *VHL* (4 relatives/proband) in the proactive cohort (**Figure 2C**).

TABLE 2 | Demographic information of relatives.

	HCS		FH	
	Diagnostic relatives (N = 14,590)	**Proactive relatives (N = 168)**	**Diagnostic relatives (N = 873)**	**Proactive relatives (N = 13)**
Sex, n (%)[a]				
Female	10,039 (68.8)	115 (68.5)	468 (53.6)	7 (53.8)
Male	4,550 (38.2)	53 (31.5)	405 (46.4)	6 (42.2)
Age, years				
Mean (SD)	46.4 (17.7)	44.6 (20.6)	27.6 (19.7)	25.9 (20.5)
Median (Q1, Q3)	6 (33, 60)	42.5 (27, 63)	22 (11, 43)	15 (9, 37)
Self-reported ancestry, n (%)				
Ashkenazi Jewish	367 (2.5)	13 (7.7)	4 (0.5)	0
Asian	336 (2.3)	9 (5.4)	39 (4.5)	10 (76.9)
Black	361 (2.5)	0	18 (2.1)	0
French-Canadian	25 (0.2)	0	1 (0.1)	0
Hispanic	920 (6.3)	14 (8.3)	44 (5.0)	0
Mediterranean	30 (0.2)	3 (1.8)	1 (0.1)	0
Native American	26 (0.2)	0	0	0
Pacific Islander	3 (0.02)	0	0	0
Sephardic Jewish	54 (0.4)	1 (0.6)	0	0
White	10,700 (73.3)	105 (62.5)	642 (73.5)	1 (7.7)
Multiple ancestries	1,061 (7.3)	14 (8.3)	35 (4.0)	2 (15.4)
Other	177 (1.2)	3 (1.8)	28 (3.2)	0
Unknown	530 (3.6)	6 (3.6)	61 (7.0)	0
Relationship to proband				
FDR	11,261 (77.2)	131 (78.0)	702 (80.4)	11 (84.6)
SDR	1469 (10.1)	15 (8.9)	92 (10.5)	2 (15.4)
TDR	682 (4.7)	17 (10.1)	47 (5.4)	0
More distant	1178 (8.1)	5 (3.0)	32 (3.7)	0

FDR, first-degree relative; FH, familial hypercholesterolemia; HCS, hereditary cancer syndrome; Q, quartile; SD, standard deviation; SDR, second-degree relative; TDR, third-degree relative.

[a]*Sex of one diagnostic relative was unknown among diagnostic probands undergoing HCS testing.*

Relatives in both cohorts were mostly female (diagnostic 68.8%, proactive 68.5%) and self-reported White (diagnostic 73.3%, proactive 62.5%), with a similar mean age at testing (diagnostic 46.4 ± 17.7 years, proactive 44.6 ± 20.6 years) (**Table 2**). A total of 6,422 (44.0%) and 69 (41.1%) of the relatives of diagnostic and proactive probands, respectively, had at least one clinically significant finding that was consistent with the positive finding in the proband. Additional findings were found in 282 relatives of diagnostic probands, 262 of whom had multigene panel testing. In total, 205 relatives had a finding in another gene on the Common Hereditary Cancers Panel, 45 had a different clinically significant finding in the same gene as the proband's clinically significant finding, and 32 had a clinically significant finding in a gene that was not analyzed in the proband. One (3.4%) relative of a proactive proband who pursued testing as a result of a positive finding in a shared HCS gene had a positive finding in another gene.

To understand which factors may increase the likelihood of cascade testing, the differences in cascade testing uptake rates among probands with a positive result were compared based on demographics (**Supplementary Table S4**), whether genetic counseling services through Invitae were utilized, whether the finding was in a gene associated with a CDC Tier 1 condition, and whether a personal history of cancer was reported (diagnostic probands only). No differences in genetic counseling utilization were observed for either cohort (**Figure 3A**). Cascade testing was more commonly pursued among proactive probands who were female (11.1 *vs.* 6.8%, $p = 0.019$), (**Figure 3B**). It was also pursued more frequently among diagnostic probands who were White (32.3 *vs.* 21.6%, $p = 2.49\times10^{-69}$) (**Figure 3C**), had a gene finding associated with a CDC Tier 1 condition (33.5 *vs.* 25.3%, $p = 5.91\times10^{-41}$) (**Figure 3D**), or had a personal history of cancer (32.7 *vs.* 18.6%, $p = 4.52\times10^{-108}$) (**Figure 3E**).

A small proportion of diagnostic (n = 5,559, 2.2%) and proactive (n = 350, 2.2%) probands had carrier results returned (in the genes included in this analysis) (**Figure 2A**). At least one relative of 9.4% (n = 524) and 1.7% (n = 6) of the diagnostic and proactive probands, respectively, had cascade testing performed as a result of carrier findings.

FH Panels: Proband Results and Cascade Testing Outcomes

A positive result in at least one of the four FH genes was returned to 1,647 (25.3%) of the diagnostic probands and 67 (0.62%) of the proactive probands (**Figure 4A**). The most common positive findings among diagnostic probands were in *LDLR* (86.4%), *APOB* (12.3%), *PCSK9* (1.3%), and *LDLRAP1* (0.3%). The most common positive findings among proactive probands were in *LDLR* (62.7%), *APOB* (32.8%), *PCSK9* (4.5%). No proactive probands had a positive finding in *LDLRAP1*, though four probands were carriers (see below).

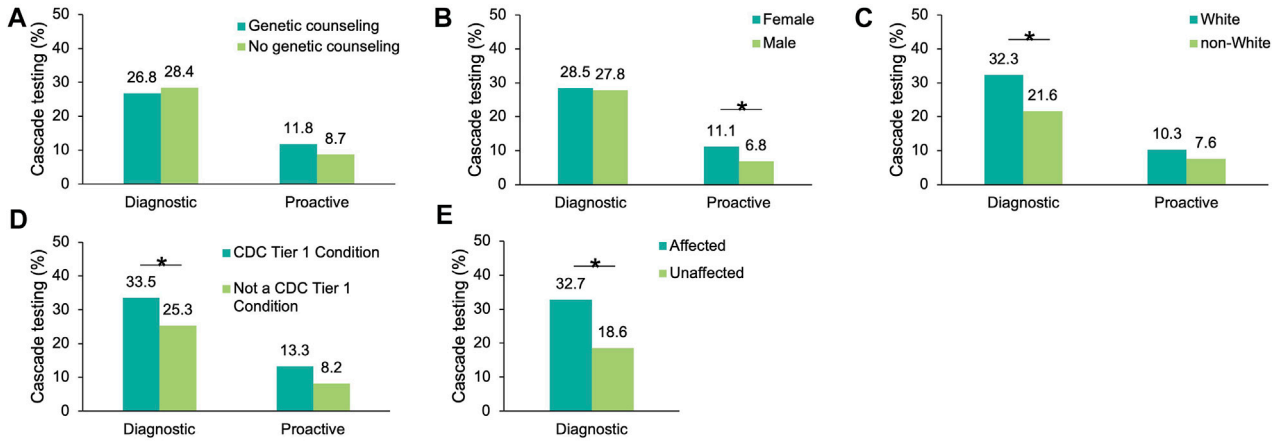

FIGURE 3 | Factors influencing cascade testing among probands with a positive result in an HCS gene. Cascade testing rates were calculated for probands with a positive finding in an HCS gene and stratified by proband characteristic: **(A)** Whether the proband had genetic counseling through Invitae, **(B)** Sex **(C)** Self-reported ancestry, **(D)** Whether the positive finding in the proband was in a gene associated with a CDC Tier 1 condition, and **(E)** Whether diagnostic probands reported a family or personal history of cancer (this information was not available for proactive probands). HCS, hereditary cancer syndrome.

A positive finding in an FH gene in 360 (21.9%) of the diagnostic probands and 4 (6.0%) of the proactive probands led to cascade testing in at least one relative ($p = 0.00183$) (**Figure 4A**). Cascade testing was pursued in relatives of diagnostic probands with positive findings in *LDLR* ($n = 304$, 21.3%), *APOB* ($n = 54$, 26.7%), and *PCSK9* ($n = 2$, 9.1%) (**Figure 4B**). Proactive probands with positive findings in *APOB* ($n = 3$, 13.6%) and *LDLR* ($n = 1$, 2.4%) led to cascade testing. A total of 873 relatives of diagnostic probands (2.4 relatives/proband) and 13 relatives of proactive probands (3.3 relatives/proband) were tested, of whom 37 (4.2%) diagnostic relatives and 2 (15.4%) proactive relatives had multigene panels ordered. The remainder had testing limited to genes with clinically significant and/or medically actionable findings in the proband. Relatives who underwent cascade testing were mostly first-degree relatives (diagnostic 80.4%, $n = 702$; proactive 84.6%, $n = 11$), with the remaining reported to be second-degree (10.5%, $n = 92$; 15.4%, $n = 2$), third-degree (5.4%, $n = 47$; $n = 0$), or more distant related (3.7%, $n = 32$; $n = 0$). The number of relatives per proband who underwent cascade testing was highest for *APOB* (3.1 relatives/proband), *PCSK9* (2.5 relatives/proband), and *LDLR* (2.3 relatives/proband) in the diagnostic cohort and for *APOB* (3.7 relatives/proband) and *LDLR* (2.0 relatives/proband) in the proactive cohort (**Figure 4C**). Demographic characteristics of relatives in both cohorts were similar (**Table 2**). A total of 496 (56.8%) and 4 (30.8%) relatives of diagnostic or proactive probands, respectively, had a positive finding, all of which were consistent with the positive finding in the proband. No relatives of diagnostic or proactive probands who pursued testing as a result of a medically actionable finding in a shared FH gene had a positive finding in another gene. Two relatives of diagnostic probands were carriers for *ABCG8* and one relative of a proactive proband who had a positive finding in *APOB* was also identified as a carrier for *RYR1*. Two (5.4%) diagnostic relatives and zero proactive relatives who had multigene panel testing had a clinically significant finding returned outside of the proband's diagnostic testing or proactive screening results.

To understand which factors may increase the likelihood of cascade testing, the differences in cascade testing uptake rates among probands with a positive result were compared based on demographics (**Supplementary Table S5**) and whether post-test genetic counseling services through Invitae were utilized. Cascade testing was more commonly pursued in proactive probands who had genetic counseling (11.8 *vs.* 8.7%, **Figure 5A**), were male (7.7 *vs.* 3.6%, **Figure 5B**), or non-White (10.1 *vs.* 8.0%, **Figure 5C**). Results in the proactive cohort should be interpreted with caution as the sample size of proactive probands with cascade testing was small ($n = 4$). Cascade testing was pursued more frequently among diagnostic probands who were younger at time of testing (29.4 ± 19.8 years *vs.* 38.6 ± 22.7 years, $p = 1.28 \times 10^{-13}$) or self-reported White (28.3 *vs.* 15.2%, $p = 1.36 \times 10^{-10}$) (**Figure 5C**).

A small proportion of diagnostic ($n = 3$, 0.05%) and proactive ($n = 4$, 0.04%) probands had carrier results returned. No relatives pursued cascade testing as a result of these carrier findings in either cohort.

Findings in Additional Genes Unique to the Diagnostic and Proactive Panels

In addition to the 49 genes that were available on both diagnostic and proactive gene panels of interest, an additional two genes (*RAD50* and *CTNNA1*) were available only on diagnostic panels. A small number (626, 0.3%) of diagnostic probands who had testing via the Invitae Common Hereditary Cancers Panel had a positive result in *RAD50* (no probands had a positive result in *CTNNA1*), 108 (17.3%) of whom had 205 relatives (1.9 relatives/proband) pursue cascade testing.

An additional 98 genes were available only on the proactive panels, including genes associated with HCS ($n = 16$), other non-FH cardiology conditions ($n = 73$), or other conditions

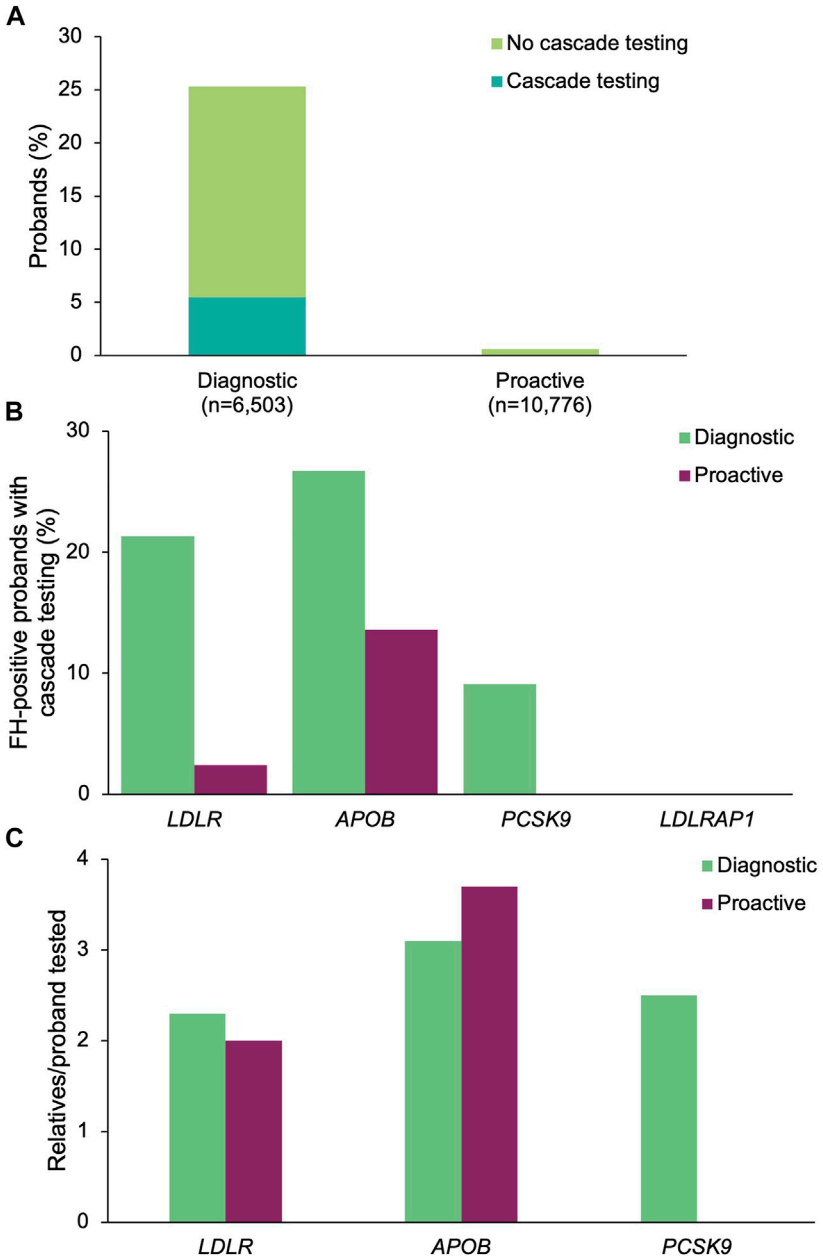

FIGURE 4 | Yield of medically actionable (positive) findings in probands who underwent diagnostic testing or proactive screening for FH genes and rates of cascade testing. **(A)** Proportion of diagnostic and proactive probands with a positive result in an FH gene, stratified by whether cascade testing was pursued. The denominator was the total number of probands who underwent diagnostic testing (n = 6,503) or proactive screening (n = 10,776) for FH genes. **(B)** Proportion of probands with a positive result in each FH gene common to both diagnostic and proactive panels of interest who had at least one relative pursue cascade testing. The denominator was the number of probands with a positive result in each FH gene for each cohort. Probands with a positive finding in more than one FH gene were included in calculations for each gene. **(C)** Mean number of relatives who pursued cascade testing per proband with a positive result in an FH gene. If cascade testing was pursued for positive findings in more than one gene detected in the proband, the relatives and probands were included in the calculations for each gene. FH, familial hypercholesterolemia.

(n = 10) (**Supplementary Table S1**). The proportion of positive results in one of these genes ranged from 0.6% in HCS genes to 9.2% in cardiology genes (**Supplementary Figure S1**). Cascade testing was most commonly pursued for positive findings in an HCS gene (HCS 10.8%, cardiology 2.4%, other clinical areas 1.6%).

DISCUSSION

In addition to the potential utility of genetic testing results to inform an individual's clinical care and outcomes, a positive result has implications for that individual's family. Studies assessing the uptake of cascade testing among relatives in a

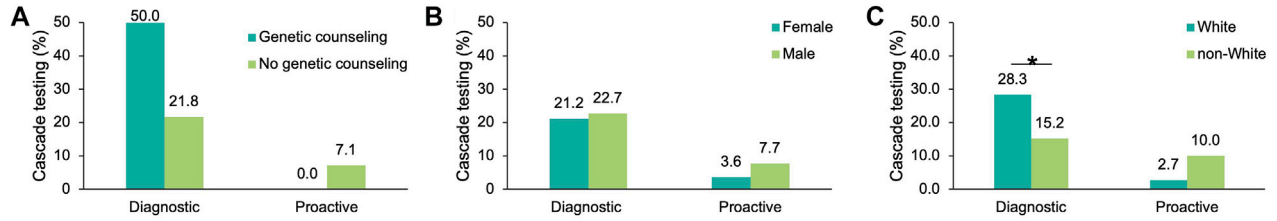

FIGURE 5 | Factors influencing cascade testing rates among probands with a positive result in an FH gene. Cascade testing rates were calculated for probands with a positive finding in an FH gene and stratified by characteristic: **(A)** Whether the proband had genetic counseling through Invitae, **(B)** Sex, and **(C)** Self-reported ancestry. FH, familial hypercholesterolemia.

diagnostic setting have consistently demonstrated that rates are generally low, though they vary based on clinical area and focus only on just a few genes (Fehniger et al., 2013; Menko et al., 2019; Ajufo et al., 2021; Lee et al., 2021). As population-based and proactive screening methods begin to become more widespread, it is critical to understand how these testing approaches may impact at-risk relatives. Currently, the utilization of cascade testing in a non-indication-based, proactive setting is less well understood and uptake rates have not yet been reported. This study compared findings between two cohorts that differed in how NGS was pursued: indication-based diagnostic testing versus non-indication-based proactive screening. The findings reported allow not only for insights into differences between diagnostic and proactive results, but also more generally to ordering patterns for diagnostic testing or proactive screening for HCS and FH. Interestingly, we also gain tangential and preliminary insights into the potential benefits of multigene panel testing in at-risk relatives. This study demonstrates that there is an even larger gap in the uptake of cascade testing in a proactive versus diagnostic setting and highlights the need for further research to understand both the reasons for underutilization of cascade testing and the approaches that could lead to increased uptake rates.

In this study, we find that cascade testing rates were significantly higher among diagnostic probands compared to proactive probands across all comparisons, including testing or screening for any CDC Tier 1 condition, for HCS, and for FH. The findings from this study are the first to begin to investigate which factors may be associated with cascade testing utilization in a proactive setting. Proband characteristics shown to be associated with cascade testing in a diagnostic setting were consistent with our cohort, including self-reported ancestry, sex, and a personal history of disease (Dugan et al., 2003; Hamilton et al., 2005; Gaff et al., 2007; Sharaf et al., 2013; Roberts et al., 2018; Caswell-Jin et al., 2019; Menko et al., 2019; Braley et al., 2021). The only factor that resulted in a significant difference in cascade testing rates in the proactive cohort was sex, with rates higher among female probands. These preliminary findings demonstrate that there may be different factors that influence the utilization of cascade testing depending on the method of testing in the index case. Further prospective studies exploring a wider variety of proband and relative characteristics in relation to cascade testing rates will be critical to developing tools for encouraging and facilitating cascade testing that are tailored to various testing methods (i.e., diagnostic versus proactive).

Two large hurdles must be overcome in order for cascade testing to be pursued; first, the proband must share results with at-risk relatives and second, the relative must make the choice to seek genetic testing. It has been established that results sharing is poor regardless of whether diagnostic testing or proactive screening is ordered (Dugan et al., 2003; Hamilton et al., 2005; Gaff et al., 2007; Elrick et al., 2017; Wurtmann et al., 2018). Reasons for a lack of cascade testing utilization is limited to a diagnostic setting, with no research yet focusing on potential barriers for proband testing in a proactive setting. However, it is likely some of the reasons are similar for both approaches. Diagnostic probands have cited a perceived lack of clinician support and familial relationships as barriers (Dugan et al., 2003; Chivers Seymour et al., 2010; Muir et al., 2012; Hardcastle et al., 2015; Pollard et al., 2020; Srinivasan et al., 2020). Among the limited pool of at-risk relatives who do have results shared with them, only a small proportion end up seeking cascade testing. Previous research has shown that relatives of diagnostic probands do not seek testing because of several perceived hurdles, including cost, the need to make an appointment with a clinician, and concerns about insurance or employment discrimination, even with current legislation barring such discrimination (EEOC, 2008; Hendricks-Sturrup et al., 2019; Srinivasan et al., 2020).

Approaches to encouraging and facilitating cascade testing have been largely limited to a diagnostic setting. However, ongoing studies, such as the IMPACT-FH (Identification Methods, Patient Activation, and Cascade Testing for FH) study (Campbell-Salome et al., 2021), are exploring strategies that increase the uptake of cascade testing in population-based screening programs. However, learnings from the diagnostic setting may provide some insights, including the availability of clinician-drafted letters (Newson and Humphries, 2005; Suthers et al., 2006; Hadfield et al., 2009; Dilzell et al., 2014; Petersen et al., 2019; Kurian and Katz, 2020; Neuner et al., 2020), access to support from foundations focused on a single condition or clinical area (Bell et al., 2015; Wald et al., 2016; McGowan et al., 2021), and access to educational materials that are easily shared outside of a clinical setting (Kardashian et al., 2012; Petersen et al., 2019; Bowen et al., 2020; Jujjavarapu et al., 2021; Nazareth et al., 2021; Nitecki et al., 2021; Snir et al., 2021). When considering approaches to encouraging at-risk

relatives to ultimately seek cascade testing, programs have been designed to offer cascade testing at reduced rates or at no-charge for relatives (Aktan-Collan et al., 2007; Caswell-Jin et al., 2019; Courtney et al., 2019; Invitae, 2021). Preliminary findings in a recent study demonstrated that chatbots are an effective means to facilitating cascade testing (data in press Schmidlen et al., 2022). Regardless of the approach, it is critical that methods used to encourage both results sharing and subsequent cascade testing are accessible to diverse populations (Milo Rasouly et al., 2021).

The sum of these observations demonstrates that there is not likely a one size fits all approach to encouraging cascade testing, and that having several avenues available for both facilitating results sharing and streamlining testing processes will maximize the success of cascade testing initiatives. Especially for probands who are identified in non-indication-based settings, additional efforts to educate probands, as well as tools to help them share information with relatives, will be essential as genetic screening in healthy individuals becomes more widespread. For example, novel approaches utilizing chatbots may not only improve communication with probands but also facilitate results sharing and subsequently help connect relatives to a clinician for cascade testing. This is especially important as genetic counseling may not be sought prior to or after screening in the proband.

In addition to insights into differences between diagnostic and proactive cohorts, ordering behaviors among probands seeking testing or screening for HCS and FH were very different. Strikingly, the absolute number of probands who were tested for HCS and FH panels was very different for both the diagnostic and proactive cohorts. It is possible that this is due to the increased awareness of and testing for hereditary breast and ovarian cancer and Lynch syndrome compared to that of FH. While we observe higher cascade testing uptake for HCS, the number of relatives tested per proband is higher for FH compared to HCS (~3 relatives/proband vs. 2 relatives/proband). We suspect that this is because genetics specialists are providing care to probands being tested for FH in collaboration with the treating clinician (Ingles et al., 2020; Musunuru et al., 2020), while oncologists may have an increased experience and comfort with ordering genetic testing themselves (Hamilton et al., 2021). So while more probands could be referred for HCS testing by a non-genetics specialist, probands tested for FH may more likely be receiving counseling from genetic counselors and as a result, may have higher numbers of relatives tested once results are shared.

Finally, though limited to a minority of relatives, anywhere from ~5 to ~25% of relatives have additional genes (often multigene panel testing) ordered. Among relatives who had probands undergo diagnostic testing or proactive screening for HCS, 7.0% of relatives of diagnostic probands and 3.4% of relatives of proactive probands had a clinically significant finding outside of the proband's findings. This finding demonstrates that panel testing does in fact identify additional risks that would have otherwise been missed had gene-specific testing been ordered. Reasons for missing these clinically significant findings could be a result of, among others, the proband not being tested for that gene or that the relative has a family history associated with another relative unrelated to the proband. Relatives who received a negative result following targeted testing based on proband results could have a false sense of reassurance without understanding that they could have medically actionable variants in other genes. This may be the case even though clinicians take into account an individual's full family history and genetic counseling based on a negative result centers around residual risk. While there may be higher costs related to testing for additional genes, these results underscore the possible benefits of considering broader testing for relatives seeking cascade testing.

Similar to other retrospective cohort studies, this study was limited in the data available for analysis. Our analysis compared two cohorts based on how probands were referred: indication-based diagnostic testing or non-indication-based proactive screening. As a commercial testing laboratory, orders are received from clinicians requesting diagnostic testing as well as individuals seeking proactive screening. The majority of individuals in these cohorts indicated a self-reported White ancestry, which may have biased the results. The socioeconomic factors demonstrated to impact the utilization of genetic testing were not controlled for in this study (Gómez-Trillos et al., 2020; McKinney et al., 2020; Giri et al., 2021). While not a focus in this study, Invitae has sponsored testing programs that eliminate potential financial barriers to diagnostic genetic testing for a number of clinical indications, in addition to research initiatives to help facilitate population screening and cascade testing across more diverse groups (staff reporter, 2021). Novel approaches to improving genetics literacy and awareness across diverse populations have proven to be successful (Milo Rasouly et al., 2021). Among diagnostic probands, the specific reason for testing could not be determined because the test requisition form did not require disclosure of whether the individual for whom testing was ordered had a personal or family history of an HCS or FH. Thus, whether a proband had a personal or family history was unknown for many individuals and was not uniform when shared. However, for a number of hereditary cancer conditions and familial cardiac conditions, current guidelines recommend that family history alone, when meeting certain requirements, is a standalone indication for diagnostic genetic testing in an otherwise unaffected individual (e.g., family history of breast cancer in multiple first degree relatives) (Daly et al., 2021). For these logistic and clinical reasons, we could only assume that diagnostic testing was warranted based on the ordering clinician's evaluation of the individual. Another limitation is that, as the testing laboratory, the total number of relatives that were offered cascade testing could not be determined. As such, the cascade testing uptake rate is based purely on those individuals tested through Invitae with reported relationships disclosed at the time of test requisition. The number of probands with clinically significant results who shared their results with relatives and the number of relatives who ultimately sought testing could not be determined. However, as reported from other studies, it is clear that results sharing and subsequent testing rates are generally low. Further, it is

unknown how many probands sought genetic counseling outside of Invitae. It is expected that most diagnostic probands, but far fewer proactive probands, had received counseling through a clinician or an adjacent clinical service (such as a medical geneticist or genetic counselor). However, this information was not well documented, so assessing the rate of cascade testing based on genetic counseling through Invitae may be an underestimate. Although limited, this study helps to establish preliminary findings that can help to guide future prospective studies.

The results of this study have demonstrated that cascade testing uptake is significantly lower among probands who seek testing in a non-indication-based, proactive setting than among those who are referred for indication-based testing. The barriers and facilitators of cascade testing seem to be similar between the two cohorts, suggesting that approaches that promote family testing in a diagnostic setting could be similarly applied to proactive settings. However, the tools and methods may need to be tailored to these different settings in order to increase cascade testing rates. Such an investigation is underway in individuals undergoing testing for FH as part of a population-based genomic research study (Campbell-Salome et al., 2021). The findings from the present study establish a baseline for future prospective studies designed to understand the reasons for results sharing (or not) among probands and the subsequent influences that encourage relatives to engage with cascade testing.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by WCG Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TS, EE, RN, and EH contributed to the conception of the study. TS, KH, SB, and EH contributed to the methodology of the study. KH generated the study databases, ran formal statistical analyses, and validated the results. TS, SB, KH, and EH curated the databases. SB prepared the first draft of the manuscript and generated figures. EH provided supervision over manuscript development. TS oversaw project administration. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.867226/full#supplementary-material

REFERENCES

Ademi, Z., Watts, G. F., Pang, J., Sijbrands, E. J. G., van Bockxmeer, F. M., O'Leary, P., et al. (2014). Cascade Screening Based on Genetic Testing Is Cost-Effective: Evidence for the Implementation of Models of Care for Familial Hypercholesterolemia. *J. of Clin. Lipidol.* 8, 390–400. doi:10.1016/j.jacl.2014.05.008

Ahmad, Z. S., Andersen, R. L., Andersen, L. H., O'Brien, E. C., Kindt, I., Shrader, P., et al. (2016). US Physician Practices for Diagnosing Familial Hypercholesterolemia: Data from the CASCADE-FH Registry. *J. of Clin. Lipidol.* 10, 1223–1229. doi:10.1016/j.jacl.2016.07.011

Ajufo, E., deGoma, E. M., Raper, A., Yu, K. D., Cuchel, M., and Rader, D. J. (2021). A Randomized Controlled Trial of Genetic Testing and Cascade Screening in Familial Hypercholesterolemia. *Genet. in Med.* 23, 1697–1704. doi:10.1038/s41436-021-01192-z

Aktan-Collan, K., Haukkala, A., Pylvanainen, K., Jarvinen, H. J., Aaltonen, L. A., Peltomaki, P., et al. (2007). Direct Contact in Inviting High-Risk Members of Hereditary Colon Cancer Families to Genetic Counselling and DNA Testing. *J. of Med. Genet.* 44, 732–738. doi:10.1136/jmg.2007.051581

Bell, D. A., Pang, J., Burrows, S., Bates, T. R., van Bockxmeer, F. M., Hooper, A. J., et al. (2015). Effectiveness of Genetic Cascade Screening for Familial Hypercholesterolaemia Using a Centrally Co-Ordinated Clinical Service: An Australian Experience. *Atherosclerosis* 239, 93–100.

Bowen, D. J., Hyams, T., Laurino, M., Woolley, T., Cohen, S., Leppig, K. A., et al. (2020). Development of FamilyTalk: An Intervention to Support Communication and Educate Families About Colorectal Cancer Risk. *J. Cancer Educ.* 35, 470–478.

Braley, E. F., Bedard, A. C., Nuk, J., Hong, Q., Bedard, J. E. J., Sun, S., et al. (2021). Patient Ethnicity and Cascade Genetic Testing: a Descriptive Study of a Publicly Funded Hereditary Cancer Program. *Fam. Cancer*, 1–6. doi:10.1007/s10689-021-00270-0

Campbell-Salome, G., Jones, L. K., Masnick, M. F., Walton, N. A., Ahmed, C. D., Buchanan, A. H., et al. (2021). Developing and Optimizing Innovative Tools to Address Familial Hypercholesterolemia Underdiagnosis. *Circulation Genomic and Precis. Med.* 14, e003120. doi:10.1161/circgen.120.003120

Caswell-Jin, J. L., Zimmer, A. D., Stedden, W., Kingham, K. E., Zhou, A. Y., and Kurian, A. W. (2019). Cascade Genetic Testing of Relatives for Hereditary Cancer Risk: Results of an Online Initiative. *J. Natl. Cancer Inst.* 111, 95–98. doi:10.1093/jnci/djy147

Centers for Disease Control and Prevention (2021). Tier 1 Genomics Applications and Their Importance to Public Health. Available at: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm [Accessed December 8, 2021].

Cernat, A., Hayeems, R. Z., and Ungar, W. J. (2021). Cascade Health Service Use in Family Members Following Genetic Testing in Children: a Scoping Literature Review. *Eur. J. Hum. Genet.* 29, 1601–1610. doi:10.1038/s41431-021-00952-4

Chivers Seymour, K., Addington-Hall, J., Lucassen, A. M., and Foster, C. L. (2010). What Facilitates or Impedes Family Communication Following Genetic Testing

for Cancer Risk? A Systematic Review and Meta-Synthesis of Primary Qualitative Research. *J. Genet. Couns.* 19, 330–342. doi:10.1007/s10897-010-9296-y

Committee on Gynecologic Practice (2018). ACOG Committee Opinion No. 727 Summary: Cascade Testing: Testing Women for Known Hereditary Genetic Mutations Associated with Cancer. *Obstet. Gynecol.* 131, 194–195. doi:10.1097/AOG.0000000000002451

Courtney, E., Chok, A. K.-L., Ting Ang, Z. L., Shaw, T., Li, S.-T., Yuen, J., et al. (2019). Impact of Free Cancer Predisposition Cascade Genetic Testing on Uptake in Singapore. *npj Genom. Med.* 4, 22. doi:10.1038/s41525-019-0096-5

Daly, M. B., Pal, T., Berry, M. P., Buys, S. S., Dickson, P., Domchek, S. M., et al. (2021). Genetic/familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Canc. Netw.* 19, 77–102. doi:10.6004/jnccn.2021.0001

Dewey, F. E., Murray, M. F., Overton, J. D., Habegger, L., Leader, J. B., Fetterolf, S. N., et al. (2016). Distribution and Clinical Impact of Functional Variants in 50,726 Whole-Exome Sequences from the DiscovEHR Study. *Science* 354, aaf6814. doi:10.1126/science.aaf6814

Dilzell, K., Kingham, K., Ormond, K., and Ladabaum, U. (2014). Evaluating the Utilization of Educational Materials in Communicating about Lynch Syndrome to At-Risk Relatives. *Fam. Cancer* 13, 381–389. doi:10.1007/s10689-014-9720-9

Dugan, R. B., Wiesner, G. L., Juengst, E. T., O'Riordan, M., Matthews, A. L., and Robin, N. H. (2003). Duty to Warn At-Risk Relatives for Genetic Disease: Genetic Counselors' Clinical Experience. *Am. J. Med. Genet.* 119C, 27–34. doi:10.1002/ajmg.c.10005

EEOC(2008). The Genetic Information Nondiscrimination Act of 2008 Available at: https://www.eeoc.gov/statutes/genetic-information-nondiscrimination-act-2008 [Accessed December 13, 2021].

Elrick, A., Ashida, S., Ivanovich, J., Lyons, S., Biesecker, B. B., Goodman, M. S., et al. (2017). Psychosocial and Clinical Factors Associated with Family Communication of Cancer Genetic Test Results Among Women Diagnosed with Breast Cancer at a Young Age. *J. Genet. Couns.* 26, 173–181. doi:10.1007/s10897-016-9995-0

Fehniger, J., Lin, F., Beattie, M. S., Joseph, G., and Kaplan, C. (2013). Family Communication of BRCA1/2 Results and Family Uptake of BRCA1/2 Testing in a Diverse Population of BRCA1/2 Carriers. *Jrnl of Gene Coun* 22, 603–612. doi:10.1007/s10897-013-9592-4

Foreman, A. K. M., Lee, K., and Evans, J. P. (2013). The NCGENES Project: Exploring the New World of Genome Sequencing. *North Carolina Med. J.* 74, 500–504. doi:10.18043/ncm.74.6.500

Gaff, C. L., Clarke, A. J., Atkinson, P., Sivell, S., Elwyn, G., Iredale, R., et al. (2007). Process and Outcome in Communication of Genetic Information within Families: a Systematic Review. *Eur. J. Hum. Genet.* 15, 999–1011. doi:10.1038/sj.ejhg.5201883

Gidding, S. S., Sheldon, A., Neben, C. L., Williams, H. E., Law, S., Zhou, A. Y., et al. (2020). Patient Acceptance of Genetic Testing for Familial Hypercholesterolemia in the CASCADE FH Registry. *J. of Clin. Lipidol.* 14, 218–223. doi:10.1016/j.jacl.2020.02.001

Giri, V. N., Shimada, A., and Leader, A. E. (2021). Predictors of Population Awareness of Cancer Genetic Tests: Implications for Enhancing Equity in Engaging in Cancer Prevention and Precision Medicine. *JCO Precis. Oncol.* 5, 1699–1708. doi:10.1200/PO.21.00231

Gómez-Trillos, S., Sheppard, V. B., Graves, K. D., Song, M., Anderson, L., Ostrove, N., et al. (2020). Latinas' Knowledge of and Experiences with Genetic Cancer Risk Assessment: Barriers and Facilitators. *J. Genet. Couns.* 29, 505–517. doi:10.1002/jgc4.1201

Green, R. C., Berg, J. S., Grody, W. W., Kalia, S. S., Korf, B. R., Martin, C. L., et al. (2013). ACMG Recommendations for Reporting of Incidental Findings in Clinical Exome and Genome Sequencing. *Genet. in Med.* 15, 565–574. doi:10.1038/gim.2013.73

Grosse, S. (2015). When Is Genomic Testing Cost-Effective? Testing for Lynch Syndrome in Patients with Newly-Diagnosed Colorectal Cancer and Their Relatives. *Healthcare* 3, 860–878. doi:10.3390/healthcare3040860

Hadfield, S. G., Horara, S., Starr, B. J., Yazdgerdi, S., Marks, D., Bhatnagar, D., et al. (2009). Family Tracing to Identify Patients with Familial Hypercholesterolaemia: the Second Audit of the Department of Health Familial Hypercholesterolaemia Cascade Testing Project. *Ann. Clin. Biochem. Biochem.* 46, 24–32. doi:10.1258/acb.2008.008094

Hamilton, J. G., Symecko, H., Spielman, K., Breen, K., Mueller, R., Catchings, A., et al. (2021). Uptake and Acceptability of a Mainstreaming Model of Hereditary Cancer Multigene Panel Testing Among Patients with Ovarian, Pancreatic, and Prostate Cancer. *Genet. in Med.* 23, 2105–2113. doi:10.1038/s41436-021-01262-2

Hamilton, R. J., Bowers, B. J., and Williams, J. K. (2005). Disclosing Genetic Test Results to Family Members. *J. Nurs. Scholarsh.* 37, 18–24. doi:10.1111/j.1547-5069.2005.00007.x

Hampel, H., Bennett, R. L., Buchanan, A., Pearlman, R., and Wiesner, G. L. (2015). Guideline Development Group, American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee and National Society of Genetic Counselors Practice Guidelines CommitteeA Practice Guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: Referral Indications for Cancer Predisposition Assessment. *Genet. in Med.* 17, 70–87. doi:10.1038/gim.2014.147

Hardcastle, S. J., Legge, E., Laundy, C. S., Egan, S. J., French, R., Watts, G. F., et al. (2015). Patients' Perceptions and Experiences of Familial Hypercholesterolemia, Cascade Genetic Screening and Treatment. *Int.J. Behav. Med.* 22, 92–100. doi:10.1007/s12529-014-9402-x

Haverfield, E. V., Esplin, E. D., Aguilar, S. J., Hatchell, K. E., Ormond, K. E., Hanson-Kahn, A., et al. (2021). Physician-directed Genetic Screening to Evaluate Personal Risk for Medically Actionable Disorders: a Large Multi-Center Cohort Study. *BMC Med.* 19, 199. doi:10.1186/s12916-021-01999-2

Hendricks-Sturrup, R. M., Mazor, K. M., Sturm, A. C., and Lu, C. Y. (2019). Barriers and Facilitators to Genetic Testing for Familial Hypercholesterolemia in the United States: A Review. *Jpm* 9, 32. doi:10.3390/jpm9030032

Ingles, J., Macciocca, I., Morales, A., and Thomson, K. (2020). Genetic Testing in Inherited Heart Diseases. *Heart, Lung and Circulation* 29, 505–511. doi:10.1016/j.hlc.2019.10.014

Invitae (2021). Flexible Follow-Up Testing. Available at: https://www.invitae.com/en/providers/follow-up-testing [Accessed May 9, 2022].

Ioannidis, J. P., Boffetta, P., Little, J., O'Brien, T. R., Uitterlinden, A. G., Vineis, P., et al. (2008). Assessment of Cumulative Evidence on Genetic Associations: Interim Guidelines. *Int. J. of Epidemiol.* 37, 120–132. doi:10.1093/ije/dym159

Jujjavarapu, C., Anandasakaran, J., Amendola, L. M., Haas, C., Zampino, E., Henrikson, N. B., et al. (2021). ShareDNA: A Smartphone App to Facilitate Family Communication of Genetic Results. *BMC Med. Genomics* 14, 10.

Kardashian, A., Fehniger, J., Creasman, J., Cheung, E., and Beattie, M. S. (2012). A Pilot Study of the Sharing Risk Information Tool (ShaRIT) for Families with Hereditary Breast and Ovarian Cancer Syndrome. *Hered. Cancer Clin. Pract.* 10, 4.

Kerr, M., Pears, R., Miedzybrodzka, Z., Haralambos, K., Cather, M., Watson, M., et al. (2017). Cost Effectiveness of Cascade Testing for Familial Hypercholesterolaemia, Based on Data from Familial Hypercholesterolaemia Services in the UK. *Eur. Heart J.* 38, 1832–1839. doi:10.1093/eurheartj/ehx111

Kurian, A. W., and Katz, S. J. (2020). Emerging Opportunity of Cascade Genetic Testing for Population-wide Cancer Prevention and Control. *Jco* 38, 1371–1374. doi:10.1200/jco.20.00140

Lee, D. S. C., Meiser, B., Mariapun, S., Hassan, T., Yip, C. H., Mohd Taib, N. A., et al. (2021). Communication about Positive BRCA1 and BRCA2 Genetic Test Results and Uptake of Testing in Relatives in a Diverse Asian Setting. *Jrnl of Gene Coun* 30, 720–729. doi:10.1002/jgc4.1360

Lincoln, S. E., Hambuch, T., Zook, J. M., Bristow, S. L., Hatchell, K., Truty, R., et al. (2021). One in Seven Pathogenic Variants Can Be Challenging to Detect by NGS: an Analysis of 450,000 Patients with Implications for Clinical Sensitivity and Genetic Test Implementation. *Genet. in Med.* 23, 1673–1680. doi:10.1038/s41436-021-01187-w

Lincoln, S. E., Kobayashi, Y., Anderson, M. J., Yang, S., Desmond, A. J., Mills, M. A., et al. (2015). A Systematic Comparison of Traditional and Multigene Panel

Testing for Hereditary Breast and Ovarian Cancer Genes in More Than 1000 Patients. *The J. of Mol. Diagnostics* 17, 533–544. doi:10.1016/j.jmoldx.2015.04.009

Lincoln, S. E., Truty, R., Lin, C.-F., Zook, J. M., Paul, J., Ramey, V. H., et al. (2019). A Rigorous Interlaboratory Examination of the Need to Confirm Next-Generation Sequencing-Detected Variants with an Orthogonal Method in Clinical Genetic Testing. *The J. of Mol. Diagnostics* 21, 318–329. doi:10.1016/j.jmoldx.2018.10.009

Marks, D., Thorogood, M., Neil, S. M., Humphries, S. E., and Neil, H. A. W. (2006). Cascade Screening for Familial Hypercholesterolaemia: Implications of a Pilot Study for National Screening Programmes. *J. Med. Screen.* 13, 156–159. doi:10.1258/096914106778440617

Marks, D., Wonderling, D., Thorogood, M., Lambert, H., Humphries, S. E., and Neil, H. A. W. (2002). Cost Effectiveness Analysis of Different Approaches of Screening for Familial Hypercholesterolaemia. *BMJ* 324, 1303. doi:10.1136/bmj.324.7349.1303

McGowan, M. P., Cuchel, M., Ahmed, C. D., Khera, A., Weintraub, W. S., Wilemon, K. A., et al. (2021). A Proof-of-Concept Study of Cascade Screening for Familial Hypercholesterolemia in the US, Adapted from the Dutch Model. *Am. J. Prev. Cardiol.* 6, 100170.

McKinney, L. P., Gerbi, G. B., Caplan, L. S., Claridy, M. D., and Rivers, B. M. (2020). Predictors of Genetic Beliefs toward Cancer Risk Perceptions Among Adults in the United States: Implications for Prevention or Early Detection. *Jrnl of Gene Coun* 29, 494–504. doi:10.1002/jgc4.1228

Menko, F. H., Ter Stege, J. A., van der Kolk, L. E., Jeanson, K. N., Schats, W., Moha, D. A., et al. (2019). The Uptake of Presymptomatic Genetic Testing in Hereditary Breast-Ovarian Cancer and Lynch Syndrome: a Systematic Review of the Literature and Implications for Clinical Practice. *Fam. Cancer* 18, 127–135. doi:10.1007/s10689-018-0089-z

Milo Rasouly, H., Cuneo, N., Marasa, M., DeMaria, N., Chatterjee, D., Thompson, J. J., et al. (2021). GeneLiFT: A Novel Test to Facilitate Rapid Screening of Genetic Literacy in a Diverse Population Undergoing Genetic Testing. *Jrnl of Gene Coun* 30, 742–754. doi:10.1002/jgc4.1364

Muir, L. A., George, P. M., and Whitehead, L. (2012). Using the Experiences of People with Familial Hypercholesterolaemia to Help Reduce the Risk of Cardiovascular Disease: a Qualitative Systematic Review. *J. Adv. Nurs.* 68, 1920–1932. doi:10.1111/j.1365-2648.2012.05957.x

Musunuru, K., Hershberger, R. E., Day, S. M., Klinedinst, N. J., Landstrom, A. P., Parikh, V. N., et al. (2020). Genetic Testing for Inherited Cardiovascular Diseases: A Scientific Statement from the American Heart Association. *Circ. Genom Precis. Med.* 13, e000067. doi:10.1161/HCG.0000000000000067

Nazareth, S., Hayward, L., Simmons, E., Snir, M., Hatchell, K. E., Rojahn, S., et al. (2021). Hereditary Cancer Risk Using a Genetic Chatbot Before Routine Care Visits. *Obstet. Gynecol.* 138, 860–870.

Neuner, J., Dimmock, D., Kirschner, A. L. P., Beaudry, H., Paradowski, J., and Orlando, L. (2020). Results and Lessons of a Pilot Study of Cascade Screening for Familial Hypercholesterolemia in US Primary Care Practices. *J. Gen. Intern. Med.* 35, 351–353. doi:10.1007/s11606-019-05485-7

Newson, A. J., and Humphries, S. E. (2005). Cascade Testing in Familial Hypercholesterolaemia: How Should Family Members Be Contacted? *Eur. J. Hum. Genet.* 13, 401–408. doi:10.1038/sj.ejhg.5201360

Nitecki, R., Moss, H. A., Watson, C. H., Urbauer, D. L., Melamed, A., Lu, K. H., et al. (2021). Facilitated Cascade Testing (FaCT): A Randomized Controlled Trial. *Int. J. Gynecol. Cancer* 31, 779–783.

Nordestgaard, B. G., Chapman, M. J., Humphries, S. E., Ginsberg, H. N., Masana, L., Descamps, O. S., et al. (2013). Familial Hypercholesterolaemia Is Underdiagnosed and Undertreated in the General Population: Guidance for Clinicians to Prevent Coronary Heart Disease: Consensus Statement of the European Atherosclerosis Society. *Eur. Heart J.* 34, 3478–3490. doi:10.1093/eurheartj/eht273

Nykamp, K., Anderson, M., Powers, M., Garcia, J., Herrera, B., Ho, Y.-Y., et al. (2017). Sherloc: a Comprehensive Refinement of the ACMG-AMP Variant Classification Criteria. *Genet. in Med.* 19, 1105–1117. doi:10.1038/gim.2017.37

O'Brien, G., Christensen, K. D., Sullivan, H. K., Stout, N. K., Diller, L., Yeh, J. M., et al. (2021). Estimated Cost-Effectiveness of Genetic Testing in Siblings of Newborns with Cancer Susceptibility Gene Variants. *JAMA Netw. Open* 4, e2129742. doi:10.1001/jamanetworkopen.2021.29742

Offit, K., Tkachuk, K. A., Stadler, Z. K., Walsh, M. F., Diaz-Zabala, H., Levin, J. D., et al. (2020). Cascading after Peridiagnostic Cancer Genetic Testing: An Alternative to Population-Based Screening. *Jco* 38, 1398–1408. doi:10.1200/jco.19.02010

Petersen, H. V., Frederiksen, B. L., Lautrup, C. K., Lindberg, L. J., Ladelund, S., and Nilbert, M. (2019). Unsolicited Information Letters to Increase Awareness of Lynch Syndrome and Familial Colorectal Cancer: Reactions and Attitudes. *Fam. Cancer* 18, 43–51. doi:10.1007/s10689-018-0083-5

Pollard, S., Kalloger, S., Weymann, D., Sun, S., Nuk, J., Schrader, K. A., et al. (2020). Genetic Testing for Hereditary Cancer Syndromes: Patient Recommendations for Improved Risk Communication. *Health Expect.* 23, 884–892. doi:10.1111/hex.13062

Randall, L. M., Pothuri, B., Swisher, E. M., Diaz, J. P., Buchanan, A., Witkop, C. T., et al. (2017). Multi-disciplinary Summit on Genetics Services for Women with Gynecologic Cancers: A Society of Gynecologic Oncology White Paper. *Gynecol. Oncol.* 146, 217–224. doi:10.1016/j.ygyno.2017.06.002

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al. (2015). Standards and Guidelines for the Interpretation of Sequence Variants: a Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet. in Med.* 17, 405–424. doi:10.1038/gim.2015.30

Roberts, M. C., Dotson, W. D., DeVore, C. S., Bednar, E. M., Bowen, D. J., Ganiats, T. G., et al. (2018). Delivery of Cascade Screening for Hereditary Conditions: A Scoping Review of the Literature. *Health Aff.* 37, 801–808. doi:10.1377/hlthaff.2017.1630

Schmidlen, T., Jones, C. L., Campbell-Salome, G., McCormick, C. Z., Vanenkevort, E., and Sturm, A. C. (2022). Use of a Chatbot to Increase Uptake of Cascade Genetic Testing. *J. Genet. Couns*. Advance Online Publication. doi:10.1002/jgc4.1592

Sharaf, R. N., Myer, P., Stave, C. D., Diamond, L. C., and Ladabaum, U. (2013). Uptake of Genetic Testing by Relatives of Lynch Syndrome Probands: a Systematic Review. *Clin. Gastroenterology and Hepatology* 11, 1093–1100. doi:10.1016/j.cgh.2013.04.044

Snir, M., Nazareth, S., Simmons, E., Hayward, L., Ashcraft, K., Bristow, S. L., et al. (2021). Democratizing Genomics: Leveraging Software to Make Genetics an Integral Part of Routine Care. *Am. J. Med. Genet. C Semin. Med. Genet.* 187, 14–27.

Srinivasan, S., Won, N. Y., Dotson, W. D., Wright, S. T., and Roberts, M. C. (2020). Barriers and Facilitators for Cascade Testing in Genetic Conditions: a Systematic Review. *Eur. J. Hum. Genet.* 28, 1631–1644. doi:10.1038/s41431-020-00725-5

staff reporter (2021). Invitae to Provide Genetic Testing within eMERGE Population Screening Study. Available at: https://www.genomeweb.com/molecular-diagnostics/invitae-provide-genetic- testing-within-emerge-population-screening-study#.YnkzFRPML0r [Accessed May 9, 2022].

Sturm, A. C., Knowles, J. W., Gidding, S. S., Ahmad, Z. S., Ahmed, C. D., Ballantyne, C. M., et al. (2018). Clinical Genetic Testing for Familial Hypercholesterolemia. *J. of the Am. Coll. of Cardiol.* 72, 662–680. doi:10.1016/j.jacc.2018.05.044

Suthers, G. K., Armstrong, J., McCormack, J., and Trott, D. (2006). Letting the Family Know: Balancing Ethics and Effectiveness when Notifying Relatives about Genetic Testing for a Familial Disorder. *J. of Med. Genet.* 43, 665–670. doi:10.1136/jmg.2005.039172

Truty, R., Patil, N., Sankar, R., Sullivan, J., Millichap, J., Carvill, G., et al. (2019). Possible Precision Medicine Implications from Genetic Testing Using Combined Detection of Sequence and Intragenic Copy Number Variants in a Large Cohort with Childhood Epilepsy. *Epilepsia Open* 4, 397–408. doi:10.1002/epi4.12348

van den Heuvel, L. M., van Teijlingen, M. O., van der Roest, W., van Langen, I. M., Smets, E. M. A., van Tintelen, J. P., et al. (2020). Long-Term Follow-Up Study on the Uptake of Genetic Counseling and Predictive DNA Testing in Inherited Cardiac Conditions. *Circ Genomic and Precis. Med.* 13, 524–530. doi:10.1161/circgen.119.002803

Wald, D. S., Bestwick, J. P., Morris, J. K., Whyte, K., Jenkins, L., and Wald, N. J. (2016). Child-Parent Familial Hypercholesterolemia Screening in Primary Care. *N. Engl. J. Med.* 375, 1628–1637.

Webber, E. M., Hunter, J. E., Biesecker, L. G., Buchanan, A. H., Clarke, E. V., Currey, E., et al. (2018). Evidence-based Assessments of Clinical Actionability in the Context of Secondary Findings: Updates from ClinGen's Actionability Working Group. *Hum. Mutat.* 39, 1677–1685. doi:10.1002/humu.23631

Wonderling, D., Umans-Eckenhausen, M., Marks, D., Defesche, J., Kastelein, J., and Thorogood, M. (2004). Cost-effectiveness Analysis of the Genetic Screening Program for Familial Hypercholesterolemia in The Netherlands. *Seminars in Vasc. Med.* 4, 97–104. doi:10.1055/s-2004-822992

Wurtmann, E., Steinberger, J., Veach, P. M., Khan, M., and Zierhut, H. (2018). Risk Communication in Families of Children with Familial Hypercholesterolemia: Identifying Motivators and Barriers to Cascade Screening to Improve Diagnosis at a Single Medical Center. *J. Genet. Couns.* 28, 50–58. doi:10.1007/s10897-018-0290-0

Wynn, J., Milo Rasouly, H., Vasquez-Loarte, T., Saami, A. M., Weiss, R., Ziniel, S. I., et al. (2021). Do research Participants Share Genomic Screening Results with Family Members? *J. of Genet. Couns.* 31, 447–458. doi:10.1002/jgc4.1511

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SYSTEMATIC REVIEW
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Barriers and Facilitators for Population Genetic Screening in Healthy Populations: A Systematic Review

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Studies suggest that 1–3% of the general population in the United States unknowingly carry a genetic risk factor for a common hereditary disease. Population genetic screening is the process of offering otherwise healthy patients in the general population testing for genomic variants that predispose them to diseases that are clinically actionable, meaning that they can be prevented or mitigated if they are detected early. Population genetic screening may significantly reduce morbidity and mortality from these diseases by informing risk-specific prevention or treatment strategies and facilitating appropriate participation in early detection. To better understand current barriers, facilitators, perceptions, and outcomes related to the implementation of population genetic screening, we conducted a systematic review and searched PubMed, Embase, and Scopus for articles published from date of database inception to May 2020. We included articles that 1) detailed the perspectives of participants in population genetic screening programs and 2) described the barriers, facilitators, perceptions, and outcomes related to population genetic screening programs among patients, healthcare providers, and the public. We excluded articles that 1) focused on direct-to-consumer or risk-based genetic testing and 2) were published before January 2000. Thirty articles met these criteria. Barriers and facilitators to population genetic screening were organized by the Social Ecological Model and further categorized by themes. We found that research in population genetic screening has focused on stakeholder attitudes with all included studies designed to elucidate individuals' perceptions. Additionally, inadequate knowledge and perceived limited clinical utility presented a barrier for healthcare provider uptake. There were very few studies that conducted long-term follow-up and evaluation of population genetic screening. Our findings suggest that these and other factors, such as prescreen counseling and education, may play a role in the adoption and implementation of

population genetic screening. Future studies to investigate macro-level determinants, strategies to increase provider buy-in and knowledge, delivery models for prescreen counseling, and long-term outcomes of population genetic screening are needed for the effective design and implementation of such programs.

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Keywords: population testing, universal genetic screening, healthy population screening, average risk, precision public health, perceptions, attitudes, outcomes

1 INTRODUCTION

Studies suggest that 1–3% of the general population in the United States carry a genetic risk factor for a common hereditary disease. Typically, genetic testing approaches for identifying these individuals are limited to testing those at high risk of hereditary disease (e.g., cascade testing for at-risk relatives of individuals with a diagnosis). Conversely, population genetic screening offers genetic testing (for common genomic variants) to otherwise healthy individuals to inform risk assessment, precision prevention and early detection of preventable, common diseases. A key example of population genetic screening is newborn screening, which is often celebrated as one of public health's best accomplishments (Murray et al., 2018).

The Centers for Disease Control and Prevention Office of Genomics and Precision Health has prioritized population genetic screening for common disease conditions (Hereditary Breast and Ovarian Cancer, Lynch Syndrome, and familial hypercholesterolemia) as Tier 1 applications for genomics due to their "significant potential for positive impact on public health" (CDC, 2021). While clinical evidence is currently insufficient to recommend widespread screening in healthy populations (Hampel and de la Chapelle, 2011; Representatives of the Global Familial Hypercholesterolemia Community, 2020), clinical pilot programs are in place to understand cost-efficiency, implementation, and other health related outcomes of population genetic screening (Hay et al., 2021; Lacson et al., 2021; Smit et al., 2021). These pilot studies are on the rise and offer promising opportunities to build the necessary knowledge base for expanding population genetic screening.

Understanding the barriers, facilitators, perceptions, and outcomes to population genetic screening of healthy populations is critical for implementing screening programs in healthcare settings. Previous systematic reviews relating to population genetic screening focus on economic and informed choice evaluations (Rogowski, 2006; Ames et al., 2015). To address this need, we conducted a systematic review of current research literature to understand the barriers, facilitators, perceptions, and outcomes that will be vital for the successful translation of research to support population genetic screening (if found to be appropriate for scaling up).

2 METHODS

2.1 Protocol and Registration

We adhered to the Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) reporting guidelines (Moher et al., 2009) for this review (**Supplementary Appendix SA**). Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198198 (Shen et al., 2022).

2.2 Search Strategy and Information Sources

We worked with a medical librarian (RC) to develop search strategies for the concept of population genetic screening in unknown- and average-risk populations in PubMed, Embase, and Scopus from date of database inception to 22 May 2020, when all searches were completed. Search filters were used to limit the results to original research articles written in English and to exclude preconception, prenatal, and carrier testing. The complete strategy for each of the searches can be found in **Supplementary Appendix SB**. We also manually examined the references of relevant literature reviews to identify additional studies that may have been missed by the database searches. All references were uploaded to Veritas Health Innovation Covidence systematic review software, 2021 (Veritas Health Innovation), a systematic review management system for study selection.

2.3 Eligibility Criteria

Conference abstracts, meeting reports, literature reviews, guidelines, and simulation modeling studies were excluded. Articles focusing on genetic literacy and research, hypothetical gene correlations, and those that lacked a methods section or relevant outcomes were also excluded. Finally, we excluded articles that focused on direct-to-consumer or high-risk genetic testing and articles that were published before 1 January 2000 to understand views of population genetic screening with the use of contemporary technology.

2.4 Study Selection

Each title and abstract were reviewed independently for eligibility by random sets of two reviewers (ES, SS, LP, CA, MD, KF, BH, LM, AS) and thematic issues were resolved by discussion. MR

TABLE 1 | Characteristics of included studies.

Study ID	Setting				Methods					Population					Intervention					
	Year Published	Country	Setting Type	Years of data collection	Scale	Study Design	Data source	Effectiveness Measures Captured	MMAT Score	Types of stakeholders	% Female	Mean Age	% White	Other race or ethnicity information	Disease Areas	Monogenic/ Polygenic Condition	Population that genetic screening was offered	Comparison Group	Type of healthcare provider available for prescreen consultation	Type of healthcare provider available for post-screen consultation
Allen et al. (2008)	2008	Australia	Community	NR	City/town	Descriptive	Questionnaire data	Results, Follow-up, Change in Health Behavior, Interpretation	5	Patients	53	41.6	NR	NR	HFE-associated hereditary haemochromatosis	Monogenic	Individuals who worked at workplaces that HaemScreen was implemented	N/A	NR	Physicians
Borry et al. (2008)	2008	European Union	NR	2006–2007	International	Descriptive	Questionnaire data	N/A	4	Providers (Clinical geneticists)	47	NR	NR	NR	A variety of conditions	Monogenic	N/A	N/A	N/A	N/A
East et al. (2019)	2019	United States	Clinic	2015–2018	Single Center	Descriptive	Survey data	N/A	4	Patients	59	40	NR	NR	NR	N/A	Patients seen at the Smith Family Clinic for Genomic Medicine, LLC. categorized as elective (part of the Insight Genome program)	Patients categorized as diagnostic (evaluated because of a personal or family history of disease)	Medical Geneticist & Genetic Counselor	NR
Fenton et al. (2018)	2018	Australia	Community	NR	State	Mixed Methods	Questionnaire	Follow-up	3	Public	50	NR	NR	NR	Melanoma	Polygenic	Individuals 18–69 years old with no personal history of melanoma who are part of the Cancer Council NSW "Join a Research Study" database	N/A	Genetic Counselor	Genetic Counselor
Godino et al. (2016)	2016	United Kingdom	Community	2011	National	RCT	Questionnaire data	Follow-up, Change in Health Behavior, Interpretation	4	Public	53	48.7	NR	NR	Type 2 diabetes mellitus	Polygenic	Individuals born between 1950 and 1975 registered with participating general practices in Cambridgeshire, United Kingdom and enrolled in the Fenland Study	Participants given no risk estimate or phenotypic risk estimate	NR	NR
Haga et al. (2011)	2011	United States	Clinic	2010	National	Descriptive	Survey data	N/A	3	Providers (Primary care)	15	NR	94	0.6% African American, 3.8% Asian, 2.5% other/ prefer not to answer, 1.9% Hispanic	A variety of conditions	Polygenic	N/A	N/A	N/A	N/A
Haga et al. (2014)	2014	United States	Clinic	NR	Single Center	RCT	Survey data	Results, Interpretation	2	Public	70	NR	60	22% Black 8% Other 1.7% Prefer not to answer 0.4% Unsure	Type 2 diabetes mellitus	Polygenic	Non-diabetic participants recruited from Duke University (Durham, NC) and surrounding areas	N/A	NR	Genetic Counselor
Hardie, (2011)	2011	Australia	NR	NR	National	Mixed Methods	Survey data	N/A	5	Public	64	54	NR	NR	NR	Polygenic	N/A	N/A	N/A	N/A
Hay et al. (2018)	2018	United States	Clinic	NR	State	RCT	RCT data	N/A	1	Public	79	54	71	48% Hispanic, 3% Black, 3% American Indian/	Melanoma and basal cell carcinoma	Polygenic	Primary care patients 18 years or older at University of New Mexico outpatient	Usual care control	NR	NR

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies.

Study ID	Setting				Methods					Population					Intervention					
	Year Published	Country	Setting Type	Years of data collection	Scale	Study Design	Data source	Effectiveness Measures Captured	MMAT Score	Types of stakeholders	% Female	Mean Age	% White	Other race or ethnicity information	Disease Areas	Monogenic/ Polygenic Condition	Population that genetic screening was offered	Comparison Group	Type of healthcare provider available for prescreen consultation	Type of healthcare provider available for post-screen consultation
														Alaska Native, 2% Asian, 21% Other including Native Hawaiian or multiple races			primary care clinic			
Henneman et al. (2011)	2011	Netherlands	Community	2007	City/town	Qualitative	Focus Group data	N/A	5	Public	100	53.4	92	NR	Breast cancer	Polygenic	N/A	N/A	N/A	N/A
Hietaranta-Luoma et al. (2015)	2015	Finland	Clinic	NR	Regional	RCT	RCT data	Follow-up, Change in Health Behavior, Interpretation	3	Patients	69	47	NR	NR	Cardiovascular disease	Polygenic	Healthy adults aged 20–67 years	Participants who had a session with a nutritionist, received general health and nutrition recommendations, and counseling/ lecture by a professor of nutrigenomics	Nutritionist	Medical Doctor
Joshi et al. (2020)	2019	Canada	Clinic	2017–2018	National	Qualitative	Interview data	N/A	5	Providers (Primary care)	NR	NR	NR	NR	NR	Monogenic	N/A	N/A	N/A	N/A
Laskey et al. (2003)	2003	United States	NR	2001	Single Center	Descriptive	Survey data	N/A	4	Public	79	NR	NR	71% African American, 11% Hispanic, 18% listed another race including Filipino, Asian, or Eastern Indian, 0.02% No Response	NR	N/A	N/A	N/A	N/A	N/A
Neghina and Anghel., (2010)	2010	Romania	Clinic	NR	Single Center	Descriptive	Questionnaire data	Results	3	Patients	58	54.8	NR	NR	Hereditary hemochromatosis	Monogenic	Patients 18 years or older who attended the ambulatory unity of the Emergency County Hospital, Timisoara, Romania	N/A	Physician And Health Professional	NR
Nicholls et al. (2016)	2016	Canada	Community	2011–2012	National	Mixed Methods	Written comments, survey, and non-participant observation data	N/A	2	Public	72	58.35	76	1% Native Canadian	Colorectal cancer and type 1 diabetes	Polygenic	N/A	N/A	N/A	N/A
Nielsen and El-Sohemy, (2012)	2012	Canada	Community	2011	National	RCT	Survey data	Interpretation	5	Public	76	26	62	21% East Asian, 11% South Asian, 7% Other	Nutrition	Polygenic	Men and women between the ages of 20–29 years from the Toronto Nutrigenomics and Health Study	Dietary recommendations from health organizations for the same dietary components without genetic information	NR	NR

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TABLE 1 | (*Continued*) Characteristics of included studies.

Study ID	Setting				Methods					Population					Intervention					
	Year Published	Country	Setting Type	Years of data collection	Scale	Study Design	Data source	Effectiveness Measures Captured	MMAT Score	Types of stakeholders	% Female	Mean Age	% White	Other race or ethnicity information	Disease Areas	Monogenic/ Polygenic Condition	Population that genetic screening was offered	Comparison Group	Type of healthcare provider available for prescreen consultation	Type of healthcare provider available for post-screen consultation
Nusbaum et al. (2013)	2013	United States	Clinic	NR	Single Center	Qualitative	Interview data	Results, Follow-up, Change in Health Behavior, Interpretation	5	Patients	60	61	65	25% African American, 10% multi-racial	Colorectal cancer	Polygenic	Primary care patients aged 40 and older recruited from the Division of General Internal Medicine at Georgetown University Hospital	N/A	Genetic Counselor	Genetic Counselor
O'Neill et al. (2015)	2015	United States	NR	2007–2008	National	Qualitative	Interview data	Results, Interpretation	4	Public	57	34.89	62	27.63% African American 10.9% Other	A variety of conditions	Polygenic	Participant between 25–40 in the National Human Genome Research Institute's NHGRI Multiplex Initiative and having no health conditions surveyed through the Multiplex Initiative	N/A	NR	NR
Rego et al. (2019)	2019	United States	Clinic	NR	Single Center	Qualitative	Interview data	Results, Interpretation	5	Public	33	NR	75	NR	A variety of conditions	Both	Adult participants who were recruited from the Integrated Personal Omics Profiling (cohort is enriched for prediabetics)	N/A	NR	Genetic Counselors (Sometimes Included Other Study Team Members: A Medical Geneticist, Neurologist or Endocrinologist, Scientist And/or Student)
Rubinsak et al. (2019)	2019	United States	Clinic	2018	Single Center	Descriptive	Survey data	N/A	3	Patients	100	37.7	37	50.5% Black, 12.1%	Hereditary Breast and Ovarian Cancer	Monogenic	N/A	N/A	N/A	N/A
Sanderson et al. (2004)	2004	United Kingdom	Community	2002	National	Descriptive	Questionnaire data	N/A	4	Public	51	47	94	6% non-Caucasian	Cancer, heart disease	Polygenic	N/A	N/A	N/A	N/A
Sanderson et al. (2016)	2016	United States	Clinic	NR	Single Center	Mixed Methods	Interview and Questionnaire data	Interpretation	2	Public	46	48	71	8.6% African American, 5.7% Hispanic/ Latino, 5.7% Asian, 5.7% Multiple Races, 2.9% Self-reported Turkish	A variety of conditions	Both	General population older than 18 at the Mount Sinai Medical Center in New York City	N/A	Genetic Counselor	NR
Sanderson et al. (2017)	2017	United States	Clinic	NR	Single Center	Mixed Methods	Interview and Questionnaire data	Results, Follow-up, Interpretation	1	Public	41	48.6	79	3.4% African American, 3.4% Asian, 6.9% Hispanic/ Latino, 6.9% More than 1 race	A variety of conditions	Both	Participants of the HealthSeq project	N/A	Study Genetic Counselor and Medical Geneticist	NR
Shaw and Bassi, (2001)	2001	United States	Community	NR	City/town	Descriptive	Survey data	N/A	2	Public	54	51.8	95	1.8% African American, 0.9% Asian American, 0.9% Native American, and 1.7% Other	NR	Monogenic	N/A	N/A	N/A	N/A

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies.

Study ID	Setting				Methods					Population					Intervention					
	Year Published	Country	Setting Type	Years of data collection	Scale	Study Design	Data source	Effectiveness Measures Captured	MMAT Score	Types of stakeholders	% Female	Mean Age	% White	Other race or ethnicity information	Disease Areas	Monogenic/ Polygenic Condition	Population that genetic screening was offered	Comparison Group	Type of healthcare provider available for prescreen consultation	Type of healthcare provider available for post-screen consultation
Shiloh et al. (2015)	2014	United States	Clinic	NR	National	Non-RCT	Interviews	Results, Interpretation	2	Public	57	35	NR	38% African American	A variety of conditions	Polygenic	Adults ages 25–40 years old, not affected by Type2 diabetes, heart disease, high cholesterol, high blood pressure, osteoporosis, or lung, colon, or skin cancer	N/A	NR	Research Educator
Smit et al. (2020)	2020	Australia	Community	NR	State	Qualitative	Interview data	N/A	5	Public	50	53	NR	NR	Melanoma	Polygenic	All participants part of a pilot trial to give information on personalized melanoma genomic risk to the public	N/A	Genetic Counselor	NR
Toivainen et al. (2003)	2003	Finland	Community	1996–1998	National	Descriptive	Survey data	N/A	3	Providers (Gynaecologist, Pediatrician, Clinical geneticist, General practitioner midwife, public health nurse and Public	66	43.5	NR	NR	A variety of conditions	Monogenic	N/A	N/A	N/A	N/A
Vassy et al. (2014)	2015	United States	Clinic	2013	City/town	Mixed Methods	Interview and survey data	N/A	5	Providers (Primary care or Cardiologist)	39	52	78	22.22% Non-white race/ ethnicity	NR	Both	N/A	Evaluating patients based on family history only	N/A	N/A
Vassy et al. (2017)	2017	United States	Clinic	NR	City/town	RCT	Survey data	Results, Follow-up, Change in Health Behavior, Interpretation	3	Patients and providers (Primary care)	58	55	89	11% Other	A variety of conditions	Monogenic	Participants (45–60) of the MedSeq Project	N/A	Primary Care provider	Primary Care Provider
Zoltick et al. (2019)	2019	United States	Clinic	2014–2017	National	Descriptive	Survey data	Change in Health Behavior, Interpretation	4	Public	38	53	92	2.8% Asian 0.6% African American/ Black 4.9% More than one race/ other	A variety of conditions	Monogenic	Adults aged 18 years or older who independently decided to pursue pre-dispositional personal genome sequencing through one of the collaborating projects (PGP, Health-Seq, and the YPO and MD/ PhD Genome Projects)	N/A	Varies By Project	Varies By Project

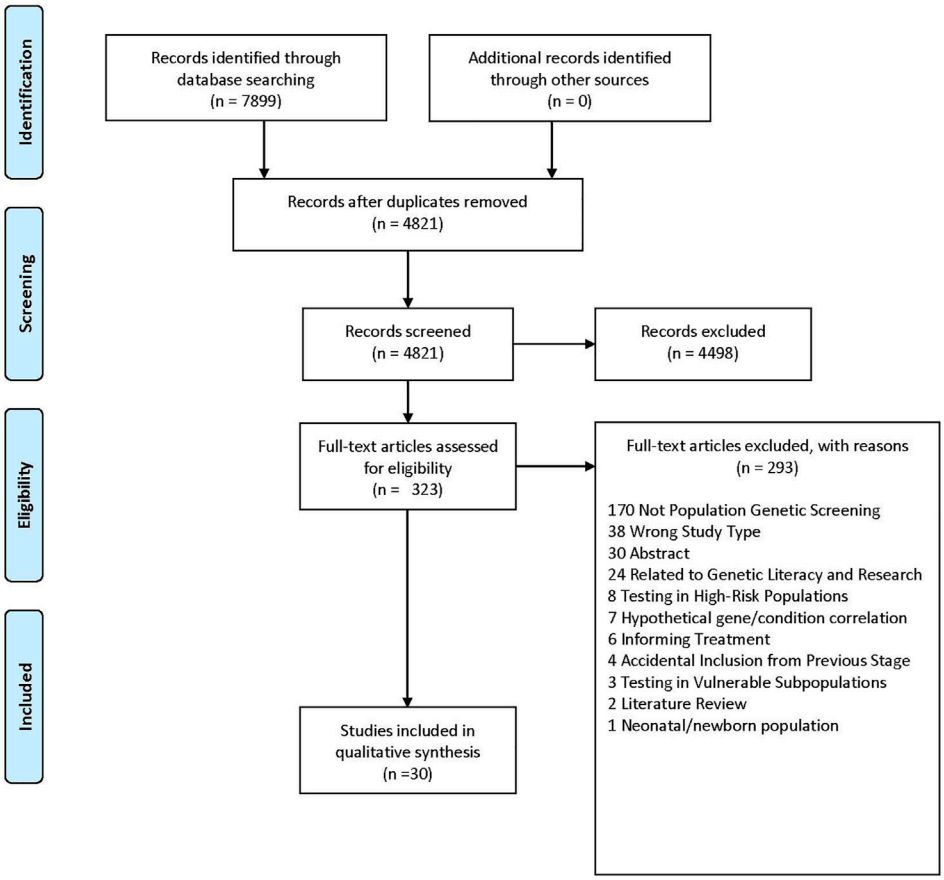

FIGURE 1 | PRISMA diagram.

oversaw the process and formally resolved specific conflicts. Each full text was assessed independently by random sets of two reviewers (ES, SS, LP, CA, MD, BH, LM, AS) and thematic issues were resolved by discussion. KF oversaw this process and formally resolved specific conflicts. We included articles that detailed the perspectives of participants of population genetic screening programs and individuals asked about population genetic screening to capture all possible barriers, facilitators, perceptions, and outcomes from the position of patients, healthcare providers, and the public.

2.5 Data Items and Data Collection Process

Data extraction forms were developed in Covidence using the PICOS framework (Schardt et al., 2007) (see **Supplementary Appendix SC**) to collect information about each study's population (patients, healthcare providers, and the public), intervention (disease area(s), whether population genetic screening was offered, and whether participants met with providers before or after screening), comparator group if applicable, outcomes (barriers, facilitators, perceptions, effectiveness measures), and setting (e.g., scale, country, type). We defined patients as healthy individuals with no known risk status who were seen in the healthcare system and the public as individuals who were selected from and represented the broader community. For studies that investigated more than three disease areas, we list their disease areas as "a variety of conditions" for simplicity. We note whether testing for monogenic or polygenic conditions were performed or proposed for consideration by the study. It can be noted that common genomic variants may vary from program to program.

We categorized effectiveness measures as Results (results of the actual screening), Follow-up, Change in Health Behavior, and Interpretation (ex: participants' emotional responses, risk perception changes, etc.).

The extraction forms were developed based on a previous review (Srinivasan et al., 2020) and four sets of two reviewers independently piloted them on a subset of five articles to agree on a final version. ES, SS, and LP resolved disagreements in data extractions and discussed specific articles as needed. We separately examined articles that had implemented population genetic screening and those that had not implemented population genetic screening to account for contextual differences before analyzing these article types together. Barriers and facilitators were arranged according to the Social Ecological Model (Golden and Earp, 2012), which views health as being affected by interactions at the intrapersonal, interpersonal, and community levels. Perceptions were categorized into favorable, unfavorable, and in-between.

TABLE 2 | Barriers to interest and participation in population genetic screening.

Reasons	Patient				Provider				Public			
	N	%	Significance	Study	N	%	Significance	Study	N	%	Significance	Study
Intrapersonal												
Psychosocial Factors, Knowledge, Attitudes, and Beliefs												
Anxiety, fear, and worry toward screening				Nusbaum et al. (2013); Rubinsak et al. (2019)								Hardie, (2011)
Potential negative psychological and emotional impacts								Joshi et al. (2020)	18	50		Sanderson et al. (2016) Henneman et al. (2011)
Mistrust												Hardie, (2011)
Possibility of unwanted information												Zoltick et al. (2019)
Belief that low risk result may not give reassurance												Henneman et al. (2011)
Inadequate knowledge						41		Haga et al. (2011) Joshi et al. (2020)				
Not having ordered a genetic test for themselves								Haga et al. (2011)				
Belief that it would not provide useful information						36		Haga et al. (2011)				
Dislike of blood		11		Neghina and Anghel., (2010)								
Moral and ethical reasons												Shaw and Bassi (2001); Hardie (2011)
Disinterest		18.5		Neghina and Anghel., (2010)								Hardie, (2011)
Belief that it would lead unnecessary testing								Vassy et al. (2014)				
Lack of information		41		Neghina and Anghel., (2010)								
				Nusbaum et al. (2013); Rubinsak et al. (2019)								
Clinical Factors												
Uncertainty of results								Vassy et al. (2014); Joshi et al. (2020)				Zoltick et al. (2019)
Limited clinical utility								(Borry et al. (2008); Vassy et al. (2014); Joshi et al. (2020)				
Other												
Cost				Rubinsak et al. (2019)								Hardie (2011); Zoltick et al. (2019)
Lack of time		32.5		(Neghina and Anghel (2010), 201)								
Higher education												Sanderson et al. (2004)
Religious reasons												Hardie (2011)
Interpersonal Barriers												
Family												
Impact on children												Sanderson et al. (2016)
Lack of family history				Rubinsak et al. (2019)								Hardie, (2011)

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TABLE 2 | (*Continued*) Barriers to interest and participation in population genetic screening.

Reasons	Patient				Provider				Public			
	N	%	Significance	Study	N	%	Significance	Study	N	%	Significance	Study
					Community							
Data												
Confidentiality/privacy				Nusbaum et al. (2013)		43		Haga et al. (2011)	20	57		Sanderson et al. (2016) Zoltick et al. (2019)
Data security								Joshi et al. (2020)				
					Healthcare System							
Potential impact on insurance						50		Haga et al. (2011)				Henneman et al. (2011); Zoltick et al. (2019)
								Joshi et al. (2020)				
Cost to health system								Joshi et al. (2020)				Henneman et al. (2011); Smit et al. (2020)
					Other							
Possibility for discrimination by employers								Joshi et al. (2020)				Henneman et al. (2011)

Select studies report the count of participants who agree with facilitator statement (which we label as column "N"), the percentage of participants (which we label as column "%"), and significance levels of the statements (which we label as column "Significance").

We initially aimed to understand barriers, facilitators, perceptions, and outcomes. It became apparent that barriers and facilitators were related to perceptions, and overall outcomes were quite diverse and hard to summarize across heterogeneous studies, therefore we focus our results on barriers and facilitators.

2.6 Risk of Bias in Individual Studies

Reviewers independently assessed the methodological quality of each study following the Mixed Method Appraisal Tool, version 2018 (Hong et al., 2018) for each study type (RCT, descriptive, observation, qualitative, or mixed methods). Meta-analysis was not conducted due to the high variation in study design, population, setting, and outcomes. Due to the small number of studies, we did not define a threshold with which to exclude "low quality" studies. To prevent highlighting any such studies, we ensured that our discussion points were present in multiple studies that mostly have an MMAT score of 3 or higher.

3 RESULTS

3.1 Study Characteristics

Characteristics of our included studies can be found in **Table 1**. Of the 4,821 unique studies that were identified through database searching, 323 articles were assessed for full-text eligibility (see **Figure 1** for PRISMA diagram). Thirty articles were included. (Shaw and Bassi, 2001; Laskey et al., 2003; Toiviainen et al., 2003; Sanderson et al., 2004, 2017; Allen et al., 2008; Borry et al., 2008; Neghina and Anghel, 2010; Haga et al., 2011; Hardie, 2011; Henneman et al., 2011; Nielsen and El-Sohemy, 2012; Nusbaum et al., 2013; Haga et al., 2014; Vassy et al., 2014; Hietaranta-Luoma et al., 2015; O'Neill et al., 2015; Shiloh et al., 2015; Godino et al., 2016; Nicholls et al., 2016; Sanderson et al., 2016; Vassy et al., 2017; Fenton et al., 2018; Hay et al., 2018; East et al., 2019; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019; Joshi et al., 2020; Smit et al., 2020).

Most studies investigated the perspectives of the public (n = 18) (Shaw and Bassi, 2001; Laskey et al., 2003; Sanderson et al., 2004, 2017; Hardie, 2011; Henneman et al., 2011; Nielsen and El-Sohemy, 2012; Haga et al., 2014; O'Neill et al., 2015; Shiloh et al., 2015; Godino et al., 2016; Nicholls et al., 2016; Sanderson et al., 2016; Fenton et al., 2018; Hay et al., 2018; Rego et al., 2019; Zoltick et al., 2019; Smit et al., 2020), while six studies investigated the perspective of patients (Allen et al., 2008; Neghina and Anghel, 2010; Nusbaum et al., 2013; Hietaranta-Luoma et al., 2015; East et al., 2019; Rubinsak et al., 2019), only four investigated the perspective of providers (Borry et al., 2008; Haga et al., 2011; Vassy et al., 2014; Joshi et al., 2020), and two investigated multiple perspectives (Toiviainen et al., 2003; Vassy et al., 2017).

For the most part, studies reported key patient characteristics; however, eleven studies did not record race or ethnicity information (Toiviainen et al., 2003; Allen et al., 2008; Borry et al., 2008; Neghina and Anghel, 2010; Hardie, 2011; Hietaranta-Luoma et al., 2015; Godino et al., 2016; Fenton et al., 2018; East

TABLE 3 | Facilitators to interest and participation in population genetic screening.

Reasons	Patient				Provider				Public			
	N	%	Significance	Study	N	%	Significance	Study	N	%	Significance	Study
Intrapersonal												
Demographics and Socio-Economic Status												
Male gender										72	$p = 0.029$	Sanderson et al. (2004)
Later middle age										78		Sanderson et al. (2004)
Younger age				Neghina and Anghel., (2010)								
Higher socio-economic status				Neghina and Anghel., (2010)								Hay et al. (2018)
Psychosocial Factors, Knowledge, Attitudes, and Beliefs												
Interest about ancestry									13			Sanderson et al. (2016) Zoltick et al. (2019)
Professional interest/utility									1			Sanderson et al. (2016) Zoltick et al. (2019)
Interest in genetics/science												Sanderson et al. (2016); Rego et al. (2019); Zoltick et al. (2019)
General curiosity				Nusbaum et al. (2013); East et al. (2019)								Hardie (2011); Zoltick et al. (2019)
										66		Sanderson et al. (2016)
Chance to learn about themselves				Rubinsak et al. (2019)						86		Nielsen and El-Sohemy, (2012)
									7			Sanderson et al. (2016)
Altruism				Nusbaum et al. (2013)								Rego et al. (2019)
									15			Sanderson et al. (2016)
Trust in provider											$p < 0.001$	Hardie, (2011)
Trust in medicine											$p < 0.001$	Hardie, (2011)
Belief that screening will yield helpful information												Shaw and Bassi, (2001)
Knowledge								Borry et al. (2008); Haga et al. (2011)				
Nothing to lose				Nusbaum et al. (2013)								
Chance to have a free screen		71.4		Neghina and Anghel., (2010)								
Novel opportunity												Sanderson et al. (2016)
Fun and entertaining												Zoltick et al. (2019)
Clinical Factors												
Known or suspected personal history												Sanderson et al. (2016); Hay et al. (2018)
Curability of condition											$p < 0.001$	Shaw and Bassi, (2001)
More certain outcome												Shaw and Bassi, (2001)
Non-fatalness of condition											$p < 0.01$	Shaw and Bassi, (2001)
Prepare for future health		57		East et al. (2019)								Nicholls et al. (2016); Sanderson et al. (2016); Rego et al. (2019); Zoltick et al. (2019)
Potential for medical intervention/ monitoring				East et al. (2019)				Borry et al. (2008); Joshi et al. (2020)		73		Nielsen and El-Sohemy, (2012)
												Sanderson et al. (2016)
Potential to encourage health improvements												Hardie (2011); Sanderson et al. (2016); Zoltick et al. (2019)
										83		Nielsen and El-Sohemy, (2012)
Seeking medical information		37		East et al. (2019)								
		85.7		Neghina and Anghel., (2010)								
				Nusbaum et al. (2013)								
Diagnostic purposes									1			Sanderson et al. (2016)
Pharmacogenomics				East et al. (2019)								Sanderson et al. (2016); Zoltick et al. (2019)
Interpersonal												
Family												
Provide information for family members		40		East et al. (2019)								Nicholls et al. (2016); Rego et al. (2019); Zoltick et al. (2019)
				Nusbaum et al. (2013); Rubinsak et al. (2019)					11			Sanderson et al. (2016)
Having family who have had their genomes sequenced												Zoltick et al. (2019)
Family history				Rubinsak et al. (2019)								Hardie (2011); Hay et al. (2018); Rego et al. (2019); Zoltick et al. (2019)
										74	$p = 0.005$	Sanderson et al. (2004)
										33		Sanderson et al. (2016)
Lack of family health history									1			Rego et al. (2019)
										70		Sanderson et al. (2004) Sanderson et al. (2016); Zoltick et al. (2019)

et al., 2019; Joshi et al., 2020; Smit et al., 2020) and one study did not record information about gender or sex (Joshi et al., 2020).

The included studies examined population genetic screening in the context of a variety of conditions, with the most common being melanoma ($n = 2$) (Fenton et al., 2018; Hay et al., 2018; Smit

et al., 2020), Type 2 diabetes mellitus (n = 2) (Haga et al., 2014; Godino et al., 2016), hereditary haemochromatosis (n = 2) (Allen et al., 2008; Neghina and Anghel, 2010), and colorectal cancer (n = 2) (Nusbaum et al., 2013; Nicholls et al., 2016).

The majority (n = 18) implemented population genetic screening programs of some kind (Allen et al., 2008; Neghina and Anghel, 2010; Nielsen and El-Sohemy, 2012; Nusbaum et al., 2013; Haga et al., 2014; Hietaranta-Luoma et al., 2015; O'Neill et al., 2015; Shiloh et al., 2015; Godino et al., 2016; Sanderson et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Fenton et al., 2018; Hay et al., 2018; East et al., 2019; Rego et al., 2019; Zoltick et al., 2019; Smit et al., 2020), and the remaining 12 investigated individuals' opinions on population genetic screening (Shaw and Bassi, 2001; Laskey et al., 2003; Toiviainen et al., 2003; Sanderson et al., 2004; Borry et al., 2008; Haga et al., 2011; Hardie, 2011; Henneman et al., 2011; Vassy et al., 2014; Nicholls et al., 2016; Rubinsak et al., 2019; Joshi et al., 2020).

Of those that implemented screening programs, many utilized genetic counseling either before screening (n = 5) (Neghina and Anghel, 2010; Sanderson et al., 2016; Sanderson et al., 2017; East et al., 2019; Smit et al., 2020), after screening (n = 4) (Allen et al., 2008; Haga et al., 2014; Shiloh et al., 2015; Rego et al., 2019), or both (n = 5) (Nusbaum et al., 2013; Hietaranta-Luoma et al., 2015; Vassy et al., 2017; Fenton et al., 2018; Zoltick et al., 2019). Four did not record counseling availability (Nielsen and El-Sohemy, 2012; O'Neill et al., 2015; Godino. et al., 2016; Hay et al., 2018).

The majority of studies (n = 16) were conducted in the US (Shaw and Bassi, 2001; Laskey et al., 2003; Haga et al., 2011; Nusbaum et al., 2013; Haga et al., 2014; Vassy et al., 2014; O'Neill et al., 2015; Shiloh et al., 2015; Sanderson et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Hay et al., 2018; East et al., 2019; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019) and were conducted in a clinical setting (n = 16) (Neghina and Anghel, 2010; Haga et al., 2011; Nusbaum et al., 2013; Haga et al., 2014; Vassy et al., 2014; Hietaranta-Luoma et al., 2015; Shiloh et al., 2015; Sanderson et al., 2016; Sanderson et al., 2017; Vassy et al., 2017; Hay et al., 2018; East et al., 2019; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019; Joshi et al., 2020) or the community setting (n = 10) (Shaw and Bassi, 2001; Toiviainen et al., 2003; Sanderson et al., 2004; Allen et al., 2008; Henneman et al., 2011; Nielsen and El-Sohemy, 2012; Godino et al., 2016; Nicholls et al., 2016; Fenton et al., 2018; Smit et al., 2020).

Included studies included a variety of study designs and received a range of MMAT scores. Of note, 23 studies received an MMAT score of 3 or greater (Laskey et al., 2003; Toiviainen et al., 2003; Sanderson et al., 2004; Allen et al., 2008; Borry et al., 2008; Neghina and Anghel, 2010; Hardie, 2011; Henneman et al., 2011; Nielsen and El-Sohemy, 2012; Nusbaum et al., 2013; Haga et al., 2014; Vassy et al., 2014; Hietaranta-Luoma et al., 2015; O'Neill et al., 2015; Godino et al., 2016; Vassy et al., 2017; Fenton et al., 2018; East et al., 2019; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019; Joshi et al., 2020; Smit et al., 2020), and only seven studies received an MMAT score below 3 (Shaw and Bassi, 2001; Haga et al., 2014; Shiloh et al., 2015; Nicholls et al., 2016; Sanderson et al., 2016; Sanderson et al., 2017; Hay et al., 2018).

3.2 Barriers

Intrapersonal, interpersonal, and community barriers are reported in **Table 2** and below.

3.2.1 Intrapersonal Barriers

3.2.1.1 Psychosocial Factors, Knowledge, Attitudes, and Beliefs

Psychosocial factors such as anxiety, fear, and worry about screening (Hardie, 2011; Nusbaum et al., 2013; Rubinsak et al., 2019), dislike of blood (Neghina and Anghel, 2010), and potential negative psychological and emotional impacts (Henneman et al., 2011; Sanderson et al., 2016; Joshi et al., 2020) were reported as reasons to reject screening. Additional factors such as mistrust (Hardie, 2011), disinterest (Neghina and Anghel, 2010; Hardie, 2011), the possibility of receiving unwanted information (Zoltick et al., 2019), and the belief that a low-risk result may not give reassurance (Henneman et al., 2011) were reported barriers.

Two studies reported moral and ethical reasons, such as the fear of eugenics and a question of human mortality, as barriers (Shaw and Bassi, 2001; Hardie, 2011). Providers cited inadequate knowledge (Haga et al., 2011; Joshi et al., 2020), not having ordered a genetic test for themselves (Haga et al., 2011), their belief that it would not provide useful information (Haga et al., 2011), and their belief that it would lead to unnecessary future testing (Vassy et al., 2014) as barriers to participating in population genetic screening programs. Additionally, patients reported a lack of information about these programs (Neghina and Anghel, 2010; Nusbaum et al., 2013; Rubinsak et al., 2019).

3.2.1.2 Clinical Factors

Providers (Vassy et al., 2014; Joshi et al., 2020) and the public (Zoltick et al., 2019) cited the uncertainty of results as a barrier for interest and/or participation in screening programs with providers additionally reporting perceived limited clinical utility (Borry et al., 2008; Vassy et al., 2014; Joshi et al., 2020).

3.2.1.3 Other

Perceived cost of population genetic screening (Hardie, 2011; Rubinsak et al., 2019; Zoltick et al., 2019), religious reasons (Hardie, 2011), and higher education (Sanderson et al., 2004) among patients and the public were reported as other barriers for interest and/or participation as well as a lack of time (Neghina and Anghel, 2010).

3.2.2 Interpersonal Barriers

3.2.2.1 Family

A perceived potential for a negative impact on children (Sanderson et al., 2016) and a lack of family history (Hardie, 2011; Rubinsak et al., 2019) were negatively associated with interest and/or participation of population genetic screening among patients and the public.

3.2.3 Community Barriers

3.2.3.1 Data

Concerns related to confidentiality and privacy (Haga et al., 2011; Nusbaum et al., 2013; Sanderson et al., 2016; Zoltick et al., 2019)

and data security (Joshi et al., 2020) were reported as barriers across stakeholders.

3.2.3.2 Healthcare System

Providers and the public reported that the potential impact of results on insurance (Haga et al., 2011; Henneman et al., 2011; Zoltick et al., 2019; Joshi et al., 2020) and the potential increased cost to the health system (Henneman et al., 2011; Joshi et al., 2020; Smit et al., 2020) would hinder their participation in population genetic screening.

3.2.3.3 Other

The possibility for discrimination by employers was reported by providers and the public (Henneman et al., 2011; Joshi et al., 2020).

3.3 Facilitators

Intrapersonal, interpersonal, and community facilitators can be found in **Table 3** and below.

3.3.1 Intrapersonal Facilitators

3.3.1.1 Demographics and Socio-Economic Status

One study (Sanderson et al., 2004) reported that male gender ($p = 0.029$) and later middle age were positively correlated with an interest in screening. On the other hand, another study (Neghina and Anghel, 2010) reported that younger age was a facilitator to uptake of screening. Higher socioeconomic status was additionally cited as a facilitator to participation (Neghina and Anghel, 2010; Hay et al., 2018).

3.3.1.2 Psychosocial Factors, Knowledge, Attitudes, and Beliefs

Attitudes related to having an interest about ancestry (Sanderson et al., 2016; Zoltick et al., 2019), professional interest (Sanderson et al., 2016; Zoltick et al., 2019), interest in genetics and/or science (Sanderson et al., 2016; Rego et al., 2019; Zoltick et al., 2019), and general curiosity (Hardie, 2011; Nusbaum et al., 2013; Sanderson et al., 2016; East et al., 2019; Zoltick et al., 2019) were reported facilitators for screening. Additional facilitators include altruism (Nusbaum et al., 2013; Sanderson et al., 2016; Rego et al., 2019) and the chance for participants to learn about themselves (Nielsen and El-Sohemy, 2012; Sanderson et al., 2016; Rubinsak et al., 2019).

Knowledge (Borry et al., 2008; Haga et al., 2011), the belief that screening will provide helpful information (Shaw and Bassi, 2001), trust in provider (Hardie, 2011) and trust in medicine (Hardie, 2011) were all associated with interest in population genetic screening, with the latter two being statistically significant.

Patients reported that the chance to have a free screen (Neghina and Anghel, 2010) and a "nothing to lose" attitude (Nusbaum et al., 2013) and the public reported that viewing population genetic screening as a novel opportunity (Sanderson et al., 2016) and a fun and entertaining activity (Zoltick et al., 2019) were facilitators for undergoing screening.

3.3.1.3 Clinical Factors

All stakeholders viewed the potential for medical intervention and/or monitoring (Borry et al., 2008; Nielsen and El-Sohemy, 2012; Sanderson et al., 2016; East et al., 2019; Joshi et al., 2020) as a facilitator to population genetic screening. The public reported that curability ($p < 0.001$) (Shaw and Bassi, 2001), non-fatalness of a condition ($p < 0.01$) (Shaw and Bassi, 2001), a more certain outcome (Shaw and Bassi, 2001), a known or suspected personal history (Sanderson et al., 2016; Hay et al., 2018), the potential to encourage health improvements through means such as behavioral changes (Hardie, 2011; Nielsen and El-Sohemy, 2012; Sanderson et al., 2016; Zoltick et al., 2019), and the use of results for future diagnostic purposes (Sanderson et al., 2016) were positively associated with interest and/or receipt of population genetic screening through a population-based context.

Additionally, patients reported their seeking medical information as a reason for receiving screening (Neghina and Anghel., 2010; Nusbaum et al., 2013; East et al., 2019). Patients and the public reported that the ability to prepare for future health (Nicholls et al., 2016; Sanderson et al., 2016; East et al., 2019; Rego et al., 2019; Zoltick et al., 2019) and the use of results for pharmacogenomics (Sanderson et al., 2016; East et al., 2019; Zoltick et al., 2019) were facilitators to population genetic screening.

3.3.2 Interpersonal Facilitators

3.3.2.1 Family

All interpersonal facilitators were related to participants' family. Patients and the public reported that the ability to provide information to family members to them (Nusbaum et al., 2013; Nicholls et al., 2016; Sanderson et al., 2016; East et al., 2019; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019). Having family who have had their genomes sequenced facilitated participation as well (Zoltick et al., 2019).

Family history positively associated with both interest and/or participation in population genetic screening (Hardie, 2011; Sanderson et al., 2016; Hay et al., 2018; Rego et al., 2019; Rubinsak et al., 2019; Zoltick et al., 2019) and labeled as a statistically significant factor in one study (Sanderson et al., 2004). On the other hand, a lack of family health history was also reported as a facilitator for both interest and/or participation in four studies (Sanderson et al., 2004; Sanderson et al., 2016; Rego et al., 2019; Zoltick et al., 2019).

3.4 Perceptions

Perceptions are summarized in **Supplementary Appendix SD**.

3.5 Effectiveness Measures

Effectiveness measures are summarized in **Supplementary Appendix SE**.

4 DISCUSSION

Overall, we identified multilevel barriers and facilitators for population genetic screening implementation. Psychosocial

and attitudinal barriers, such as anxiety and worry toward screening and the possibility for negative psychological and emotional impacts, were the most reported individual-level barriers across stakeholders, even though studies to date have demonstrated limited impacts on psychological and emotional outcomes with any adverse responses dissipating over time (Hietaranta-Luoma et al., 2015; Hollands et al., 2016; Frieser et al., 2018; Smit et al., 2020).

Skeptical healthcare providers cited a perceived lack of clinical utility as a barrier, reporting that although they believe population genetic screening is valuable, they do not believe that it is ready for clinical use (Joshi et al., 2020). On the other hand, healthcare providers who supported population genetic screening reported the potential for results to inform medical intervention and/or monitoring as a reason for their support. Our findings are consistent with previous literature indicating that obtaining provider buy-in is needed for the implementation of large-scale screening (Peterson et al., 2016). Additionally, the current perception of clinical utility places value on genomic medicine in relation to informing treatment, and excludes other applications for screening such as risk prediction and prognosis (Joseph et al., 2016). The Association for Molecular Pathology (Joseph et al., 2016) recommends expanding the definition of clinical utility for molecular tools through approaches such as utilizing a modified ACCE model (CDC, 2019) and promoting patient-centered definitions of clinical utility. Our data suggests the need for interventions directed toward obtaining buy-in and expanding the definition of clinical utility to include the context of population genetic screening.

Studies also reported potential ethical issues, concerns relating to data management, and potential discrimination as barriers to interest in population genetic screening. These factors are especially important in the age of "big data" (Price and Cohen, 2019), and previous literature has called for the consideration of ethical questions in implementing population genetic screening (Murray et al., 2018). The BabySeq Project is assessing ethical, legal, and social implications (ELSI) relating to the ethical issues of result return (Friedman et al., 2017) and the medical, behavioral, and economic impacts (Holm et al., 2018) of newborn screening. These studies, along with essential ELSI questions raised by newborn screening (Goldenberg et al., 2019), may provide a potential framework that can be adapted for assessing ELSI considerations in evaluating general population genetic screening.

Many of our included studies investigated the general public's perspective of population genetic screening. This presents an opportunity to focus on the roles of other stakeholders within the larger societal systems, such as healthcare providers and public health officials. Primary care providers, who will likely be the touchpoint for many interested in population genetic screening, reported inadequate knowledge as a barrier to ordering screening. In one study (Haga et al., 2011), roughly half of providers reported that they felt prepared to order population genetic screening. Previous literature has noted the limited evidence regarding the views and roles of healthcare providers in genomic medicine (Hann et al., 2017a; Hauser et al., 2018; Crellin et al., 2019), identified the importance of educational resources for provider preparedness to order and interpret results (Rohrer Vitek et al., 2017; Hauser et al., 2018; Smit et al., 2019), and described the integral role that public health officials will play in insuring proper implementation of population genetic screening (Molster et al., 2018). With few provider-based studies (most of which studied primary care providers) and no public health-based studies, we see a need for increased studies to investigate the viewpoints of these providers and develop the necessary educational interventions.

Furthermore, the current state of research in population genetic screening focuses on individuals, with most studies revealing barriers and facilitators to interest and/or participation in population genetic screening at an individual level. We identified few interpersonal facilitators and barriers and no community-level facilitators. All our included studies were designed to elucidate stakeholders' views and attitudes. This leaves a large gap in the literature in understanding the complex interactions between communities, the healthcare system, and the public health system. The studies which revealed interpersonal and community factors conducted surveys or semi-structured interviews, suggesting a need for additional studies to explicitly investigate macro-level determinants for population genetic screening that are suited to quantitative methods.

Most (all but two) were conducted in racially/ethnically diverse countries (Australia, Canada, United States, and United Kingdom), however roughly one third did not include information on the race or ethnicity of individuals receiving population genetic screening. This is of particular importance as studies have found ethnic minorities to be generally more apprehensive toward genetic testing than white individuals (Hann et al., 2017b). Without data on race and ethnicity of study populations the generalizability of findings is unclear and we remain unable to monitor disparities in access to population genetic screening. This suggests a need for improved reporting of race/ethnicity in population genetic screening research and a need to focus on health equity.

In addition to this challenge, more general agreement on the terminology and reporting of race, ethnicity, and ancestry in genomic research with an eye toward reproducible, ethical, and equitable research is warranted (Flanagin et al., 2021). Though the National Human Genome Research Institute (NHGRI) boldly predicts that "research in human genomics will have moved beyond population descriptors based on historic social constructs such as race" by 2030 (Green et al., 2020), there are currently numerous challenges inherent in standardizing the use (or disuse) of race and ethnicity and other population descriptors in clinical genetics. Fortunately, the National Academies of Sciences, Engineering, and Medicine established a multi-disciplinary committee to examine the current use of population descriptors in genomics research and identify best practices for improving the use of the terminology in the future.

Many studies incorporated genetic counseling; however, they had varying forms of preintervention information content and delivery and only a few assessed the efficacy of different delivery methods. The best approach and timing for genetic counseling delivery has not yet been determined. To date, there is some evidence showing that different contexts will likely have different requirements (Evans and Manchanda, 2020). For example, while this review explicitly excluded

reproductive genetic testing, population-wide screening will nonetheless have profound implications for individuals of reproductive age who would be at risk of passing a hereditary predisposition for a life-threatening condition to existing or future children. This provides an opportunity to implement studies specifically designed to investigate the best manner of prescreen education and counseling specific to the delivery context, such as health literacy levels, cultural considerations, reproductive age, and disease type.

Finally, out of the studies that implemented population genetic screening and collected post-intervention data, only one followed participants for more than 12 months (Allen et al., 2008). Without sufficient long-term data, it is difficult to assess the efficacy of the screening programs at the population level. There is a need for prospective cohort studies and randomized controlled trials to evaluate any long-term benefits, such as clinical and economic outcomes, to population-level genetic screening implementation (Murray et al., 2018, 2020). The BabySeq project provides a model for identifying these long-term outcomes (Holm et al., 2018), which may be adapted to the context of population genetic screening. Such studies will likely address our previous points of determining ELSI factors to population genetic screening and assessing the effects of prescreen education methods as well.

5 LIMITATIONS

There is a potential for bias as we reported missing items as "not reported" and did not contact authors for additional information. Articles varied as to which outcome was reported (barrier, facilitator, perception, and/or outcome), so some articles may be more represented than others. Our included studies did not assess effect sizes of barriers and facilitators on interest and/or uptake of population genetic screening, which prevented us from conducting a meta-analysis. Additionally, the heterogeneity in disease states and reported effectiveness measures prevented us from fully synthesizing the data. With all systematic reviews, there is the possibility that we missed relevant literature.

6 CONCLUSION

We found that 1) psychosocial, attitudinal, and belief-related factors present a barrier for stakeholders to participate in screening, 2) perceived limited clinical utility presents a barrier for provider uptake, 3) there is a need for additional studies investigating healthcare and public health provider roles and education, 4) research in population genetic screening has focused on stakeholder attitudes, and 5) there is a need for long-term follow-up studies and health equity-focused studies of population genetic screening. Future research should 1) evaluate the best manner for prescreen education and counseling for specific contexts, 2) examine provider buy-in and clinical utility expansion, 3) investigate the views of providers and develop educational resources, 4) investigate macro-level determinants of and address ELSI questions toward population genetic screening, and 5) assess the long-term outcomes of population genetic screening. Taken together this data can inform future interventions to improve the development and implementation of population genetic screening.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

ES, SS, and MR conceived of the study and designed the protocol. RC conducted database searches. ES, SS, LP, MD, KF, BH, and LM participated in the screening, full-text review, and data abstraction processes. AS and CA participated in the screening and full-text review. MR participated in the screening and data abstraction processes. ES synthesized the data and prepared the first draft of the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.865384/full#supplementary-material

REFERENCES

Allen, K. J., Nisselle, A. E., Collins, V. R., Williamson, R., and Delatycki, M. B. (2008). Asymptomatic Individuals at Genetic Risk of Haemochromatosis Take Appropriate Steps to Prevent Disease Related to Iron Overload. *Liver Int.* 28, 363–369. doi:10.1111/j.1478-3231.2008.01661.x

Ames, A. G., Metcalfe, S. A., Archibald, A. D., Duncan, R. E., and Emery, J. (2015). Measuring Informed Choice in Population-Based Reproductive Genetic Screening: a Systematic Review. *Eur. J. Hum. Genet.* 23, 8–21. doi:10.1038/ejhg.2014.89

Borry, P., Goffin, T., Nys, H., and Dierickx, K. (2008). Attitudes Regarding Predictive Genetic Testing in Minors: a Survey of European Clinical Geneticists. *Am. J. Med. Genet.* 148c, 78–83. doi:10.1002/ajmg.c.30165

CDC (2019). ACCE Model List of 44 Targeted Questions. Available at: https://www.cdc.gov/genomics/gtesting/acce/acce_proj.htm (Accessed January 12, 2022).

CDC (2021). Tier 1 Genomics Applications and their Importance to Public Health. Available at: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm (Accessed December 28, 2021).

Crellin, E., McClaren, B., Nisselle, A., Best, S., Gaff, C., and Metcalfe, S. (2019). Preparing Medical Specialists to Practice Genomic Medicine: Education an Essential Part of a Broader Strategy. *Front. Genet.* 10, 789. doi:10.3389/fgene.2019.00789

East, K. M., Cochran, M., Kelley, W. V., Greve, V., Emmerson, K., and Raines, G. (2019). Understanding the Present and Preparing for the Future: Exploring the Needs of Diagnostic and Elective Genomic Medicine Patients. *J. Genet. Couns.* 28, 438–448. doi:10.1002/jgc4.1114

Evans, O., and Manchanda, R. (2020). Population-based Genetic Testing for Precision Prevention. *Cancer Prev. Res. phila. Pa.)* 13, 643. doi:10.1158/1940-6207.CAPR-20-0002

Fenton, G. L., Smit, A. K., Freeman, L., Badcock, C., Dunlop, K., Butow, P. N., et al. (2018). Development and Evaluation of a Telephone Communication Protocol for the Delivery of Personalized Melanoma Genomic Risk to the General Population. *J. Genet. Couns.* 27, 370–380. doi:10.1007/s10897-017-0183-7

Flanagin, A., Frey, T., and Christiansen, S. L. (2021). AMA Manual of Style Committee. Updated Guidance on the Reporting of Race and Ethnicity in Medical and Science Journals. *JAMA* 326 (7), 621–627. doi:10.1001/jama.2021.13304

Friedman, J. M., Cornel, M. C., Goldenberg, A. J., Lister, K. J., Sénécal, K., Vears, D. F., et al. (2017). Genomic Newborn Screening: Public Health Policy Considerations and Recommendations. *BMC Med. Genomics* 10, 9. doi:10.1186/s12920-017-0247-4

Frieser, M. J., Wilson, S., and Vrieze, S. (2018). Behavioral Impact of Return of Genetic Test Results for Complex Disease: Systematic Review and Meta-Analysis. *Health Psychol. Off. J. Div. Health Psychol. Am. Psychol. Assoc.* 37, 1134–1144. doi:10.1037/hea0000683

Godino, J. G., van Sluijs, E. M. F., Marteau, T. M., Sutton, S., Sharp, S. J., and Griffin, S. J. (2016). Lifestyle Advice Combined with Personalized Estimates of Genetic or Phenotypic Risk of Type 2 Diabetes, and Objectively Measured Physical Activity: A Randomized Controlled Trial. *PLoS Med.* 13. doi:10.1371/journal.pmed.1002185

Golden, S. D., and Earp, J. A. L. (2012). Social Ecological Approaches to Individuals and Their Contexts: Twenty Years of Health Education & Behavior Health Promotion Interventions. *Health Educ. Behav.* 39, 364–372. doi:10.1177/1090198111418634

Goldenberg, A. J., Lloyd-Puryear, M., Brosco, J. P., Therrell, B., Bush, L., Berry, S., et al. (2019). Including ELSI Research Questions in Newborn Screening Pilot Studies. *Genet. Med.* 21, 525–533. doi:10.1038/s41436-018-0101-x

Green, E. D., Gunter, C., Biesecker, L. G., Di Francesco, V., Easter, C. L., Feingold, E. A., et al. (2020). Strategic Vision for Improving Human Health at the Forefront of Genomics. *Nature* 586, 683–692. Epub 2020 Oct 28. PMID: 33116284; PMCID: PMC7869889. doi:10.1038/s41586-020-2817-4

Haga, S. B., Barry, W. T., Mills, R., Svetkey, L., Suchindran, S., Willard, H. F., et al. (2014). Impact of Delivery Models on Understanding Genomic Risk for Type 2 Diabetes. *Public Health Genomics* 17, 95–104. doi:10.1159/000358413

Haga, S. B., Carrig, M. M., O'Daniel, J. M., Orlando, L. A., Killeya-Jones, L. A., Ginsburg, G. S., et al. (2011). Genomic Risk Profiling: Attitudes and Use in Personal and Clinical Care of Primary Care Physicians Who Offer Risk Profiling. *J. Gen. Intern Med.* 26, 834–840. doi:10.1007/s11606-011-1651-7

Hampel, H., and de la Chapelle, A. (2011). The Search for Unaffected Individuals with Lynch Syndrome: Do the Ends Justify the Means? *Cancer Prev. Res. phila. Pa* 4, 1–5. doi:10.1158/1940-6207.CAPR-10-0345

Hann, K. E. J., Fraser, L., Side, L., Gessler, S., Waller, J., Sanderson, S. C., et al. (2017a). Health Care Professionals' Attitudes towards Population-Based Genetic Testing and Risk-Stratification for Ovarian Cancer: a Cross-Sectional Survey. *BMC Womens Health* 17, 132. doi:10.1186/s12905-017-0488-6

Hann, K. E. J., Freeman, M., Fraser, L., Waller, J., Sanderson, S. C., Rahman, B., et al. (2017b). Awareness, Knowledge, Perceptions, and Attitudes towards Genetic Testing for Cancer Risk Among Ethnic Minority Groups: a Systematic Review. *BMC Public Health* 17, 503. doi:10.1186/s12889-017-4375-8

Hardie, E. A. (2011). Australian Community Responses to the Use of Genetic Testing for Personalised Health Promotion. *Aust. J. Psychol.* 63, 119–129. doi:10.1111/j.1742-9536.2011.00017.x

Hauser, D., Obeng, A. O., Fei, K., Ramos, M. A., and Horowitz, C. R. (2018). Views of Primary Care Providers on Testing Patients for Genetic Risks for Common Chronic Diseases. *Health Aff. Proj. Hope* 37, 793–800. doi:10.1377/hlthaff.2017.1548

Hay, J. L., Kaphingst, K. A., Buller, D., Schofield, E., Meyer White, K., Sussman, A., et al. (2021). Behavioral and Psychological Outcomes Associated with Skin Cancer Genetic Testing in Albuquerque Primary Care. *Cancers* 13, 4053. doi:10.3390/cancers13164053

Hay, J. L., Zielaskowski, K., Meyer White, K., Kaphingst, K., Robers, E., Guest, D., et al. (2018). Interest and Uptake of MC1R Testing for Melanoma Risk in a Diverse Primary Care Population a Randomized Clinical Trial. *JAMA Dermatol* 154, 684–693. doi:10.1001/jamadermatol.2018.0592

Henneman, L., Timmermans, D. R., Bouwman, C. M., Cornel, M. C., and Meijers-Heijboer, H. (2011). A Low Risk Is Still a Risk": Exploring Women's Attitudes towards Genetic Testing for Breast Cancer Susceptibility in Order to Target Disease Prevention. *Public Health Genomics* 14, 238–247. doi:10.1159/000276543

Hietaranta-Luoma, H.-L., Luomala, H. T., Puolijoki, H., and Hopia, A. (2015). Using ApoE Genotyping to Promote Healthy Lifestyles in Finland - Psychological Impacts: Randomized Controlled Trial. *J. Genet. Couns.* 24, 908–921. doi:10.1007/s10897-015-9826-8

Hollands, G. J., French, D. P., Griffin, S. J., Prevost, A. T., Sutton, S., King, S., et al. (2016). The Impact of Communicating Genetic Risks of Disease on Risk-Reducing Health Behaviour: Systematic Review with Meta-Analysis. *BMJ* 352, i1102. doi:10.1136/bmj.i1102

Holm, I. A., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., Frankel, L. A., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18, 225. doi:10.1186/s12887-018-1200-1

Hong, Q., Pluye, P., Fabregues, S., Bartlett, G., Boardman, F., Cargo, M., et al. (2018). *Mixed Methods Appraisal Tool (MMAT).* version 2018. Montréal: Department of Family Medicine, McGill University.

Joseph, L., Cankovic, M., Caughron, S., Chandra, P., Emmadi, R., Hagenkord, J., et al. (2016). The Spectrum of Clinical Utilities in Molecular Pathology Testing Procedures for Inherited Conditions and Cancer: A Report of the Association for Molecular Pathology. *J. Mol. Diagn.* 18, 605–619. doi:10.1016/j.jmoldx.2016.05.007

Joshi, E., Mighton, C., Clausen, M., Casalino, S., Kim, T. H. M., Kowal, C., et al. (2020). Primary Care Provider Perspectives on Using Genomic Sequencing in the Care of Healthy Children. *Eur. J. Hum. Genet.* 28, 551–557. doi:10.1038/s41431-019-0547-6

Lacson, J. C. A., Doyle, S. H., Qian, L., Del Rio, J., Forgas, S. M., Valavanis, S., et al. (2021). A Randomized Trial of Precision Prevention Materials to Improve Primary and Secondary Melanoma Prevention Activities Among Individuals with Limited Melanoma Risk Phenotypes. *Cancers* 13, 3143. doi:10.3390/cancers13133143

Laskey, S. L., Williams, J., Pierre-Louis, J., O'Riordan, M., Matthews, A., and Robin, N. H. (2003). Attitudes of African American Premedical Students toward Genetic Testing and Screening. *Genet. Med.* 5, 49–54. doi:10.1097/00125817-200301000-00008

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *BMJ* 339, b2535. doi:10.1136/bmj.b2535

Molster, C. M., Bowman, F. L., Bilkey, G. A., Cho, A. S., Burns, B. L., Nowak, K. J., et al. (2018). The Evolution of Public Health Genomics: Exploring its Past, Present, and Future. *Front. Public Health* 6. doi:10.3389/fpubh.2018.00247

Murray, M. F., Evans, J. P., Angrist, M., Chan, K., Uhlmann, W. R., Doyle, D. L., et al. (2018). *A Proposed Approach for Implementing Genomics-Based Screening Programs for Healthy Adults*. Washington, DC: NAM Perspectives. doi:10.31478/201812a

Murray, M. F., Evans, J. P., and Khoury, M. J. (2020). DNA-based Population Screening: Potential Suitability and Important Knowledge Gaps. *JAMA* 323, 307–308. doi:10.1001/jama.2019.18640

Neghina, A. M., and Anghel, A. (2010). Hereditary Hemochromatosis: Awareness and Genetic Testing Acceptability in Western Romania. *Genet. Test. Mol. Biomark.* 14, 847–850. doi:10.1089/gtmb.2010.0109

Nicholls, S. G., Etchegary, H., Carroll, J. C., Castle, D., Lemyre, L., Potter, B. K., et al. (2016). Attitudes to Incorporating Genomic Risk Assessments into Population

Screening Programs: The Importance of Purpose, Context and Deliberation Donna Dickenson, Sandra Soo-Jin Lee, and Michael Morrison. *BMC Med. Genomics* 9. doi:10.1186/s12920-016-0186-5

Nielsen, D. E., and El-Sohemy, A. (2012). A Randomized Trial of Genetic Information for Personalized Nutrition. *Genes Nutr.* 7, 559–566. doi:10.1007/s12263-012-0290-x

Nusbaum, R., Leventhal, K.-G., Hooker, G. W., Peshkin, B. N., Butrick, M., Salehizadeh, Y., et al. (2013). Translational Genomic Research: Protocol Development and Initial Outcomes Following SNP Testing for Colon Cancer Risk. *Transl. Behav. Med.* 3, 17–29. doi:10.1007/s13142-012-0149-0

O'Neill, S. C., Tercyak, K. P., Baytop, C., Hensley Alford, S., and McBride, C. M. (2015). A New Approach to Assessing Affect and the Emotional Implications of Personal Genomic Testing for Common Disease Risk. *Public Health Genomics* 18, 104–112. doi:10.1159/000370101

Peterson, J. F., Field, J. R., Shi, Y., Schildcrout, J. S., Denny, J. C., McGregor, T. L., et al. (2016). Attitudes of Clinicians Following Large-Scale Pharmacogenomics Implementation. *Pharmacogenomics J.* 16, 393–398. doi:10.1038/tpj.2015.57

Price, W. N., and Cohen, I. G. (2019). Privacy in the Age of Medical Big Data. *Nat. Med.* 25, 37–43. doi:10.1038/s41591-018-0272-7

Rego, S., Dagan-Rosenfeld, O., Bivona, S. A., Snyder, M. P., and Ormond, K. E. (2019). Much Ado about Nothing: A Qualitative Study of the Experiences of an Average-Risk Population Receiving Results of Exome Sequencing. *J. Genet. Couns.* 28, 428–437. doi:10.1002/jgc4.1096

Representatives of the Global Familial Hypercholesterolemia Community (2020). Reducing the Clinical and Public Health Burden of Familial Hypercholesterolemia: A Global Call to Action. *JAMA Cardiol.* 5, 217–229. doi:10.1001/jamacardio.2019.5173

Rogowski, W. (2006). Genetic Screening by DNA Technology: a Systematic Review of Health Economic Evidence. *Int. J. Technol. Assess. Health Care* 22, 327–337. doi:10.1017/s0266462306051221

Rohrer Vitek, C. R., Abul-Husn, N. S., Connolly, J. J., Hartzler, A. L., Kitchner, T., Peterson, J. F., et al. (2017). Healthcare Provider Education to Support Integration of Pharmacogenomics in Practice: the eMERGE Network Experience. *Pharmacogenomics* 18, 1013–1025. doi:10.2217/pgs-2017-0038

Rubinsak, L. A., Kleinman, A., Quillin, J., Gordon, S. W., Sullivan, S. A., Sutton, A. L., et al. (2019). Awareness and Acceptability of Population-Based Screening for Pathogenic BRCA Variants: Do Race and Ethnicity Matter? *Gynecol. Oncol.* 154, 383–387. doi:10.1016/j.ygyno.2019.06.009

Sanderson, S. C., Linderman, M. D., Suckiel, S. A., Diaz, G. A., Zinberg, R. E., Ferryman, K., et al. (2016). Motivations, Concerns and Preferences of Personal Genome Sequencing Research Participants: Baseline Findings from the HealthSeq Project. *Eur. J. Hum. Genet.* 24, 14–20. doi:10.1038/ejhg.2015.118

Sanderson, S. C., Linderman, M. D., Suckiel, S. A., Zinberg, R., Wasserstein, M., Kasarskis, A., et al. (2017). Psychological and Behavioural Impact of Returning Personal Results from Whole-Genome Sequencing: the HealthSeq Project. *Eur. J. Hum. Genet.* 25, 280–292. doi:10.1038/ejhg.2016.178

Sanderson, S. C., Wardle, J., Jarvis, M. J., and Humphries, S. E. (2004). Public Interest in Genetic Testing for Susceptibility to Heart Disease and Cancer: a Population-Based Survey in the UK. *Prev. Med.* 39, 458–464. doi:10.1016/j.ypmed.2004.04.051

Schardt, C., Adams, M. B., Owens, T., Keitz, S., and Fontelo, P. (2007). Utilization of the PICO Framework to Improve Searching PubMed for Clinical Questions. *BMC Med. Inf. Decis. Mak.* 7, 16. doi:10.1186/1472-6947-7-16

Shaw, J. S., and Bassi, K. L. (2001). Lay Attitudes toward Genetic Testing for Susceptibility to Inherited Diseases. *J. Health Psychol.* 6, 405–423. doi:10.1177/135910530100600404

Shen, E. C., Swetha, S., Passero, L., Allen, C., Dixon, M., Foss, K., et al. (2022). *Barriers and Facilitators for Universal Genetic Testing in Healthy Populations: A Systematic Review*. Research Square.

Shiloh, S., deHeer, H. D., Peleg, S., Hensley Alford, S., Skapinsky, K., Roberts, J. S., et al. (2015). The Impact of Multiplex Genetic Testing on Disease Risk Perceptions. *Clin. Genet.* 87, 117–123. doi:10.1111/cge.12403

Smit, A. K., Allen, M., Beswick, B., Butow, P., Dawkins, H., Dobbinson, S. J., et al. (2021). Impact of Personal Genomic Risk Information on Melanoma Prevention Behaviors and Psychological Outcomes: a Randomized Controlled Trial. *Genet. Med. Off. J. Am. Coll. Med. Genet.* 23, 2394–2403. doi:10.1038/s41436-021-01292-w

Smit, A. K., Newson, A. J., Keogh, L., Best, M., Dunlop, K., Vuong, K., et al. (2019). GP Attitudes to and Expectations for Providing Personal Genomic Risk Information to the Public: a Qualitative Study. *BJGP Open* 3, bjgpopen18X101633. doi:10.3399/bjgpopen18X101633

Smit, A. K., Reyes-Marcelino, G., Keogh, L., Cust, A. E., and Newson, A. J. (2020). There Is a Lot of Good in Knowing, but There Is Also a Lot of Downs": Public Views on Ethical Considerations in Population Genomic Screening. *J. Med. Ethics* medethics-2019, 105934. doi:10.1136/medethics-2019-105934

Srinivasan, S., Won, N. Y., Dotson, W. D., Wright, S. T., and Roberts, M. C. (2020). Barriers and Facilitators for Cascade Testing in Genetic Conditions: a Systematic Review. *Eur. J. Hum. Genet.* 28, 1631–1644. doi:10.1038/s41431-020-00725-5

Toiviainen, H., Jallinoja, P., Aro, A. R., and Hemminki, E. (2003). Medical and Lay Attitudes towards Genetic Screening and Testing in Finland. *Eur. J. Hum. Genet.* 11, 565–572. doi:10.1038/sj.ejhg.5201006

Vassy, J. L., Christensen, K. D., Schonman, E. F., Blout, C. L., Robinson, J. O., Krier, J. B., et al. (2017). The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients: A Pilot Randomized Trial. *Ann. Intern Med.* 167, 159–169. doi:10.7326/m17-0188

Vassy, J. L., Christensen, K. D., Slashinski, M. J., Lautenbach, D., Robinson, J. O., Blumenthal-Barby, J. A., et al. (2014). Someday it Will Be the Norm": Physician Perceptions of the Clinical Utility of Whole Genome Sequencing. *J. Gen. Intern. Med.* 29, S4.

Veritas Health Innovation Covidence systematic review software (2021). Covidence. Available at: https://www.covidence.org/(Accessed December 28, 2021).

Zoltick, E. S., Linderman, M. D., McGinniss, M. A., Ramos, E., Ball, M. P., Church, G. M., et al. (2019). Predispositional Genome Sequencing in Healthy Adults: Design, Participant Characteristics, and Early Outcomes of the PeopleSeq Consortium. *Genome Med.* 11. doi:10.1186/s13073-019-0619-9

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Exome/Genome-Wide Testing in Newborn Screening: A Proportionate Path Forward

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Population-based newborn screening (NBS) is among the most effective public health programs ever launched, improving health outcomes for newborns who screen positive worldwide through early detection and clinical intervention for genetic disorders discovered in the earliest hours of life. Key to the success of newborn screening programs has been near universal accessibility and participation. Interest has been building to expand newborn screening programs to also include many rare genetic diseases that can now be identified by exome or genome sequencing (ES/GS). Significant declines in sequencing costs as well as improvements to sequencing technologies have enabled researchers to elucidate novel gene-disease associations that motivate possible expansion of newborn screening programs. In this paper we consider recommendations from professional genetic societies in Europe and North America in light of scientific advances in ES/GS and our current understanding of the limitations of ES/GS approaches in the NBS context. We invoke the principle of proportionality—that benefits clearly outweigh associated risks—and the human right to benefit from science to argue that rigorous evidence is still needed for ES/GS that demonstrates clinical utility, accurate genomic variant interpretation, cost effectiveness and universal accessibility of testing and necessary follow-up care and treatment. Confirmatory or second-tier testing using ES/GS may be appropriate as an adjunct to conventional newborn screening in some circumstances. Such cases could serve as important testbeds from which to gather data on relevant programmatic barriers and facilitators to wider ES/GS implementation.

Keywords: exome sequencing, genome sequecing, newborn screening, population health genomics, access, public health ethics

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INTRODUCTION

Population-based newborn screening (NBS) is among the most effective public health programs ever launched (Tonniges, 2000; Sahai and Marsden, 2009; Berry, 2015). Updated national estimates in the United States suggest nearly 12,900 newborns screened positive for childhood onset disorders that previously led to severe morbidity or mortality and were listed on the Recommended Universal Screening Panel (RUSP) (5) between 2015 and 2017 (Sontag et al., 2020). Key to the success of NBS programs has been their affordability and near universal access and participation. Pre-symptomatic treatment of newborns who screen positive for some of these conditions is much more cost-effective

and less burdensome on healthcare systems than treating the conditions once they become symptomatic (Carroll and Downs, 2006). Preventing the development of symptomatic disease is a particularly important consideration with respect to genetic diseases that can be detected by ES/GS analysis because most do not have specific treatments that can prevent disease onset or progression.

Since early validation studies of mass screening tests for metabolic disorders in the 1960s (McCandless and Wright, 2020), NBS methods as well as their formal adoption and oversight have evolved considerably. Interest has been building to expand NBS programs to also include more rare genetic diseases that can be identified using ES/GS approaches (Holm et al., 2018; Genomics England and the UK National Screening Committee, 2021; Gold et al., 2022; Lu et al., 2022). Improvements to genome sequencing technologies that enable researchers to elucidate novel gene-disease associations and to diagnose conditions undiscoverable using traditional biochemical or other biomarker testing, and the wide availability and declining costs of genomic testing are among the reasons ES/GS might be advantageous as a first-tier clinical test for diagnosing genetic diseases.

At the outset, it is important to distinguish NBS meant to identify pre-symptomatic infants rare but potentially devastating conditions e.g., phenylketonuria (PKU), severe combined immunodeficiency disease of congenital heart defects, from screening for risk stratification meant to guide lifestyle modification or surveillance protocols routinely offered to adults. Current universal NBS protocols fall into the first category; ES/GS of newborn infants for most genetic diseases would fall into the second category. This is true whether one considers all known genetic diseases or only a subset in which non-specific interventions may be able to reduce the risk or age of symptomatic onset.

Using ES/GS as a tool in NBS may also inappropriately conflate the recognition of a disease-associated genetic variant with diagnosis of the disease. Diagnosing a genetic disease requires a physician to interpret an ES/GS result in the context of an individual's complete clinical picture–the medical history, family history, physical exam, and other laboratory and imaging studies–in light of what is known about the range of clinical manifestations, inheritance pattern, penetrance, and variability of the disease. Complete clinical assessment is the only confirmatory "test" available for most genetic diseases. If universal NBS relied on sequencing the entire genome, exome or specific regions of the exome, then complete clinical assessment for the genetic disease indicated would be necessary to confirm the molecular "diagnosis" in every case. Population-based NBS of any kind should only be offered as part of a comprehensive public health program that includes clinical follow-up, therapeutic interventions, quality assurance, governance and oversight, and public and professional education (Friedman et al., 2017) in addition to the confirmatory complete clinical assessment and genetic counselling (if the condition found is a genetic disease). If ES/GS is being considered as a replacement for current NBS, evidence that the ES/GS methods are superior to the existing methods is necessary. Adoption of sequencing-based NBS without consideration of the unique ethical, legal and social issues it raises (Eichinger et al., 2021; Woerner et al., 2021) risks widening disparities in availability and access to standard NBS, particularly in under-resourced settings.

In this paper, we review recommendations from professional bodies regarding integration of genomic sequencing methods in public NBS programs in Europe (Howard et al., 2015) and North America, where the authors are based. We limit our discussion of relevant ethical, legal and social issues associated with universal ES/GS as a population screening tool for newborns, acknowledging, as others do (Johnston et al., 2018), that different professional obligations and standards exist in clinical screening, diagnostic, and direct-to-consumer contexts. Our analysis focuses on applications of universal genomic sequencing of the genome, exome, or a portion of the exome that includes a large number of disease-associated genes. We refer to as "ES/GS," rather than on targeted sequencing of one or a few genes for confirmatory testing of conditions identified by conventional NBS (Bhattacharjee et al., 2015).

Indeed, there are compelling advantages for supporting genomic sequencing method applied in the NBS context. Genomic sequencing has been shown to detect previously fatal diseases in affected newborns, as well as provide information to patients and families about genetic predisposition risks for later onset diseases (Holm et al., 2018) and inform preventative clinical action. Scholars have also argued that biological family may receive ancillary benefits from recognition of disease-associated variants in an infant by enabling prenatal diagnosis or specialized care for future pregnancies, earlier diagnosis or prevention of disease in relatives, or the empowerment provided by better knowledge (Ceyhan-Birsoy et al., 2019; Biesecker et al., 2021). However, the "gap between what sequencing results can reveal and the kinds of information most people need to improve their health, combined with widely publicized hopes for the revolutionary power of genomics, creates the very real risk that patients, research participants, health care professionals, policy-makers, and others may have unrealistic expectations of what sequencing can achieve and little appreciation for its downsides" (Johnston et al., 2018).

Public opinion research suggests that family preferences vary considerably regarding whether and how to return genomic sequencing results (Lipstein et al., 2010; Fernandez et al., 2014; Botkin et al., 2015; Joseph et al., 2016; Pereira et al., 2021), to say nothing of current shortages of genetic counsellors and genetic specialist physicians needed or enhancements to genomic literacy and education for health professionals and the general public should ES/GS become routine in NBS (Lewis et al., 2016). Key policy questions also remain unresolved. These include: What rights and protections apply for genomic and related health data involving newborns when they become adults? How will public health agencies ensure that appropriate infrastructures for sequencing, variant interpretation, diagnostic confirmation, treatment or non-medical interventions, genetic counselling, clinical follow-up, and program governance and quality assurance are in place and accessible to all infants, even those in under-resourced settings? And whether requirements for

explicit informed consent to ES/GS-based NBS would need to obtained from the parents and, if so, should it include permission for others (researchers, family members, police, etc.) to access stored newborn sequencing data in the future.

We assess these questions by evaluating the proposed benefits and foreseeable risks of implementing ES/GS in NBS. In our analysis, we apply the principle of proportionality to our discussion—that benefits of sequencing should clearly outweigh associated risks—and consider the human right to benefit from science -especially that of the asymptomatic, at-risk newborn to be found. We conclude that routine universal ES/GS implementation is not justified at the present time, even if the analysis is restricted to a subset of disease-associated genes. Stronger evidence is needed to establish the clinical utility of ES/GS, accurate genomic variant interpretation, and cost effectiveness for newborn screening, as well as policies ensuring universal access and equitable resourcing for not only the testing but also for comprehensive diagnostic confirmation, treatment, genetic counselling, and clinical follow-up of affected patients. Moreover, this evidence should demonstrate the population health benefits of universal ES/GS-wide screening of newborns and not simply that anticipated harms of incorporating ES/GS are minimal. Prioritizing expanded access over expanded testing is likely to lead to more equitable distribution of the public health benefits of newborn screening programs.

PRINCIPLE OF PROPORTIONALITY

The principle of proportionality suggests an intervention may be ethically permissible if its anticipated benefits on balance justify exposure to associated harms and hence a helpful framework with which to assess ES/GS-based screening (Sénécal et al., 2018). The principle is rooted in moral and legal theory of punishment. 17th Century constitutional law theorists, for example, invoked the principle to judge the statutory fairness between restrictions imposed to implement a corrective measure and the severity of the act(s) the measure purports to mitigate (Walen, 2021). In research, the proportionality principle underpins decisions institutional/ethics review boards make regarding the relative risks and benefits of a study to prospective participants and is subsequently codified in national human subjects research regulations (OHRP, 2017; Canadian Institutes of Health Research, 2018) and international biomedical research norms (Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization, 2016; WMA, 2022). It has also been has more recently been applied to guide privacy protections when sharing genomic and related health data (Wright et al., 2016).

And last, but not least, some more recent versions of the normative framework for screening add the principle of proportionality as a central, over-arching, screening criterion: "The overall benefits of screening should outweigh the harm" (Andermann et al., 2008; Health Council of the Netherlands, 2008). The appeal of the proportionality principle to the NBS debate is astutely summarized by Kalkman and Dondorp in their position against screening newborns for non-treatable conditions: "the dividing line in the debate is . . . whether such screening should be regarded as catering to a parental "right to know," or as a public health service that should be subject to standards of evidence and proportionality" (Kalkman and Dondorp, 2022).

The Benefits of Accurate and Timely Diagnosis

New precision methods to detect disease-causing genetic variants have greatly improved (Dondorp and de Wert, 2013). ES/GS could identify infants with rare genetic diseases not currently recognized using standard NBS. In theory, newborns who screen positive by ES/GS have the potential to benefit from: early diagnosis; disease onset prevention using available approaches; opportunities for genetic counselling for their families; eligibility for participation in clinical trials or other research studies; and avoiding long and difficult diagnostic odysseys.

ES/GS should not, in our view, replace standard methods for any disease screening unless the former has been shown to have better sensitivity and specificity for the disease. For conditions that are not included in current NBS programs, development and uniform adoption of an approach will be needed to select the conditions for which ES/GS are expected to provide tangible benefit to the newborn. An exome- or genome-wide analysis that generates more harms than benefits or for which the harms and benefits have not been established is ethically unjustifiable–a more targeted analysis is to be preferred; see for example (Milko et al., 2019). But agreement on a uniform approach for selecting conditions detectable only using ES/GS is proving elusive for NBS programs worldwide (Jansen et al., 2017). Assuming agreement on the approach were achieved, the question would become whether every disease gene that we look for using ES/GS must meet the same criteria required to add conditions to the RUSP.

The benefit-harm calculus is further complicated by the type of disorder being screened. One significant challenge facing public health decision-makers and clinicians alike is determining when to add conditions to the RUSP that are identifiable only through ES/GS methods. For diseases for which standard screening is superior, ES/GS may be considered as an add-on to current first-tier screening programs. Findings from a comparison study for example showed that traditional NBS using tandem mass spectrometry had greater sensitivity and specificity than ES for the diseases that are currently being screened, but ES was useful for confirmatory (Adhikari et al., 2020).

Screening for Late-Onset Conditions

Debates abound in the literature regarding the ethics of testing children for conditions likely to present later in life or which may be clinically relevant for parents or other biological family members in the immediate term. The presumption of clinical benefit to the parents and family members, however, has been challenged (Buchbinder and Timmermans, 2011; Ross and Clayton, 2019). Screening parents themselves using ES/GS for

previously unrecognized conditions would not only be more clinically effective but, most importantly, avoids instrumentalizing the child for parental benefit. We furthermore object to predictive testing for later-onset disorders taking account both the harm principle and the principle of respect for the child's future right to informational self-determination, a specification of the child's proposed right to an open future (Davis, 1997). Professional guidelines are consistent with these principles, advocating that publicly funded, universal NBS should be limited to diseases that can be diagnosed in the newborn period and which can be effectively treated or prevented during childhood (de Wert et al., 2021; Miller et al., 2021). As others have argued, "Providing additional genomic information beyond the most actionable conditions, while potentially of interest to many parents, may increase the complexity of informed consent and thereby serve to distract from the primary health benefits" (Roman et al., 2020). Broadening the scope of NBS beyond its primary aim of detecting rare disorders in asymptomatic children has the potential to adversely impact the universal delivery of NBS, to say nothing of the impacts on public trust and widespread support for NBS.

Testing Capability and Challenges in Genomic Variant Interpretation

Standard clinical analyses of ES/GS data do not reliably identify some kinds of disease-causing genetic variants, including short tandem repeat expansions, mobile element insertions, and complex or small structural variants. Knowing that ES/GS-based NBS has been done may preclude or delay appropriate genetic testing for symptomatic genetic disease in an older child or adult.

Interpretation of NBS results requires extensive knowledge of benign, as well as disease-causing variants for every gene tested. The sensitivity and specificity of ES/GS for most rare genetic diseases are unknown and likely to remain so because sample sizes are small and studies difficult to power sufficiently. In addition, the penetrance and phenotypic spectrum associated with pathogenic variants for most genetic disease loci are unknown. Thus, it is difficult or impossible to know if an asymptomatic baby with a "molecular diagnosis" of a rare genetic disease will ever develop the disease or, in the event the child does develop the disease, when it will occur or how severe it will be. Moreover, genetic disease diagnosis is Bayesian. That is, the probability of finding a pathogenic variant is small in a healthy newborn with no family history of the genetic disease. Since there is no primary indication for NBS, the *a priori* risk that an infant will develop any particular genetic disease is extremely small. This makes "positive" results more likely to be false positives and less likely to be true positives, even if the analytical validity of the test is very high.

Our inability at the present time to interpret the pathogenicity of most genomic variants is perhaps the strongest reason against adopting ES/GS in population-based NBS, despite improvements to clinical annotation of variants (Amendola et al., 2020) and broader accessibility to relevant databases at the point of care (Rehm et al., 2015). The problems of interpretation also exacerbate the effects of false positives/negatives on families and the healthcare system that are likely to result if variants of hundreds or thousands of potential disease genes are analyzed (Adhikari et al., 2020).

The confidence of variant classification and clinical interpretation of genetic results will determine their predictive value. In line with the ethical principle of proportionality, proponents of ES/GS-based NBS will need to specify thresholds for what genes and/or variants should be disclosed in a screening context based on better understanding of anticipated benefits and harms associated with those decisions. The general issue remains that ES/GS is currently used as a diagnostic test, i.e., to confirm a clinical diagnosis of suspected genetic disease. However, in NBS, ES/GS would be used as a screening test to identify children who are at high risk of a genetic disease implied by the "molecular diagnosis." If ES/GS were indeed used as a screening test, confirmatory testing to manage the inevitable false positives must be available. The distinction between the ES/GS result, regardless of its ACMG classification, and the actual diagnosis of a disease in the child would have to be explicit, generally accepted, and universally understood to avoid stigmatization, discrimination, insurance coverage, among other social issues.

Interpretation of ES/GS variants requires comparisons to allele frequencies in both diagnosed and healthy populations and has direct implications for justice and health equity. This is because ES/GS interpretation is dependent on genetic ancestry. Variant interpretation upon which positive predictive values for ES/GS are measured has been established almost exclusively from individuals of European descent (Popejoy and Fullerton, 2016; Peterson et al., 2019). Given such underrepresentation of diverse ancestries, clinical interpretation of ES/GS results could be less reliable for newborns of non-European ancestry. Without adequate representation in datasets from individuals with diverse genetic ancestry, some newborns will benefit more from ES/GS than others. Clinical variant interpretation using resources such as ClinVar (Wain et al., 2018) and gnomAD (Gudmundsson et al., 2021) is therefore growing in importance, given they provide clinical assertions about genomic variants and associations with disease across genetically diverse populations. In general, problems of underrepresentation have prompted the development of new tools to monitor trends and identify gaps in genomic databases (Wang et al., 2022). Indeed, the global catalog of clinically actionable variants is expected to grow as reference data sets become larger, better curated and strive to be more representative of world populations.

Re-Analysis and Obligations to Update Variant Interpretation

It is anticipated that routine re-analysis of "negative" screens might increase the diagnostic rate by 3%–5% per year and identify variants of concern in children who later present with clinical features suggestive of a genetic disease (Wenger et al., 2017; Costain et al., 2018). To capture these clinical benefits, NBS programs would need to systematically update screens and store

ES/GS datasets in the health record to ensure results reflect up-to-date classification of genomic variants and take into account attendant costs and privacy risks. The treating physician may no longer be following the family and follow up with a new provider may be difficult and expensive. If a variant of uncertain significance were reclassified but not reported to the family based on clinical course, would NBS programs be subject to legal action if a child later manifests the disease (Clayton et al., 2021)? The expenditures and risks of storing all children's genomic data long-term to enable such systematic re-analysis may also exceed those of re-sequencing only those children for whom it is clinically indicated in the future (Veenstra et al., 2021).

Stigma, Psychological Impacts and Medicalization

Recent studies investigating the psychosocial impacts of expanding ES/GS in the newborn context have yielded different results. In a randomized trial of NBS with and without ES, researchers found both clinicians and parents valued information gleaned from standard of care NBS more than from exome sequencing but for different reasons (Pereira et al., 2019). Parents expressed knowing in advance how to prepare for a child with special needs was a benefit to sequencing, but worried about the psychosocial distresses brought on by variants of unknown significance and potential for discrimination among other things (Pereira et al., 2019). The potential for social stigma and medicalization of children with a molecular diagnosis who are pre-symptomatic (or destined never to exhibit the disease because it is non-penetrant) is also a concern. This scenario would be particularly concerning if enhanced surveillance or prophylactic treatments impinge on the child's quality of life or expose them to interventions with adverse effects.

Genomic Data Privacy and Protection

Key policy questions persist with respect to what rights and protections should apply to genomic and related health data collected at birth when newborns reach adulthood. The moral justification for mandatory NBS rests on the premise that finding the asymptomatic, at risk child is within the child's best interests (United Nations Convention on the Rights of the Child, 1989). Child welfare considerations and the "the opportunity to intervene and dramatically alter a child's life course and expectancy has been regarded as sufficient to preempt any claims of parental autonomy" (Goldenberg and Sharp, 2012). It is unlikely, however, that the huge volumes of data generated from ES/GS followed by untargeted whole exome/genome analysis will meet the criteria needed to justify overruling parental decision-making authority.

Yet samples taken from dried blood spots collected and stored using Guthrie cards are rich data sources needed to advance population health research. While most samples are de-identified or pseudonymized according to applicable laws/regulations when used for research, the generation of ES/GS data as part of NBS introduces novel ethical, legal and social challenges for data protection, agency and consent for the future adult (Khoury et al., 2003; Lewis, 2014). Genomic data are highly identifying and may implicate not only the individual tested but also their biological relatives. Concerns regarding loss of privacy and misuse of genomic data have emerged as key themes in the empirical literature on expansion of sequencing in NBS, and were found to be especially acute among participants of color (Joseph et al., 2016; Tsosie et al., 2021). It is unclear if the benefits of storing children's genomic data in a centralized research data repository outweighs the privacy and security risks, particularly if children are not given the opportunity to consent themselves.

Re-consenting minors when they become adults to the continued use of their data collected at birth is supported in theory but logistically challenging to implement in practice (Knoppers et al., 2016; Rothwell et al., 2017; Nordfalk and Ekstrøm, 2019). Legislation passed in the United States in 2014, for example, requires that researchers seek broad consent for the use of the child's dried blood spots for research beyond NBS (Newborn Screening Saves Lives Reauthorization Act, 2014). However this law preceded revisions to the United States Common Rule which now exempts research using de-identified data, thus removing a layer of specific consent (Lewis and Goldenberg, 2015; Rothwell et al., 2017). Empirical studies involving parents of both healthy and affected newborns suggest NBS programs should err on the side of greater transparency in terms of when, how and for what purposes their child's samples and data will be used (Downie et al., 2021). Policy makers would need to determine whether, or how permissions for future use of ES/GS data for research will be incorporated into screening, and it remains unknown what effect this will have on public willingness to sustain state sponsored NBS programs that adopt ES/GS.

ES/GS and the Wilson and Jungner Criteria

Disagreement regarding which disorders are screened for has largely (though not entirely) been avoided in some jurisdictions through standardization (Advisory Committee on Heritable Disorders in Newborns and Children, 2018) and concerted efforts are ongoing to harmonize screening lists internationally (Vittozzi et al., 2010; Franková et al., 2021). Wilson and Jungner anticipated such discrepancies and in 1968, developed criteria that outlined practical principles for screening services (**Box 1**) (Wilson and Jungner, 1968). While there have been recent calls to update the criteria to better align with technological advances in testing methods (King et al., 2021) and apply more nuanced decision analysis approaches (Prosser et al., 2012), the Wilson and Jungner criteria remain the generally accepted guidelines.

The threat to NBS participation should be a top concern if conditions are added to mandatory screening that challenge the Wilson-Jungner criteria or do not reflect how healthcare is accessed or paid for in a particular jurisdiction. Universal ES/GS with untargeted analysis in the NBS context poses several direct challenges to these criteria.

First, while there are many accepted treatments for conditions commonly screened for, most rare genetic diseases that are detectable by ES/GS do not have proven therapies.

BOX 1 | PROPOSED GUIDE TO SCREENING FOR DISEASE (WILSON-JUNGNER, 1968)

1) The condition sought should be an important health problem.
2) There should be an accepted treatment for patients with recognized disease.
3) Facilities for diagnosis and treatment should be available.
4) There should be a recognizable latent or early symptomatic stage.
5) There should be a suitable test or examination.
6) The test should be acceptable to the population.
7) The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8) There should be an agreed policy on whom to treat as patients.
9) The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10) Case-finding should be a continuing process and not a "once and for all" project.

Second, establishing a clinical diagnosis in an asymptomatic infant with a "molecular diagnosis" of a rare variant is resource-intensive, requiring specialized clinical assessment and variant interpretation, additional testing, and counseling services (Appelbaum et al., 2020). Newborn screening by any method should be accessible to every infant (Friedman et al., 2017; de Wert et al., 2021). To meet this universality target, healthcare centers must be equipped with appropriate sequencing infrastructure. Both human and material resources will therefore be needed in addition to those already allocated for existing NBS programs. At present, ES is available as a diagnostic tool primarily from certain clinical laboratories and through direct-to-consumer genetic testing services. A comparison of community report cards published by the National Organization for Rare Disorders (National Organization for Rare Disorders Newborn screening State report card, 2021) demonstrates that many NBS programs already face various resource limitations and vast differences exist in screening availability by U.S. states (Roman et al., 2020).

Disparities in NBS access and quality could be seen to violate the *parens patriae* doctrine which upholds that it is the duty of the State and its courts to protect the interests of persons in situations of vulnerability, for example children. NBS programs organized by the State are an extension of this duty (Knoppers, 1992), and the reasons many jurisdictions adopt an implied consent to NBS.

GS/ES-based NBS may well be different; if explicit consent is required, extant research suggests families are more likely to refuse consent, thus inadvertently denying their child the benefits of current NBS(Bombard et al., 2014; Joseph et al., 2016; Friedman et al., 2017; Genetti et al., 2019).

Moreover, the right of everyone to benefit from science and its applications is protected under Article 27 of the United Nations Declaration of Human Rights. While not a legally binding agreement, 193 countries have ratified at least one of the nine core international treaties which codify the Declaration's commitments to basic rights and freedoms. Article 24 of the Convention on the Rights of the Child further obligates signatories to implement interventions that reduce infant and child mortality, to provide effective health care, and to combat childhood disease, among other legally binding responsibilities. Taken together, international conventions have been powerful tools for motivating the development and sustainability of public health programs (Reinbold, 2019) including NBS. Applying a human rights frame to the current debate favors expanding access to established NBS methods that have shown to be clinically effective, and which enable more children to directly benefit from proven methods. Ensuring universal access to high quality NBS irrespective of birthplace, gender and income, however, continues to be a global challenge (Krotoski et al., 2009; Borrajo, 2021).

Third, most genetic conditions diagnosed through ES/GS in early childhood have unknown natural histories or are unrecognizable during early childhood because the diseases are so rare and have only been described in a small number of patients.

Fourth, ES/GS is widely misunderstood among patients and clinicians alike, challenging overall public acceptance as a testing method. Issues of particular concern include data privacy, family decision-making when faced with an uncertain result and possible insurance discrimination (Pereira et al., 2019; Wojcik et al., 2021).

Fifth, recent analyses of global NBS coverage indicate that cost remains a barrier to even standard NBS access in low- and middle-income countries (Therrell et al., 2015, 2020; Howson et al., 2018; Therrell and Padilla, 2018). Since ES/GS cannot replace all current NBS by other methods, sequencing computing and storage costs for genomic data would be needed in addition to current laboratory costs to mitigate real privacy and security risks. Studies further show that clinical demand for medical geneticists and genetic counsellors far exceeds available services (O'Daniel, 2010; Boothe et al., 2021). Ultimately, however, NBS alone cannot reasonably be expected to universally improve health outcomes without addressing systemic health disparities, underlying social determinants of health (Melzer, 2022) and barriers to healthcare access (Goldstein et al., 2020) experienced predominantly by marginalized racial/ethnic groups (Sohn and Timmermans, 2019).

CONCLUSION

Owing to the public health importance of universal access to NBS, applying ES/GS as screening tools in the newborn context is unsubstantiated as yet clinically and pragmatically. Ongoing translational research and technological advances will emerge in the coming years which are sure to improve our

understanding of the opportunities and limitations of ES/GS in detecting and preventing early disease. Considering this evolving evidence, policy makers ought to be persuaded by a burden a proof that clearly demonstrates superior public health benefits of ES/GS beyond those achievable through traditional NBS methods. Attempts to concentrate efforts only on justifying the minimalness of any anticipated harms associated with ES/GS in NBS risks sidelining the real ethical, legal and social issues which have thus far tempered the promises of precision medicine in general.

Our position thus exposes a central tension in the debate between providing universal access to traditional NBS and respecting parents' decision-making about much more extensive screening that they may perceive to be in the child's best interests but that many adults may not opt for themselves. All screening programs expose individuals to potential harms that must be balanced against the benefits anticipated. This is not unique to genome-wide sequencing-based screening programs and is true even if only a selected "slice" of genes represented in the exome data were analyzed. The reality that some infants will screen positive and never experience symptoms does not justify excluding possible ES/GS for NBS. Rather the balance of benefits and harms must be quantified and considered in any policy decision regarding screening programs to ensure aggregate benefits outweigh foreseeable aggregate harms. Indeed, NBS programs must expand to provide all newborns access to screening that is of proven value, meet established criteria for proportionality (e.g., Wilson-Jungner) and shown to yield greater and more equitably distributed public health gains.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors conceived of and contributed to the ideas represented in this paper. Author VR drafted the initial and revised manuscripts following peer review. Authors JF, GdW, and BK contributed to both editorial and substantive revisions to earlier drafts of the manuscript and during peer review. All authors approved the final version of the manuscript.

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REFERENCES

Adhikari, A. N., Gallagher, R. C., Wang, Y., Currier, R. J., Amatuni, G., Bassaganyas, L., et al. (2020). The Role of Exome Sequencing in Newborn Screening for Inborn Errors of Metabolism. *Nat. Med.* 26, 1392–1397. doi:10.1038/s41591-020-0966-5

Advisory Committee on Heritable Disorders in Newborns and Children (2018). *Recommended Uniform Screening Panel*.

Amendola, L. M., Muenzen, K., Biesecker, L. G., Bowling, K. M., Cooper, G. M., Dorschner, M. O., et al. (2020). Variant Classification Concordance Using the ACMG-AMP Variant Interpretation Guidelines across Nine Genomic Implementation Research Studies. *Am. J. Hum. Genet.* 107, 932–941. doi:10.1016/j.ajhg.2020.09.011

Andermann, A., Blancquaert, I., Beauchamp, S., and Déry, V. (2008). Revisting Wilson and Jungner in the Genomic Age: a Review of Screening Criteria over the Past 40 Years. *Bull. World Health Organ* 86, 317–319. doi:10.2471/blt.07.050112

Appelbaum, P. S., Parens, E., Berger, S. M., Chung, W. K., and Burke, W. (2020). Is There a Duty to Reinterpret Genetic Data? the Ethical Dimensions. *Genet. Med.* 22, 633–639. doi:10.1038/s41436-019-0679-7

Berry, S. A. (2015). Newborn Screening. *Clin. Perinatology* 42, 441–453. doi:10.1016/j.clp.2015.03.002

Bhattacharjee, A., Sokolsky, T., Wyman, S. K., Reese, M. G., Puffenberger, E., Strauss, K., et al. (2015). Development of DNA Confirmatory and High-Risk Diagnostic Testing for Newborns Using Targeted Next-Generation DNA Sequencing. *Genet. Med.* 17, 337–347. doi:10.1038/gim.2014.117

Biesecker, L. G., Green, E. D., Manolio, T., Solomon, B. D., and Curtis, D. (2021). Should All Babies Have Their Genome Sequenced at Birth? *BMJ*, n2679. doi:10.1136/bmj.n2679

Bombard, Y., Miller, F. A., Hayeems, R. Z., Barg, C., Cressman, C., Carroll, J. C., et al. (2014). Public Views on Participating in Newborn Screening Using Genome Sequencing. *Eur. J. Hum. Genet.* 22, 1248–1254. doi:10.1038/ejhg.2014.22

Boothe, E., Greenberg, S., Delaney, C. L., and Cohen, S. A. (2021). Genetic Counseling Service Delivery Models: A Study of Genetic Counselors' Interests, Needs, and Barriers to Implementation. *Jrnl Gene Coun* 30, 283–292. doi:10.1002/jgc4.1319

Borrajo, G. J. C. (2021). Newborn Screening in Latin America: A Brief Overview of the State of the Art. *Am. J. Med. Genet. C Semin. Med. Genet.* 187, 322. doi:10.1002/ajmg.c.31899

Botkin, J. R., Belmont, J. W., Berg, J. S., Berkman, B. E., Bombard, Y., Holm, I. A., et al. (2015). Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am. J. Hum. Genet.* 97, 6–21. doi:10.1016/j.ajhg.2015.05.022

Buchbinder, M., and Timmermans, S. (2011). Newborn Screening and Maternal Diagnosis: Rethinking Family Benefit. *Soc. Sci. Med.* 73, 1014–1018. doi:10.1016/j.socscimed.2011.06.062

Canadian Institutes of Health Research (2018). *Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council, Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*.

Carroll, A. E., and Downs, S. M. (2006). Comprehensive Cost-Utility Analysis of Newborn Screening Strategies. *Pediatrics* 117, S287–S295. doi:10.1542/peds.2005-2633H

Ceyhan-Birsoy, O., Murry, J. B., Machini, K., Lebo, M. S., Yu, T. W., Fayer, S., et al. (2019). Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project. *Am. J. Hum. Genet.* 104, 76–93. doi:10.1016/j.ajhg.2018.11.016

Clayton, E. W., Appelbaum, P. S., Chung, W. K., Marchant, G. E., Roberts, J. L., and Evans, B. J. (2021). Does the Law Require Reinterpretation and Return of Revised Genomic Results? *Genet. Med.* 23, 833–836. doi:10.1038/s41436-020-01065-x

Costain, G., Jobling, R., Walker, S., Reuter, M. S., Snell, M., Bowdin, S., et al. (2018). Periodic Reanalysis of Whole-Genome Sequencing Data Enhances the Diagnostic Advantage over Standard Clinical Genetic Testing. *Eur. J. Hum. Genet.* 26, 740–744. doi:10.1038/s41431-018-0114-6

Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (2016). *International Ethical Guidelines for Health-Related Research Involving Humans*. Geneva, Switzerland: World Health Organization.

Davis, D. S. (1997). Genetic Dilemmas and the Child's Right to an Open Future. *Hastings Cent. Rep.* 27, 7. doi:10.2307/3527620

de Wert, G., Dondorp, W., Dondorp, W., Clarke, A., Dequeker, E. M. C., Cordier, C., et al. (2021). Opportunistic Genomic Screening. Recommendations of the European Society of Human Genetics. *Eur. J. Hum. Genet.* 29, 365–377. doi:10.1038/s41431-020-00758-w

Dondorp, W. J., and de Wert, G. M. W. R. (2013). The 'thousand-Dollar Genome': an Ethical Exploration. *Eur. J. Hum. Genet.* 21, S6–S26. doi:10.1038/ejhg.2013.73

Downie, L., Halliday, J., Lewis, S., and Amor, D. J. (2021). Principles of Genomic Newborn Screening Programs. *JAMA Netw. Open* 4, e2114336. doi:10.1001/jamanetworkopen.2021.14336

Eichinger, J., Elger, B. S., Koné, I., Filges, I., Shaw, D., Zimmermann, B., et al. (2021). The Full Spectrum of Ethical Issues in Pediatric Genome-wide Sequencing: a Systematic Qualitative Review. *BMC Pediatr.* 21, 387. doi:10.1186/s12887-021-02830-w

Fernandez, C. V., Bouffet, E., Malkin, D., Jabado, N., O'Connell, C., Avard, D., et al. (2014). Attitudes of Parents toward the Return of Targeted and Incidental Genomic Research Findings in Children. *Genet. Med.* 16, 633–640. doi:10.1038/gim.2013.201

Franková, V., Driscoll, R. O., Jansen, M. E., Loeber, J. G., Kožich, V., Bonham, J., et al. (2021). Regulatory Landscape of Providing Information on Newborn Screening to Parents across Europe. *Eur. J. Hum. Genet.* 29, 67–78. doi:10.1038/s41431-020-00716-6

Friedman, J. M., Cornel, M. C., Goldenberg, A. J., Lister, K. J., Sénécal, K., Vears, D. F., et al. (2017). Genomic Newborn Screening: Public Health Policy Considerations and Recommendations. *BMC Med. Genomics* 10, 9. doi:10.1186/s12920-017-0247-4

Genetti, C. A., Schwartz, T. S., Robinson, J. O., VanNoy, G. E., Petersen, D., Pereira, S., et al. (2019). Parental Interest in Genomic Sequencing of Newborns: Enrollment Experience from the BabySeq Project. *Genet. Med.* 21, 622–630. doi:10.1038/s41436-018-0105-6

Genomics England and the UK National Screening Committee (2021). *Implications of Whole Genome Sequencing for Newborn Screening: A Public Dialogue*.

Gold, N. B., Harrison, S. M., Rowe, J. H., Gold, J., Furutani, E., Biffi, A., et al. (2022). Low Frequency of Treatable Pediatric Disease Alleles in gnomAD: An Opportunity for Future Genomic Screening of Newborns. *Hum. Genet. Genomics Adv.* 3, 100059. doi:10.1016/j.xhgg.2021.100059

Goldenberg, A. J., and Sharp, R. R. (2012). The Ethical Hazards and Programmatic Challenges of Genomic Newborn Screening. *JAMA* 307, 461. doi:10.1001/jama.2012.68

Goldstein, N. D., Palumbo, A. J., Bellamy, S. L., Purtle, J., and Locke, R. (2020). State and Local Government Expenditures and Infant Mortality in the United States. *Pediatrics* 146, e20201134. doi:10.1542/peds.2020-1134

Gudmundsson, S., Singer-Berk, M., Watts, N. A., Phu, W., Goodrich, J. K., Solomonson, M., et al. (2021). Variant Interpretation Using Population Databases: Lessons from gnomAD. *Hum. Mutat.* doi:10.1002/humu.24309

Health Council of the Netherlands (2008). *Screening: Between Hope and Hype*.

Holm, I. A., Agrawal, P. B., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18, 225. doi:10.1186/s12887-018-1200-1

Howard, H. C., Knoppers, B. M., Knoppers, B. M., Cornel, M. C., Wright Clayton, E., Sénécal, K., et al. (2015). Whole-genome Sequencing in Newborn Screening? A Statement on the Continued Importance of Targeted Approaches in Newborn Screening Programmes. *Eur. J. Hum. Genet.* 23, 1593–1600. doi:10.1038/ejhg.2014.289

Howson, C. P., Cedergren, B., Giugliani, R., Huhtinen, P., Padilla, C. D., Palubiak, C. S., et al. (2018). Universal Newborn Screening: A Roadmap for Action. *Mol. Genet. Metabolism* 124, 177–183. doi:10.1016/j.ymgme.2018.04.009

Jansen, M. E., Metternick-Jones, S. C., and Lister, K. J. (2017). International Differences in the Evaluation of Conditions for Newborn Bloodspot Screening: a Review of Scientific Literature and Policy Documents. *Eur. J. Hum. Genet.* 25, 10–16. doi:10.1038/ejhg.2016.126

Johnston, J., Lantos, J. D., Goldenberg, A., Chen, F., Parens, E., Koenig, B. A., et al. (2018). Sequencing Newborns:A Call for Nuanced Use of Genomic Technologies. *Hastings Cent. Rep.* 48, S2–S6. doi:10.1002/hast.874

Joseph, G., Chen, F., Harris-Wai, J., Puck, J. M., Young, C., and Koenig, B. A. (2016). Parental Views on Expanded Newborn Screening Using Whole-Genome Sequencing. *PEDIATRICS* 137, S36–S46. doi:10.1542/peds.2015-3731H

Kalkman, S., and Dondorp, W. (2022). The Case for Screening in Early Life for 'non-Treatable' Disorders: Ethics, Evidence and Proportionality. A Report from the Health Council of the Netherlands. *Eur. J. Hum. Genet.* doi:10.1038/s41431-022-01055-4

Khoury, M. J., McCabe, L. L., and McCabe, E. R. B. (2003). Population Screening in the Age of Genomic Medicine. *N. Engl. J. Med.* 348, 50–58. doi:10.1056/NEJMra013182

King, J. R., Notarangelo, L. D., and Hammarström, L. (2021). An Appraisal of the Wilson & Jungner Criteria in the Context of Genomic-Based Newborn Screening for Inborn Errors of Immunity. *J. Allergy Clin. Immunol.* 147, 428–438. doi:10.1016/j.jaci.2020.12.633

Knoppers, B. M., Sénécal, K., Boisjoli, J., Borry, P., Cornel, M. C., Fernandez, C. V., et al. (2016). Recontacting Pediatric Research Participants for Consent when They Reach the Age of Majority. *IRB* 38, 1–9.

Knoppers, B. M. (1992). *Canadian Child Health Law: Health Rights and Risks of Children*. Toronto, Ont., Canada: Thompson Educational Publishing, Inc.

Krotoski, D., Namaste, S., Raouf, R. K., El Nekhely, I., Hindi-Alexander, M., Engelson, G., et al. (2009). Conference Report: Second Conference of the Middle East and North Africa Newborn Screening Initiative: Partnerships for Sustainable Newborn Screening Infrastructure and Research Opportunities. *Genet. Med.* 11, 663–668. doi:10.1097/GIM.0b013e3181ab2277

Lewis, M. A., Paquin, R. S., Roche, M. I., Furberg, R. D., Rini, C., Berg, J. S., et al. (2016). Supporting Parental Decisions about Genomic Sequencing for Newborn Screening: The NC NEXUS Decision Aid. *Pediatrics* 137, S16–S23. doi:10.1542/peds.2015-3731E

Lewis, M. H., and Goldenberg, A. J. (2015). Return of Results from Research Using Newborn Screening Dried Blood Samples. *J. Law. Med. Ethics* 43, 559–568. doi:10.1111/jlme.12299

Lewis, M. H. (2014). Newborn Screening Controversy. *JAMA Pediatr.* 168, 199. doi:10.1001/jamapediatrics.2013.4980

Lipstein, E. A., Nabi, E., Perrin, J. M., Luff, D., Browning, M. F., and Kuhlthau, K. A. (2010). Parents' Decision-Making in Newborn Screening: Opinions, Choices, and Information Needs. *Pediatrics* 126, 696–704. doi:10.1542/peds.2010-0217

Lu, C. Y., McMahon, P. M., and Wu, A. C. (2022). Modeling Genomic Screening in Newborns. *JAMA Pediatr.* 176, 344. doi:10.1001/jamapediatrics.2021.5798

McCandless, S. E., and Wright, E. J. (2020). Mandatory Newborn Screening in the United States: History, Current Status, and Existential Challenges. *Birth Defects Res.* 112, 350–366. doi:10.1002/bdr2.1653

Melzer, S. M. (2022). Addressing Social Determinants of Health in Pediatric Health Systems: Balancing Mission and Financial Sustainability. *Curr. Opin. Pediatr.* 34, 8–13. doi:10.1097/MOP.0000000000001083

Milko, L. V., O'Daniel, J. M., DeCristo, D. M., Crowley, S. B., Foreman, A. K. M., Wallace, K. E., et al. (2019). An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screening. *J. Pediatr.* 209, 68–76. doi:10.1016/j.jpeds.2018.12.027

Miller, D. T., Lee, K., Gordon, A. S., Amendola, L. M., Adelman, K., Bale, S. J., et al. (2021). Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2021 Update: a Policy Statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23, 1391–1398. doi:10.1038/s41436-021-01171-4

National Organization for Rare Disorders Newborn screening State report card (2021). National Organization for Rare Disorders Newborn Screening State Report Card. Available at: https://rarediseases.org/policy-issues/newborn-screening/.

Newborn Screening Saves Lives Reauthorization Act (2014). *Newborn Screening Saves Lives Reauthorization Act of 2014, 42 U.S.C. §§ 300b-8 to 300b-17*.

Nordfalk, F., and Ekstrøm, C. T. (2019). Newborn Dried Blood Spot Samples in Denmark: the Hidden Figures of Secondary Use and Research Participation. *Eur. J. Hum. Genet.* 27, 203–210. doi:10.1038/s41431-018-0276-2

O'Daniel, J. M. (2010). The Prospect of Genome-Guided Preventive Medicine: A Need and Opportunity for Genetic Counselors. *J. Genet. Couns.* 19, 315–327. doi:10.1007/s10897-010-9302-4

OHRP (2017). *United States Common Rule*. Rockville, MD: OHRP.

Pereira, S., Robinson, J. O., Gutierrez, A. M., Petersen, D. K., Hsu, R. L., Lee, C. H., et al. (2019). Perceived Benefits, Risks, and Utility of Newborn Genomic Sequencing in the BabySeq Project. *Pediatrics* 143, S6–S13. doi:10.1542/peds.2018-1099C

Pereira, S., Smith, H. S., Frankel, L. A., Christensen, K. D., Islam, R., Robinson, J. O., et al. (2021). Psychosocial Effect of Newborn Genomic Sequencing on Families in the BabySeq Project. *JAMA Pediatr.* 175, 1132–1141. doi:10.1001/jamapediatrics.2021.2829

Peterson, R. E., Kuchenbaecker, K., Walters, R. K., Chen, C.-Y., Popejoy, A. B., Periyasamy, S., et al. (2019). Genome-wide Association Studies in Ancestrally Diverse Populations: Opportunities, Methods, Pitfalls, and Recommendations. *Cell.* 179, 589–603. doi:10.1016/j.cell.2019.08.051

Popejoy, A. B., and Fullerton, S. M. (2016). Genomics Is Failing on Diversity. *Nature* 538, 161–164. doi:10.1038/538161a

Prosser, L. A., Grosse, S. D., Kemper, A. R., Tarini, B. A., and Perrin, J. M. (2012). Decision Analysis, Economic Evaluation, and Newborn Screening: Challenges and Opportunities. *Genet. Med.* 14, 703–712. doi:10.1038/gim.2012.24

Rehm, H. L., Berg, J. S., Brooks, L. D., Bustamante, C. D., Evans, J. P., Landrum, M. J., et al. (2015). ClinGen - the Clinical Genome Resource. *N. Engl. J. Med.* 372, 2235–2242. doi:10.1056/NEJMsr1406261

Reinbold, G. W. (2019). Effects of the Convention on the Rights of the Child on Child Mortality and Vaccination Rates: a Synthetic Control Analysis. *BMC Int. Health Hum. Rights* 19, 24. doi:10.1186/s12914-019-0211-9

Roman, T. S., Crowley, S. B., Roche, M. I., Foreman, A. K. M., O'Daniel, J. M., Seifert, B. A., et al. (2020). Genomic Sequencing for Newborn Screening: Results of the NC NEXUS Project. *Am. J. Hum. Genet.* 107, 596–611. doi:10.1016/j.ajhg.2020.08.001

Ross, L. F., and Clayton, E. W. (2019). Ethical Issues in Newborn Sequencing Research: The Case Study of BabySeq. *Pediatrics* 144, e20191031. doi:10.1542/peds.2019-1031

Rothwell, E., Goldenberg, A., Johnson, E., Riches, N., Tarini, B., and Botkin, J. R. (2017). An Assessment of a Shortened Consent Form for the Storage and Research Use of Residual Newborn Screening Blood Spots. *J. Empir. Res. Hum. Res. Ethics* 12, 335–342. doi:10.1177/1556264617736199

Sahai, I., and Marsden, D. (2009). Newborn Screening. *Crit. Rev. Clin. Laboratory Sci.* 46, 55–82. doi:10.1080/10408360802485305

Sénécal, K., Unim, B., Unim, B., and Maria Knoppers, B. (2018). Newborn Screening Programs: Next Generation Ethical and Social Issues. *Obm Genet.* 2, 1. doi:10.21926/obm.genet.1803027

Sohn, H., and Timmermans, S. (2019). Inequities in Newborn Screening: Race and the Role of Medicaid☆. *SSM - Popul. Health* 9, 100496. doi:10.1016/j.ssmph.2019.100496

Sontag, M. K., Yusuf, C., Grosse, S. D., Edelman, S., Miller, J. I., McKasson, S., et al. (2020). Infants with Congenital Disorders Identified through Newborn Screening - United States, 2015-2017. *MMWR Morb. Mortal. Wkly. Rep.* 69, 1265–1268. doi:10.15585/mmwr.mm6936a6

Therrell, B. L., Lloyd-Puryear, M. A., Lloyd-Puryear, M. A., Ohene-Frempong, K., Ware, R. E., Padilla, C. D., et al. (2020). Empowering Newborn Screening Programs in African Countries through Establishment of an International Collaborative Effort. *J. Community Genet.* 11, 253–268. doi:10.1007/s12687-020-00463-7

Therrell, B. L., Padilla, C. D., Loeber, J. G., Kneisser, I., Saadallah, A., Borrajo, G. J. C., et al. (2015). Current Status of Newborn Screening Worldwide: 2015. *Seminars Perinatology* 39, 171–187. doi:10.1053/j.semperi.2015.03.002

Therrell, B. L., and Padilla, C. D. (2018). Newborn Screening in the Developing Countries. *Curr. Opin. Pediatr.* 30, 734–739. doi:10.1097/MOP.0000000000000683

Tonniges, T. F. (2000). Serving the Family from Birth to the Medical Home. Newborn Screening: a Blueprint for the Future - a Call for a National Agenda on State Newborn Screening Programs. *Pediatrics* 106, 389–422.

Tsosie, K. S., Yracheta, J. M., Kolopenuk, J. A., and Geary, J. (2021). We Have "Gifted" Enough: Indigenous Genomic Data Sovereignty in Precision Medicine. *Am. J. Bioeth.* 21, 72–75. doi:10.1080/15265161.2021.1891347

United Nations Convention on the Rights of the Child (1989). United Nations Convention on the Rights of the Child. Available at: https://www.ohchr.org/en/professionalinterest/pages/crc.aspx (Accessed January 24, 2022).

Veenstra, D. L., Rowe, J. W., Pagán, J. A., Shelton Brown, H., Schneider, J. E., Gupta, A., et al. (2021). Reimbursement for Genetic Variant Reinterpretation: Five Questions Payers Should Ask. *Am. J. Manag. Care* 27, e336–e338. doi:10.37765/ajmc.2021.88763

Vittozzi, L., Hoffmann, G. F., Cornel, M., and Loeber, G. (2010). Evaluation of Population Newborn Screening Practices for Rare Disorders in Member States of the European Union. *Orphanet J. Rare Dis.* 5, P26. doi:10.1186/1750-1172-5-S1-P26

Wain, K. E., Palen, E., Savatt, J. M., Shuman, D., Finucane, B., Seeley, A., et al. (2018). The Value of Genomic Variant ClinVar Submissions from Clinical Providers: Beyond the Addition of Novel Variants. *Hum. Mutat.* 39, 1660–1667. doi:10.1002/humu.23607

Walen, A. (2021). "Retributive Justice," in *The Stanford Encyclopedia of Philosophy*. Editor E. N. Zalta (Stanford, CA: Metaphysics Research Lab, Stanford University). Available at: https://plato.stanford.edu/archives/sum2021/entries/justice-retributive/(Accessed April 13, 2022).

Wang, T., Antonacci-Fulton, L., Howe, K., Lawson, H. A., Lucas, J. K., Phillippy, A. M., et al. (2022). The Human Pangenome Project: a Global Resource to Map Genomic Diversity. *Nature* 604, 437–446. doi:10.1038/s41586-022-04601-8

Wenger, A. M., Guturu, H., Bernstein, J. A., and Bejerano, G. (2017). Systematic Reanalysis of Clinical Exome Data Yields Additional Diagnoses: Implications for Providers. *Genet. Med.* 19, 209–214. doi:10.1038/gim.2016.88

Wilson, J. M. G., and Jungner, G. (1968). *Principles and Practice of Screening for Disease*. Geneva: World Health Organization.

WMA (2022). WMA - the World Medical Association-WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Available at: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/(Accessed February 11, 2022).

Woerner, A. C., Gallagher, R. C., Vockley, J., and Adhikari, A. N. (2021). The Use of Whole Genome and Exome Sequencing for Newborn Screening: Challenges and Opportunities for Population Health. *Front. Pediatr.* 9, 663752. doi:10.3389/fped.2021.663752

Wojcik, M. H., Zhang, T., Ceyhan-Birsoy, O., Genetti, C. A., Lebo, M. S., Yu, T. W., et al. (2021). Discordant Results between Conventional Newborn Screening and Genomic Sequencing in the BabySeq Project. *Genet. Med.* 23, 1372–1375. doi:10.1038/s41436-021-01146-5

Wright, C. F., Hurles, M. E., and Firth, H. V. (2016). Principle of Proportionality in Genomic Data Sharing. *Nat. Rev. Genet.* 17, 1–2. doi:10.1038/nrg.2015.5

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Parental Hopes and Understandings of the Value of Prenatal Diagnostic Genomic Sequencing: A Qualitative Analysis

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Objective: To provide qualitative empirical data on parental expectations of diagnostic prenatal genomic sequencing and the value of the results to families.

Methods: We interviewed 15 families—mothers and/or fathers—who had had prenatal genomic sequencing about their expectations and their respective evaluations of the benefits of genomic sequencing.

Results: Families' hopes for genetic sequencing clustered around three themes: hoping to identify the cause of the fetal anomaly in a terminated pregnancy; hopes for guidance as to the likely outcome of current pregnancy; and hopes for information to support future family planning. In addition, hopes were discussed in terms of the potential for results to be beneficial in acquiring greater knowledge, while at the same time recognizing that new knowledge may raise more questions. Assessment of the value of sequencing largely mirrored these expectations when positive results seen. Negative results can also be seen as valuable in ruling out a genetic cause and in providing certainty that families had done everything that they could to know about the cause of fetal demise.

Conclusion: It would appear that with guidance from genetic counsellors, families were largely able to navigate the many uncertainties of prenatal genomic sequencing and thus see themselves as benefitting from sequencing. However, support structures are essential to guide them through their expectations and interpretations of results to minimize possible harms. Engaging in the process of genomic sequencing was seen as beneficial in of itself to families who would otherwise be left without any options to seek diagnostic answers.

Keywords: prenatal, genomics, sequencing, interviews (qualitative), empowerment

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INTRODUCTION

Technological innovations, falling costs, and the development of rapid exome testing technologies suggest that prenatal diagnostic genomic sequencing is highly likely to become part of standard clinical practice in the near future if fetal anomalies are detected through ultrasound or other methods (Drury et al., 2015; Pangalos et al., 2016; Quinlan-Jones et al., 2017; Harris et al., 2018; Mellis et al., 2018; Richardson and Ormond, 2018; Ferretti et al., 2019; Sullivan et al., 2019). Fetal anomalies are identified in 2%–5% of pregnancies, the cause of which may remain unknown

following chromosomal microarray and karyotype diagnosis. The employment of prenatal whole exome sequencing to identify etiology has drawn particular attention given that the cost of sequencing may be lower than for whole genome sequencing and may provide quicker results. Given that many treatment options are time-sensitive in a prenatal context, the speed of the sequencing process of key importance in respect to its clinical utility (Best et al., 2018; Lord et al., 2019). Studies have provided a wide range of figures in respect to diagnostic yield, with considerable variation due to study design, the fetal anomaly identified, and population intake (Best et al., 2018; Petrovski et al., 2019). However, a recent meta-analysis by Mellis et al. (2022) concludes that "prenatal ES [exome sequencing] provides a diagnosis in an additional 31% of structurally abnormal fetuses when CMA [chromosomal microarray]/karyotype is non-diagnostic."

The psychological impact of receiving a prenatal diagnostic test showing fetal anomaly has been studied extensively (Werner-Lin et al., 2016; Wilpers et al., 2017; Hodgson and McClaren, 2018; Teefey et al., 2020; Bardi et al., 2021). Finding a fetal anomaly is self-evidently unwelcome and has been shown to increase the likelihood of anxiety, stress, and depression both within the time of the pregnancy and postpartum. It is possible that the increased diagnostic yield (over and above microarray and karyotype testing) provided by whole exome sequencing may offer opportunities to families for whom fetal anomalies have been detected to understand the cause of these respective anomalies and thus reduce stress. Clinical assessments, based upon the results of genomic sequencing, may also inform pregnancy management, help families prepare for the future after their child is born, and identify the risk of recurring issues in any future pregnancies. Conversely, the relatively low diagnostic yield for prenatal sequencing (with positive results of around 20%–30%) means that in most cases families will not receive a definitive genetic etiology. Moreover, even in cases where positive results are seen, care or treatment options are often limited (Quinlan-Jones et al., 2017; Abou Tayoun et al., 2018; Best et al., 2018; Horn and Parker, 2018; Mellis et al., 2018; Richardson and Ormond, 2018; Sullivan et al., 2019).

While both pediatric and prenatal genomic testing share commonalities in respect to the complexity of interpretation, prenatal genomic sequencing is likely to more challenging for clinicians to interpret and thus more difficult to clinicians and genomic counsellors to provide specific guidance to families. Fundamentally, the problem is that the phenotypic features of concern are not yet possible to observe within the fetus. As Horn and Parker state within the prenatal context, it is exceptionally difficult to "determine whether a variant will affect the resulting child if the pregnancy were to be continued." Indeed, the extrapolation of prenatal genomic sequencing testing findings to make informed clinical decisions (including treatment, termination, and early screening for future pregnancy) is based upon knowledge from postnatally-derived (adult and minors) classifications found in ClinVar or the Human Gene Mutation Database along with emerging case studies in the literature (prenatal and postnatal). As several authors have noted development of a prenatal database might help to advance prenatal sequencing, but this is yet to be available (Drury et al., 2015; Aarabi et al., 2018; Abou Tayoun et al., 2018; Best et al., 2018; Horn and Parker, 2018; Mellis et al., 2018; Ferretti et al., 2019). Moreover, even if predictions about postnatal outcomes can be made with a strong degree of certainty, prenatal treatment options are often highly limited (Westerfield et al., 2015). These limitations are especially problematic given that decisions need to be made quickly during ongoing pregnancies.

Ethical Concerns and the Need for Empirical Data

Ethical discussion of prenatal sequencing has frequently explored these counter-forces—the potential for genomic sequencing to provide strong indicators of treatment options with the likelihood of negative or uncertain results and limited treatment options. Much of the focus upon ethical concerns over prenatal testing is upon the potential for results to influence parental decisions as to whether to continue or end current pregnancies. Indeed, such life-changing decisions are all the more the problematic given the potential for results to be re-analyzed as more comparative data emerges (Horn and Parker, 2018; Mellis et al., 2018). More broadly, literature examines the degree to which families might be over-optimistic about the ability of sequencing to answer questions and perhaps underestimate the likelihood of an uncertainty future after results (Yurkiewicz et al., 2014; Kalynchuk et al., 2015; Chandler et al., 2018; Richardson and Ormond., 2018).

The contrast between the potential for genomic sequencing to inform families and enable some form of pregnancy management and the limitations of prenatal genomic sequencing make it important to talk with families, particularly mothers, about their experiences. Empirical data is only just emerging in respect to the experiences of families who have undertaken to have prenatal genomic sequencing (Kalynchuk et al., 2015; Quinlan-Jones et al., 2017; Richardson and Ormond, 2018; Wou et al., 2018; Plantinga et al., 2021; Talati et al., 2021). These studies have highlighted that sequencing may answer some questions but may also create difficult choices with respect to continuing a pregnancy. In addition, sequencing may identify likely postnatal outcomes needing considerable clinical intervention and high levels of risk for future pregnancy, potentially adding to parental stress. However, studies of families also indicate that despite limited options and uncertainties, for many the price of knowing is preferable to having little or no etiological information about the fetal anomaly identified (Quinlan-Jones et al., 2017; Plantinga et al., 2021). These studies are complimented by empirical data on the views and experiences of families who undertake microarray testing (Bernhardt et al., 2013; Hillman et al., 2013; Lewis et al., 2021) and those of healthcare providers and other experts on prenatal genomic testing and microarray testing (Shkedi-Rafid et al., 2016; Narayanan et al., 2018). Knowing the expectations of families and the value that they placed upon genomic sequencing enables clinicians

and genetic counsellors to tailor their communication to provide neither false hope nor diminished enthusiasm.

In the following study, we talked with 15 families (mothers and/or fathers) about their experiences in respect to prenatal testing from an amniotic sample. This research was undertaken as a sub-study within a large whole exome sequencing research study undertaken at UCSF (details of the study are provided below). We talked to families about their expectations (and concerns) and what they thought about having had genomic sequencing. Families were interviewed twice, 2–4 weeks and 6 months after return of results. In doing so, the primary intention was to see whether the respective hopes of families for sequencing were matched to their evaluation of the benefits of sequencing. This paper is of relevance to clinicians, genetic counsellors, and policymakers who are broadly interested in knowing whether genomic sequencing provides a service that is helpful to families in their current pregnancies and in respect to family planning. More specifically, it is relevant to genetic counsellors and clinicians tasked with providing information to families who may be considering their options as to whether to have genetic sequencing following the detection of fetal anomalies.

METHODS

Study Population Characteristics

The data presented in this paper was collected through interview and ethnographic observational analysis conducted within the University of California, San Francisco (UCSF) Program in Prenatal and Pediatric Genome Sequencing (P3EGS) study. The P3EGS study was approved by the IRB of USCF. A total 845 families (one or more parent) were enrolled in the study, of which 316 families were enrolled into the prenatal arm of the study. The P3EGS study is one site in a multi-sited research program, the Clinical Sequencing Evidence-Generating Research (CSER) Consortium. Parents of children with fetal anomalies the cause of which was not determined by amniocentesis were offered the opportunity to participate in the study free of charge. Participants underwent a lengthy process of genetic counselling at enrollment and during the return of results which highlighted the likelihood of negative results, limitations of any diagnosis in respect to the provision of treatment, and generally helped families prepare for the possibility of more uncertainty even after results are returned. Many of these sessions were observed by the ethnographic team (15 observations of enrollment and 32 observations of results sessions).

Recruitment for Interviews

At the time of consent to the sequencing study families were informed verbally and in written documentation that they may be contacted by the ethnographic study to ask if they would be willing to be interviewed about their experiences. They were given the option to decline. This possibility was reiterated at the results session by genetic counsellors, clinical research coordinators, or members of ethnographic team when present (although in particularly stressful situations this offer of an interview was not made at the time of results).

Sampling

Participants were selected for interviews based upon their results—positive, negative, or uncertain. The sampling was purposive, with the intention to over-sample families with positive and uncertain results (compared to the study population overall). Early interviews suggested that parents with negative results did not have much to say regarding the utility of genomic sequencing. As such, in order to maximize our qualitative understanding of the benefits (or otherwise) of sequencing results, it was important to over-sample positive and uncertain results.

Data Collection

Of the 30 families contacted to request interviews 15 declined; those families who declined interviews were either passive decliners (no response to three requests by phone) or stated that they did not want to be interviewed. The dominant reason given for declining to be interviewed was lack of time.

Interviews were conducted between 2 and 4 weeks after results sessions and a follow-up interview was conducted 6 months after results sessions. Interviews generally lasted between 30 and 60 min with an average of 40 min. They included in-person, online, and phone interviews. Interviews were conducted between 2 April 2018, and 29 October 2020.

Interviews were arranged by phone and interviewees were fully informed that their decision to participate or not participate would in no manner influence ongoing clinical care. Potential interviewees (families who had agreed verbally to being asked about an interview) were called between 10 and 20 days after return of results to arrange interviews. In accordance with COREQ guidelines (Tong et al., 2007), interviewer credentials are provided in **Table 1**, below.

The semi-structured interview guide included a wide range of topics including diagnostic journey, experience of enrollment and return of results, and subsequent understanding of results among others. Audio recordings of results sessions and interviews were professionally transcribed and were checked for quality and anonymity by the UCSF ethnographic study team.

Analysis

The ethnographic and analytical approach taken is aligned to that Interpretative Description (Thompson Burdine et al., 2021) as employed in multiple studies exploring patient experiences for the purpose of developing educational tools or guidance to providers based upon these experiences. Interview analysis follows a data-driven themed analytical process as developed by Boyatzis (1998) and Braun and Clarke (2006) and further described by Deterding and Waters (2021) in respect to the employment of qualitative software to analyze interviews. Fieldnotes and interview transcripts were uploaded to Dedoose qualitative software

TABLE 1 | Interviewer credentials.

Interviewer	Credentials	Occupation	Gender	Experience/Training
ID 1	PhD	Research specialist	Male	Multiple years of interviewing experience. Training/experience in ethnography and social scientific methods
ID 2	PhD/MPH	Associate professor	Female	Multiple years of interviewing. Training/experience in ethnography and social scientific methods
ID 3	BA	Research analyst	Female	Training and experience in interviewing. Currently in a genetic counseling master's program. Fluent in spanish

TABLE 2 | Key interviewee characteristics.

FAM	Interviewed	Race/ethnicity	Classification of exome sequencing result	Pregnancy status at the time of results and interview
11	Mother	Hispanic	Negative	Terminated (prior to enrollment in study)
41	Mother	Asian/White	Inconclusive	Terminated (prior to enrollment in study)
86	Mother	White	Positive/*De Novo*	Terminated (prior to enrollment in study)
153	Mother & Father	Hispanic (Mother) & Asian (Father)	Inconclusive	Ongoing (at time of results and interview)
195	Mother	White	Positive/*De Novo*	Ongoing (at time of results and interview)/Deceased shortly after birth (prior to results and interview)
230	Mother & Father	Hispanic (Mother) & Hispanic (Father)	Positive/*De Novo*	Ongoing
260	Mother & Father	Hispanic/Asian (Mother) & Asian (Father)	Positive/*De Novo*	Ongoing
273	Mother	Asian	Inconclusive	Terminated (prior to enrollment in study)
309	Mother	White	Positive/*De Novo*	Ongoing at Results—Termination shortly after (prior to interview)
348	Mother	White	Negative	Terminated (prior to enrollment in study)
370	Mother	White	Negative	Ongoing
398	Mother	White	Positive/Maternal Inheritance	Ongoing
442	Mother	White	Negative	Terminated (prior to enrollment in study)
565	Mother & Father	Asian (Mother) & Asian (Father)	Negative	Ongoing
596	Mother	Hispanic	Inconclusive	Ongoing

allowing for multiple persons within the analysis team to share data. Thematic codes were developed in accordance with what was being learned through initial observations and interviews. These were reviewed and amended following their trial application within Dedoose. Upon finalization of codes and their application, each document (fieldnotes and interview transcripts) was reviewed by at least two members of the team for consistency. It is estimated that consistency between reviewers (overlapping coding using a blinded-coding methods) was approximately 75%–85%. Of the codes applied, the codes entitled "Expectations," "Concerns," and "Feelings about Results" were the most often applied to the following analysis but other findings outside of these codes were employed to add interpretive depth to the results presented below. Given the conceptual and methodological approach taken, a Kappa Coefficient was not produced for codes. Instead, coding overlap is provided as an indication of how themes were discussed among the team and consensus reached as to their interpretation and application. Lack of overlap was not necessarily something to be rectified, but instead was seen as an opportunity to widen the scope of interpretation for a particular code.

RESULTS

Interviewee Population

A total of 15 families were included in the interview study. **Table 2**, below, provides key information on the 15 families interviewed. Of the 15 families interviewed, 6/15 [40%] received positive results, 4/15 received inconclusive results [27%], and 5/15 [33%] received negative results. Pregnancy status was also recorded with 8/15 [53%] families receiving results in respect to an ongoing pregnancy at time of enrollment and 7/15 families with terminated pregnancies. 8/15 [53%] families were members of an under-represented minority population. It is important to note that many of the participants had already ended their pregnancies—either spontaneously or electively—prior to enrollment in the study and/or prior to receiving genetic results (please see **Table 2**).

Thematic Analysis

Interviewee quotes have been organized to address the overarching question of whether the respective hopes of families were matched in their evaluation of the benefits of sequencing. Families' hopes for genomic sequencing clustered

around causality, likely outcomes, and implications for future pregnancy. Families also reflected upon how they entered sequencing with some concerns about how they might be left with difficult questions when results were returned. Their respective assessment of the value of prenatal genomic sequencing reflected these hopes and clustered around what they had learned in respect to the cause of fetal demise, implications of the results for outcomes in current pregnancy, and implications of results for future pregnancy. Interviewees also talked about upon the value of having done something to reduce uncertainty, regardless of test outcomes.

HOPES FOR GENOMIC SEQUENCING

Identifying Cause in Terminated Pregnancy

As might be expected when pregnancy has been ended, families wanted to find out what happened to cause the fetal anomaly and thus gain a form of closure. As one parent stated,

> Like you could do whatever you need to do. We want to find out like what caused it. [0011/Negative Result/Termination]

This was sometimes combined with families wanting to know if the genetic variant that caused fetal demise had been passed down, as seen in the following excerpt,

> MOTHER: I wanted to find out what happened. I wanted some answers about what happened to the fetus, and did it come from one of our genetic imprints, like "did we pass this on to the baby or was it an anomaly?" [0041/Positive Result/Termination]

Likely Outcomes in Ongoing Pregnancy

In ongoing pregnancies with fetal complications, further information as to the likely outcome of the current pregnancy was of key importance, as seen below,

> INTERVIEWER: What did you hope to learn from participating in this study?
>
> MOTHER: If there was anything that—for lack of a better word—generally wrong with myself or my baby . . . She [the clinician] said that this study would give me, I think, 90% certainty that the baby was fine or not. That's why I accepted to do the test. [0398/Positive Result/Ongoing]

In addition, as well as pregnancy outcome, it was hoped that sequencing might provide some indication as to postnatal care requirements,

> MOTHER: So that was, I guess, what we were hoping is to see if there is anything else that we should be aware of in the future for us or for the baby. And so that is what we were kind of hoping to get out of it. And we did. [0565/Negative/Ongoing]
>
> MOTHER: They would tell us what care we should have once she was born, knowing exactly what she had, and that they would give us much more information, like places where we could go after she was born to know exactly what to do. [0230/Positive/Ongoing]

Implications for Future Pregnancies

Families who had terminated pregnancies and those with ongoing pregnancies both wanted to know if sequencing might provide information regarding future pregnancies.

> MOTHER: Well I just wanted to, you know, learn why in some cases this happens and how does it—like—affected our future kids, if we planned on having any [0011/Negative Result/Termination]
>
> MOTHER: I guess, what we were hoping is to see if there is anything else that we should be aware of in the future for us or for the baby. And so that is what we were kind of hoping to get out of it. [0565/Negative Result/Ongoing]

One specific reason for having sequencing was to inform IVF, as seen below,

> MOTHER: We already have two more embryos frozen. So if there was any risk to those embryos, we wanted to know before we implanted them. So for us it is important to see if there was some genetic cause [0442/Negative/Terminated]

Knowledge Is Powerful but Could Create Uncertainty

Finally, the theme of whether knowing is better than not knowing was reflected up on by some interviewees. In the following instance, the mother highlighted that they felt that the knowledge gained from sequencing could be powerful,

> MOTHER: I wanted to know if anything was wrong. I believe knowledge is power—so I did not have any fears about it. [0398/Positive/Ongoing]

For others their hopes for sequencing were mixed with a certain degree of concern that knowing more might create more uncertainty. In the following example the mother highlighted that they might see knowledge as troubling and potentially worth avoiding, while their husband felt differently,

> MOTHER: Well he [father] was. He's more for like, you know, knowing everything, you know, information is power. Me, I am more of a, you know, ignorance is bliss. So I think I would have been okay without knowing too much. [0260/Positive/Ongoing]

Finally, in the following instance the interviewee had initially turned down sequencing, but then decided to have sequencing based on not wanting to miss out on potentially important information sooner rather than later. The mother was also explicit in saying that at-first she did not want to do the exome test as she was worried that it would add an even greater strain (greater than the early tests showing problems with the fetus).

> MOTHER: My immediate reaction was no; we should not do this. I thought it was going to bring up more questions than answers . . . I was really worried that we were going to get more uncertain answers that would be even harder to make a decision on because we would know there was something but we would not know what it meant . . . I think we just wanted to know—I guess really, I was hoping to learn that there was nothing wrong, but if there was something wrong, I wanted to know sooner rather than later. [0309/Positive Result/Ongoing]

ASSESSMENT OF VALUE

Identifying Cause

Arguably the simplest form of evaluative framework was in respect to a positive result providing knowledge of the cause of fetal demise,

> They were able to pinpoint, you know, what happened and what was the gene that caused it and, you know, that's all we could ask for really, just finding exactly what happened. . . They knew there was a variant, but they could not pinpoint what it was, so I think this test definitely gave us the information that we needed. [0195/Positive Result/Deceased after birth]

However, the benefits of identifying causality might be interpreted in more nuanced and sometimes ambiguous manners. For example, a negative result might be seen as beneficial because the alternative—finding a genetic cause—might present a worst-case scenario. The fear of finding a genetic cause may be linked to the fear of being culpable for passing on a variant (as discussed below),

> MOTHER: Like, nobody told us, "We guarantee there is no genetic link". However, what we did hear is, "Based on everything that we know today, there was no genetic link," essentially. And so, I think that is the best news that we could have hoped for. I think the only way that we would have gotten the clarity that we would have liked to hear is if they did find a link, and that would have been bad news. 0348/Negative/Terminated]

Not finding an identifiable cause might also be seen beneficial to families in the reassurance provided that there was nothing that could have been done (again, possibly suggesting that if a genetic cause had been identified it may have indicated a degree of parental culpability in passing on the variant),

> INTERVIEWER: Do you still think about the results you received . . . is it something that is on your mind?
>
> MOTHER: If it was genetic, I guess there would be something we could almost tangibly do with it and be like, "Okay, there is something wrong with one of us." But it was not. So we think of it in the fact that again, there is nothing we can do. So it was just very unfortunate. So I guess that when I look back at everything that happened, that is how I look at it, is there was nothing we could have done to prevent this. [0442/Negative/Terminated]

This sense of relief that those families were not responsible for the fetal anomaly was also seen in positive cases that were *de Novo* (not inherited), as seen below,

> FATHER: It's nobody's fault, it's something they do not know why it happened. That is the purpose of the tests, to clarify. And it's very helpful because it's easy to say, "No, it's your fault." But the tests have clarified all that and they explained it very well to us. That's the purpose of the test, to clarify. [0230/Positive/Ongoing]

Finally, it was notable that having a positive result was not always seen as the end of the story—especially when there was some ambiguity in the interpretation. It was still something to hold onto, in the hope that science might catch up one day,

> MOTHER: So, I am happy thereis like something to hold onto. There is a name, and maybe it did not fit the complete profile, but maybe that profile will even change over time as more of these occur. And then, maybe like in a few years, I will even know that oh yeah, for sure, that was that it—the thing. [0041/Positive/Terminated]

Implications for Current Pregnancy and Postnatal Care

A positive sequencing result might be seen as helpful in planning for the future, as seen in the following instance,

> MOTHER: And the defect had a name so, you know, it was not anything out of the ordinary. So, you know, there was a solution. There was surgery. It was open-heart surgery but, you know, yeah, but it was something that could be fixed. [0260/Positive/Ongoing]

However, it was not always the case that a positive result clarified issues around current pregnancy and postnatal care.

In the following instances, positive results left them with more questions than answers,

> MOTHER: I was confused, I guess. It was nice to know, then some of the things that they said that were associated with this made sense when it came to me . . . but then it just made me super confused. I have this, "is there levels? Is there different degrees? Is there different severities? Is my daughter going to be just like me?" So it just made me have more questions. [0398/Positive/Ongoing]
>
> MOTHER: All the information they gave us made it very hard for us to decide whether we would continue with the pregnancy or not. It put us between a rock and a hard place . . . I think we made the right decision, and it was not based on the genetic test. The test helped us to be prepared because we knew that she was going to be born with difficulties and all that. So, it helped us but it did not help us make the decision whether to have her or not. It is very hard to explain it and it's very hard for people to understand. [0230/Positive/Ongoing]

Others noted that while cause might have been identified, the course of pregnancy management and postnatal care was not necessarily altered by the result, this might be the case due to uncertainty of result or even when the result is positive, as seen below,

> MOTHER: All this is new so, as I said, when they told me I felt sad to know what could happen. However, I have more faith in God regarding how the baby will be born. Now, you can not see her. The ultrasounds are fine, the results of the heart ultrasound was normal, she moves, so, all we have to do is wait. [0596/Inconclusive/Ongoing]
>
> MOTHER: I do not know that I felt any different because the confirmation that it was genetic, we did not change anything because nothing changed—you know, because the outcome does not change. It does not—that does not change. We are still having surgery, [0260/Positive/Ongoing].

Implications for Identifying Carrier Status and Likely Outcomes in Future Pregnancy

Multiple interviewees highlighted the importance of prenatal sequencing for planning future pregnancies, including positive and negative results. What was of particular significance was identification of whether one or more parent is a carrier.

> MOTHER: It was really reassuring to know that neither of us—both of us are not carriers—for this, you know, like a horrific genetic condition that our child seemed to be presenting with. [0086/Positive Result/Terminated]

Others reflected upon how it was useful to know the likely odds of having a child with the same condition in future,

> MOTHER: So from that perspective, I guess this is the better result because it allows us to try again with some peace of mind that, again, no guarantees, but it's a little bit easier to try again when you know that you are not facing 50% odds, or whatever was quoted initially. [0348/Negative Result/Terminated]
>
> MOTHER: They had told us that there was nothing in our genetics that caused [Proband's] heart condition. . .but they had said that there was like a 13% chance that my future child would have the heart condition as well, [0370/Negative Result/Ongoing]

However, inconclusive results might be seen as especially unhelpful for planning for future pregnancies given that such a result re-enforces uncertainty, as seen below,

> So the result itself I feel like was rather unhelpful because I fell into the unfortunate bucket of, there is something but we do not know if it's good or bad. So, it's not enough to make decisions on [referring to IVF], it's not definitive but it's also not as reassuring. [0273/Inconclusive Result/Terminated]

Finally, in the one instance wherein sequencing appears to have a direct impact upon termination, the mother reported her feelings about how sequencing had changed her perception of pregnancy, perhaps increasing concerns and uncertainties about the fragility of life,

> I think it just opened my eyes to all of the things that can possibly go wrong. I think this was just one little, tiny thing that went wrong in one gene out of, I do not know how many genes you have, thousands and thousands of genes. And it's like, that could happen anytime. And it's really amazing that so many children are born normal . . . I worry about future pregnancies, probably more than I would have. But I, if you think about it, if we would have had that kid, I would have been even just as worried because of all the issues that the kid would have had. [0309/Positive Result/Ongoing]

The Value of Knowledge

While increased or perhaps continued uncertainty was a significant element for some families in how they might interpret results, for others having genomic sequencing provided knowledge that they otherwise would not have had, and thus the process itself was valued. This was seen with positive and negative results, as seen below,

> MOTHER: I feel grateful to have some more information that we otherwise would not have had [0086/Positive/Terminated].

MOTHER: I am like—really happy and like thankful that we actually went through this and like, you know, just learn a little more about it. [0011/Negative/ Terminated]

FATHER: I think, at least, it gives us choices, and where knowledge is better than not having nothing. [0309/ Positive Result/ Ongoing]

MOTHER: I feel reassured because I feel like we have done what we can to really find out about the baby's condition and with this additional study, it just kind of provides us even more information and being just educated. I feel like it's one less thing that we have to worry about for the baby, I guess? [0565/Negative/ Ongoing]

DISCUSSION

The hopes expressed by families in our study are similar to those found in non-prenatal contexts; they include a hope that sequencing can find cause, guide treatment, and predict risk and family planning (Khan et al., 2016; Wynn et al., 2018; Donohue et al., 2021). Our results suggest that in evaluating the benefits of prenatal genomic sequencing, the families in this study construed benefits in a variety of ways that allow for considerable flexibility of interpretation. In general, this flexibility of interpretation enabled them to infer largely positive evaluations of the experience of genomic sequencing; again, reflecting findings outside of the prenatal context (Biesecker et al., 2014; Stivers and Timmermans, 2017; Robinson et al., 2019; Mollison et al., 2020; Donohue et al., 2021).

Despite the presence of continued uncertainty in respect to treatment, care, and family planning options, families in the study largely valued the opportunity to have greater etiological knowledge. This was true for families with ongoing and terminated pregnancies. Positive results were seen to provide some degree of closure through knowledge of the cause of fetal demise and/or the potential that more would be known in the future about the cause of this and other forms of fetal demise. In respect to ongoing pregnancies, positive results were seen to provide a degree of foresight; even if this foresight included likely hospitalization and knowledge that the variant did not provide clear clinical interventions. A positive result allowed families to move forward, or at least have some insight into what lay ahead for them. Negative results in ongoing and terminated pregnancies were viewed as helpful in two instances. Firstly, that everything had been done to find out the cause of fetal anomalies. Secondly, that a negative result suggested that future pregnancies are unlikely to be impacted (as the condition was not genetically inherited). The latter interpretation may be tied to a broader sense of relief among the families interviewed of being absolved of guilt for passing on a deleterious genetic variant. Overall, negative and positive *de novo* results (which accounted for five out the six positive cases) results may have allowed families to move on in their lives after sequencing without feeling guilty for passing on a genetic variant. The importance of guilt and absolution from guilt in passing on a deleterious genetic variant is also seen in families in a pediatric setting (Stivers and Timmermans 2017; Malek et al., 2019; Mollison et al., 2020). Finally, several interviewees reflected upon how undertaking sequencing allowed them to meet a sense of obligation to do something. Again, this sense of having or wanting to do something is found in literature on pediatric exome sequencing for rare conditions, and in respect to how sequencing offers an opportunity to be pro-active in trying to at least find out more about a condition or set of symptoms (Malek et al., 2019; Luksic et al., 2020; Mollison et al., 2020; Donohue et al., 2021).

This generally positive overview of the value of sequencing to families must be seen against the notable limitations of sequencing to identify treatment or care options (or identify the best family planning options). At times family hopes were not fulfilled. This was largely seen in terms of how families described the ambivalence of results in respect to treatment or care options. This ambivalence was especially evident with an uncertain result, but even with positive results, prenatal genomic sequencing was sometimes perceived by families in the study to add uncertainty as to the course of treatment or where to go from this point onwards.

Unfortunately, due to the size of the population and study intake, the degree to which genomic sequencing plays a role in the termination of pregnancy was difficult to interpret. In this study—as with the study by Wou et al. (2018) in a vast majority of cases the decision to terminate was based upon prior findings of fetal anomalies. In the one instance wherein sequencing played a major role in termination, there was still a sense that it was better to know than not know. However, it is also the case that at least two families reflected upon (hypothetically) how genomic sequencing could provide information that may force them into making the difficult decision about whether to continue a pregnancy; a decision that they might otherwise avoid having to make if the information was not available to them. This nuanced, individualized, and non-deterministic view of sequencing in respect to pregnancy termination is similar to the findings of other literature (Kalynchuk et al., 2015; Richardson and Ormond, 2018). However, any such conclusions about pregnancy decision making are highly tentative given the size of the study.

Families in this study appeared be attuned to dealing with the uncertainties that may arise from receiving results of any kind. As our study strongly suggests, families believed that genomic sequencing could help them in their diagnostic journey and were prepared for the uncertainties and limitations that are inherent to sequencing. In reflecting upon how this study might inform genetic counselling, it is notable that while families seemed able to navigate many of the uncertainties of prenatal genomic sequencing, their relative success may well be a function of the extended counselling sessions observed. Ultimately, it is essential that genomic counsellors (among others) prepare families for these uncertainties and guide families through their respective results (Yurkiewicz et al., 2014; Harris et al., 2018; Mellis et al., 2018; Ferretti et al., 2019; Lewis et al., 2021; Talati et al., 2021).

Limitations/Further Studies

Our sample size of 15 families means that subdivisions into representative groups by result and by pregnancy context allow for only limited examples of each group. Further research with larger samples is needed to see whether these findings can be replicated through surveys and interview-based studies. Nevertheless, it is argued that there is sufficient distinction to warrant highlighting the differences and similarities in expectations and assessments of the benefits and limitations of genomic sequencing in a prenatal context. It should also be noted that these conditions were rare, making these interpretations perhaps somewhat distinct from more commonly seen genetic variants or fetal anomalies. It is also notable that in the vast majority of interviews the decision whether to continue the pregnancy was taken prior to genomic sequencing, making it difficult to interpret the role of sequencing on termination decisions. Finally, this study was too small to explore cultural differences in attitudes to prenatal genomic testing (Chen et al., 2013; Tsai et al., 2017)

CONCLUSION

Although our sample is small, it suggests that families may be willing to live with the uncertainties presented by prenatal genomic sequencing pre- and post-results and are potentially able to benefit through the knowledge gained through sequencing. This may well be a function or indicator of the success of genetic counsellors in guiding families through the process of genomic sequencing. We have noted that uncertainties are likely to remain a strong feature of prenatal genomic sequencing for a considerable period. Our data suggest that families may be willing to live with this uncertainty for the present, but that support structures are essential to guide them through their expectations and interpretations of results. Finally, one should not underestimate the importance to families of simply trying to do something to gain knowledge, and the inherent value of sequencing in meeting the desire to try anything to reduce uncertainty.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the study includes qualitative interview data. I can confirm that I [SO] have full access to all the data in the study and responsibility for the integrity of the data and the accuracy of the data analysis. The datasets from which excerpts are presented in this article are not readily available as a condition of the study is that raw data will not be shared outside of the research team. Upon request, sections of the data may be provided for specific research requests after the permissions of participants are requested and received. Requests to access the datasets should be directed to simon.outram@ucsf.edu.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Research Protection Program Institutional Review Board (IRB)—UCSF. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SO - Manuscript drafting, editing, data analysis. JB, AZ, NS-H, and SA - substantial contribution to manuscript editing and data analysis.

REFERENCES

Aarabi, M., Sniezek, O., Jiang, H., Saller, D. N., Bellissimo, D., Yatsenko, S. A., et al. (2018). Importance of Complete Phenotyping in Prenatal Whole Exome Sequencing. *Hum. Genet.* 137 (2), 175–181. doi:10.1007/s00439-017-1860-1

Abou Tayoun, A. N., Spinner, N. B., Rehm, H. L., Green, R. C., and Bianchi, D. W. (2018). Prenatal DNA Sequencing: Clinical, Counseling, and Diagnostic Laboratory Considerations. *Prenat. Diagn.* 38 (1), 26–32. doi:10.1002/pd.5038

Bardi, F., Bakker, M., Kenkhuis, M. J. A., Ranchor, A. V., Bakker, M. K., Elvan, A., et al. (2021). Psychological Outcomes, Knowledge and Preferences of Pregnant Women on First-Trimester Screening for Fetal Structural Abnormalities: A Prospective Cohort Study. *PloS one* 16 (1), e0245938. doi:10.1371/journal.pone.0245938

Bernhardt, B. A., Soucier, D., Hanson, K., Savage, M. S., Jackson, L., and Wapner, R. J. (2013). Women's Experiences Receiving Abnormal Prenatal Chromosomal Microarray Testing Results. *Genet. Med.* 15 (2), 139–145. doi:10.1038/gim.2012.113

Best, S., Wou, K., Vora, N., Van der Veyver, I. B., Wapner, R., and Chitty, L. S. (2018). Promises, Pitfalls and Practicalities of Prenatal Whole Exome Sequencing. *Prenat. Diagn.* 38 (1), 10–19. doi:10.1002/pd.5102

Biesecker, B. B., Klein, W., Lewis, K. L., Fisher, T. C., Wright, M. F., Biesecker, L. G., et al. (2014). How Do Research Participants Perceive "Uncertainty" in Genome Sequencing? *Genet. Med.* 16, 977–980. doi:10.1038/gim.2014.57

Boyatzis, R. E. (1998). "Transforming Qualitative Information: Thematic Analysis and Code Development," *Sage* (United States: Case Western Reserve University).

Braun, V., and Clarke, V. (2006). Using Thematic Analysis in Psychology *Qual. Res. Psychol.* 3 (2), 77–101.

Chandler, N., Best, S., Hayward, J., Faravelli, F., Mansour, S., Kivuva, E., et al. (2018). Rapid Prenatal Diagnosis Using Targeted Exome Sequencing: A Cohort Study to Assess Feasibility and Potential Impact on Prenatal Counseling and Pregnancy Management. *Genet. Med.* 20 (11), 1430–1437. doi:10.1038/gim.2018.30

Chen, L.-S., Xu, L., Huang, T.-Y., and Dhar, S. U. (2013). Autism Genetic Testing: a Qualitative Study of Awareness, Attitudes, and Experiences Among Parents of Children with Autism Spectrum Disorders. *Genet. Med.* 15 (4), 274–281. doi:10.1038/gim.2012.145

Deterding, N. M., and Waters, M. C. (2021). Flexible Coding of In-Depth Interviews: A Twenty-First-Century Approach. *Sociol. Methods Res.* 50 (2), 708–739.

Donohue, K. E., Dolan, S. M., Watnick, D., Gallagher, K. M., Odgis, J. A., Suckiel, S. A., et al. (2021). Hope versus Reality: Parent Expectations of Genomic Testing. *Patient Educ. Couns.* 104, 2073–2079. doi:10.1016/j.pec.2021.01.030

Drury, S., Williams, H., Trump, N., Boustred, C., LenchLench, N., Scott, R. H., et al. (2015). Exome Sequencing for Prenatal Diagnosis of Fetuses with Sonographic Abnormalities. *Prenat. Diagn.* 35 (10), 1010–1017. doi:10.1002/pd.4675

Ferretti, L., Mellis, R., and Chitty, L. S. (2019). Update on the Use of Exome Sequencing in the Diagnosis of Fetal Abnormalities. *Eur. J. Med. Genet.* 62 (8), 103663. doi:10.1016/j.ejmg.2019.05.002

Harris, S., Gilmore, K., Hardisty, E., Lyerly, A. D., and Vora, N. L. (2018). Ethical and Counseling Challenges in Prenatal Exome Sequencing. *Prenat. Diagn.* 38 (12), 897–903. doi:10.1002/pd.5353

Hillman, S. C., Skelton, J., Quinlan-Jones, E., Wilson, A., and Kilby, M. D. (2013). "If it Helps …" the Use of Microarray Technology in Prenatal Testing: Patient and Partners Reflections. *Am. J. Med. Genet.* 161 (7), 1619–1627. doi:10.1002/ajmg.a.35981

Hodgson, J., and McClaren, B. J. (2018). Parental Experiences after Prenatal Diagnosis of Fetal Abnormality. *Semin. Fetal Neonat. Med.* 23 (No. 2), 150–154. WB Saunders. doi:10.1016/j.siny.2017.11.009

Horn, R., and Parker, M. (2018). Health Professionals' and Researchers' Perspectives on Prenatal Whole Genome and Exome Sequencing: 'We Can't Shut the Door Now, the Genie's Out, We Need to Refine it'. *PloS One* 13 (9), e0204158. doi:10.1371/journal.pone.0204158

Kalynchuk, E. J., Althouse, A., Parker, L. S., Saller, D. N., Jr, and Rajkovic, A. (2015). Prenatal Whole-Exome Sequencing: Parental Attitudes. *Prenat. Diagn.* 35 (10), 1030–1036. doi:10.1002/pd.4635

Khan, C. M., Moore, E. G., Leos, C., and Rini, C. (2016). Patient Hopes for Diagnostic Genomic Sequencing: Roles of Uncertainty and Social Status. *Eur. J. Hum. Genet.* 24 (6), 803–808. doi:10.1038/ejhg.2015.204

Lewis, C., Hammond, J., Klapwijk, J. E., Harding, E., Lou, S., Vogel, I., et al. (2021). Dealing with Uncertain Results from Chromosomal Microarray and Exome Sequencing in the Prenatal Setting: An International Cross-Sectional Study with Healthcare Professionals. *Prenat. Diagn.* 41, 720–732. doi:10.1002/pd.5932

Lord, J., McMullan, D. J., Eberhardt, R. Y., Rinck, G., Hamilton, S. J., Quinlan-Jones, E., et al. (2019). Prenatal Exome Sequencing Analysis in Fetal Structural Anomalies Detected by Ultrasonography (PAGE): A Cohort Study. *Lancet* 393 (10173), 747–757. doi:10.1016/S0140-6736(18)31940-8

Luksic, D., Sukhu, R., Koval, C., Cho, M. T., Espinal, A., Rufino, K., et al. (2020). A Qualitative Study of Latinx Parents' Experiences of Clinical Exome Sequencing. *J. Gene Coun.* 29, 574–586. doi:10.1002/jgc4.1276

Malek, J., Pereira, S., Robinson, J. O., Gutierrez, A. M., Slashinski, M. J., Parsons, D. W., et al. (2019). Responsibility, Culpability, and Parental Views on Genomic Testing for Seriously Ill Children. *Genet. Med.* 21, 2791–2797. doi:10.1038/s41436-019-0570-6

Mellis, R., Chandler, N., and Chitty, L. S. (2018). Next-generation Sequencing and the Impact on Prenatal Diagnosis. *Expert Rev. Mol. Diagn.* 18 (8), 689–699. doi:10.1080/14737159.2018.1493924

Mellis, R., Oprych, K., Scotchman, E., Hill, M., and Chitty, L. S. (2022). Diagnostic Yield of Exome Sequencing for Prenatal Diagnosis of Fetal Structural Anomalies: A Systematic Review and Meta-Analysis. *Prenat. Diagn.* 42 (6), 662–685. doi:10.1002/pd.6115

Mollison, L., O'Daniel, J. M., Henderson, G. E., Berg, J. S., and Skinner, D. (2020). Parents' Perceptions of Personal Utility of Exome Sequencing Results. *Genet. Med.* 22, 752–757. doi:10.1038/s41436-019-0730-8

Narayanan, S., Blumberg, B., Clayman, M. L., Pan, V., and Wicklund, C. (2018). Exploring the Issues Surrounding Clinical Exome Sequencing in the Prenatal Setting. *J. Genet. Couns.* 27 (5), 1228–1237. doi:10.1007/s10897-018-0245-5

Pangalos, C., Hagnefelt, B., Lilakos, K., and Konialis, C. (2016). First Applications of a Targeted Exome Sequencing Approach in Fetuses with Ultrasound Abnormalities Reveals an Important Fraction of Cases with Associated Gene Defects. *PeerJ* 4, e1955. doi:10.7717/peerj.1955

Petrovski, S., Aggarwal, V., Giordano, J. L., Stosic, M., Wou, K., Bier, L., et al. (2019). Whole-Exome Sequencing in the Evaluation of Fetal Structural Anomalies: A Prospective Cohort Study. *Lancet* 393 (10173), 758–767. doi:10.1016/S0140-6736(18)32042-7

Plantinga, M., Zwienenberg, L., Dijk, E., Breet, H., Diphoorn, J., El Mecky, J., et al. (2021). Parental Experiences of Rapid Exome Sequencing in Cases with Major Ultrasound Anomalies during Pregnancy. *Prenat. Diagn.* 42, 762–774. doi:10.1002/pd.6056

Quinlan-Jones, E., Hillman, S. C., Kilby, M. D., and Greenfield, S. M. (2017). Parental Experiences of Prenatal Whole Exome Sequencing (WES) in Cases of Ultrasound Diagnosed Fetal Structural Anomaly. *Prenat. Diagn.* 37 (12), 1225–1231. doi:10.1002/pd.5172

Richardson, A., and Ormond, K. E. (2018). Ethical Considerations in Prenatal Testing: Genomic Testing and Medical Uncertainty. *Semin. Fetal Neonat. Med.* 23 (1), 1–6. doi:10.1016/j.siny.2017.10.001

Robinson, J. O., Wynn, J., Biesecker, B., Biesecker, L. G., Bernhardt, B., Brothers, K. B., et al. (2019). Psychological Outcomes Related to Exome and Genome Sequencing Result Disclosure: a Meta-Analysis of Seven Clinical Sequencing Exploratory Research (CSER) Consortium Studies. *Genet. Med.* 21, 2781–2790. doi:10.1038/s41436-019-0565-3

Shkedi-Rafid, S., Fenwick, A., Dheensa, S., Wellesley, D., and Lucassen, A. M. (2016). What Results to Disclose, when, and Who Decides? Healthcare Professionals' Views on Prenatal Chromosomal Microarray Analysis. *Prenat. Diagn.* 36 (3), 252–259. doi:10.1002/pd.4772

Stivers, T., and Timmermans, S. (2017). The Actionability of Exome Sequencing Testing Results. *Sociol. Health Illn.* 39, 1542–1556. doi:10.1111/1467-9566.12614

Sullivan, H. K., Bayefsky, M., Wakim, P. G., Huddleston, K., Biesecker, B. B., Hull, S. C., et al. (2019). Noninvasive Prenatal Whole Genome Sequencing: Pregnant Women's Views and Preferences. *Obstet. Gynecol.* 133 (3), 525–532. doi:10.1097/aog.0000000000003121

Talati, A. N., Gilmore, K. L., Hardisty, E. E., Lyerly, A. D., Rini, C., and Vora, N. L. (2021). Impact of Prenatal Exome Sequencing for Fetal Genetic Diagnosis on Maternal Psychological Outcomes and Decisional Conflict in a Prospective Cohort. *Genet. Med.* 23 (4), 713–719. doi:10.1038/s41436-020-01025-5

Teefey, C. P., Hertzog, J., Morris, E. D., Moldenhauer, J. S., and Cole, J. C. M. (2020). The Impact of Our Images: Psychological Implications in Expectant Parents after a Prenatal Diagnosis. *Pediatr. Radiol.* 50 (13), 2028–2033. doi:10.1007/s00247-020-04765-3

Thompson Burdine, J., Thorne, S., and Sandhu, G. (2021). Interpretive Description: a Flexible Qualitative Methodology for Medical Education Research. *Med. Educ.* 55 (3), 336–343. doi:10.1111/medu.14380

Tong, A., Sainsbury, P., and Craig, J. (2007). Consolidated Criteria for Reporting Qualitative Research (COREQ): A 32-Item Checklist for Interviews and Focus Groups. *Int. J. Qual. Health Care* 19 (6), 349–357. doi:10.1093/intqhc/mzm042

Tsai, G. J., Cameron, C. A., Czerwinski, J. L., Mendez-Figueroa, H., Peterson, S. K., and Noblin, S. J. (2017). Attitudes towards Prenatal Genetic Counseling, Prenatal Genetic Testing, and Termination of Pregnancy Among Southeast and East Asian Women in the United States. *J. Genet. Couns.* 26 (5), 1041–1058. doi:10.1007/s10897-017-0084-9

Werner-Lin, A., Barg, F. K., Kellom, K. S., Stumm, K. J., Pilchman, L., Tomlinson, A. N., et al. (2016). Couple's Narratives of Communion and Isolation Following Abnormal Prenatal Microarray Testing Results. *Qual. Health Res.* 26 (14), 1975–1987. doi:10.1177/1049732315603367

Westerfield, L. E., Stover, S. R., Mathur, V. S., Nassef, S. A., Carter, T. G., Yang, Y., et al. (2015). Reproductive Genetic Counseling Challenges Associated with Diagnostic Exome Sequencing in a Large Academic Private Reproductive Genetic Counseling Practice. *Prenat. Diagn.* 35 (10), 1022–1029. doi:10.1002/pd.4674

Wilpers, A. B., Kennedy, H. P., Wall, D., Funk, M., and Bahtiyar, M. O. (2017). Maternal Anxiety Related to Prenatal Diagnoses of Fetal Anomalies that Require Surgery. *J. Obstet. Gynecol. Neonat. Nurs.* 46 (3), 456–464. doi:10.1016/j.jogn.2017.02.001

Wou, K., Weitz, T., McCormack, C., Wynn, J., Spiegel, E., Giordano, J., et al. (2018). Parental Perceptions of Prenatal Whole Exome Sequencing (PPPWES) Study. *Prenat. Diagn.* 38 (11), 801–811. doi:10.1002/pd.5332

Wynn, J., Ottman, R., Duong, J., Wilson, A. L., Ahimaz, P., Martinez, J., et al. (2018). Diagnostic Exome Sequencing in Children: a Survey of Parental Understanding, Experience and Psychological Impact. *Clin. Genet.* 93, 1039–1048. doi:10.1111/cge.13200

Yurkiewicz, I. R., Korf, B. R., and Lehmann, L. S. (2014). Prenatal Whole-Genome Sequencing: Is the Quest to Know a Fetus's Future Ethical? *Obstet. Gynecol. Surv.* 69 (4), 197–199. doi:10.1097/01.ogx.0000446907.09890.ff

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Population-Based Screening of Newborns: Findings From the NBS Expansion Study (Part One)

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Each year, through population-based newborn screening (NBS), 1 in 294 newborns is identified with a condition leading to early treatment and, in some cases, life-saving interventions. Rapid advancements in genomic technologies to screen, diagnose, and treat newborns promise to significantly expand the number of diseases and individuals impacted by NBS. However, expansion of NBS occurs slowly in the United States (US) and almost always occurs condition by condition and state by state with the goal of screening for all conditions on a federally recommended uniform panel. The Newborn Screening Translational Research Network (NBSTRN) conducted the NBS Expansion Study to describe current practices, identify expansion challenges, outline areas for improvement in NBS, and suggest how models could be used to evaluate changes and improvements. The NBS Expansion Study included a workshop of experts, a survey of clinicians, an analysis of data from online repositories of state NBS programs, reports and publications of completed pilots, federal committee reports, and proceedings, and the development of models to address the study findings. This manuscript (Part One) reports on the design, execution, and results of the NBS Expansion Study. The Study found that the capacity to expand NBS is variable across the US and that nationwide adoption of a new condition averages 9.5 years. Four factors that delay and/or complicate NBS expansion were

identified. A companion paper (Part Two) presents a use case for each of the four factors and highlights how modeling could address these challenges to NBS expansion.

Keywords: research, genomics, ACMG, NBSTRN, newborn screening

1 INTRODUCTION

Each year in the United States (US), at least 12,905 (Sontag et al., 2020) infants are identified with a genetic disease through the multi-component, multi-stakeholder system of newborn screening (NBS). NBS is recognized as one of the most successful public health programs in the US (Centers for Disease Control: Morbidity and Mortality Weekly Report (MMWR)) because it provides the opportunity to identify at-risk infants in a population regardless of race, income, or location of birth. Early identification of these at-risk infants facilitates timely diagnosis and administration of often life-saving treatment.

NBS began in the 1960s when a longitudinal study funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) discovered that newborns who were identified as having phenylketonuria (PKU) on a screening test using a blood spot on filter paper taken shortly after birth benefited from early diagnosis and treatment (Alexander, 2003). This discovery led to newborn screening pilots for PKU in several states and eventual nationwide screening of essentially all newborns using state-based public health laboratories.

Over the past 60 years, the number of possible screened conditions has increased from 1 to 81, with 75% (61/81) of these conditions recommended for screening by a federal advisory committee (Advisory Committee on Heritable Disorders in Newborns and Children (Advisory Committee on Heritable Disorders in Newborns and Children, 2010) Recommended Uniform Screening Panel (RUSP) (Advisory Committee on Heritable Disorders in Newborns and Children, 2011 RUSP)). Sixty-one conditions are included in the RUSP, and an additional 20 conditions are screened in at least one state as reported to the Association of Public Health Laboratories (Association of Public Health Laboratories Newborn Screening, 2020) Newborn Screening Technical assistance and Evaluation Program (NewSTEPs). This increase is largely due to advances in screening methodologie,s including the development of tandem mass spectrometry (MS/MS) in particular. The feasibility of screening for more than one condition using a single technology platform dramatically increased the number of conditions amenable to NBS (Ombrone et al., 2016; Farrell et al., 2020; Martin et al., 2020). In the future, the addition of genomic technologies to NBS would similarly increase the number of conditions that are candidates for NBS.

The composition of NBS panels and screening recommendations have been based on Wilson and Jungner's criteria as outlined in "Principles and practice of mass screening for disease" (Wilson and Jungner, 1968). In addition, consideration for adding a condition to NBS panels has historically required onset in the neonatal period and effective treatment early in life thapreventsed or significantly reduces morbidity and mortality (Watson et al., 2006). Treatment regimens have now evolved to include gene therapy, stem cell transplant, cochlear implants, surgical repair of congenital heart defects, enzyme replacement, and genotype-specific therapies, (Puck, 2019; De Vivo et al., 2019; Dabbous et al., 2019), leading to many more conditions for which there may be early, effective treatment. Moreover, even the tenet of early treatment is being challenged by the expansions of NBS panels to include conditions with later childhood and adult-onset forms.

As outlined in the Newborn Screening Saves Lives Reauthorization Act of 2014 (NBSSLA) (Senate of the United States, 2019), three federal agencies each play a key role in advancing and maintaining NBS. 1) The NICHD is charged with supporting NBS research, including funding and administering the Newborn Screening Translational Research Network (Newborn Screening Translational Research Network, 2011), as well as investigator-driven NBS research to discover novel screening, diagnostic, and treatment technologies, nd NBS research and implementation pilots. 2) The Health Resources and Services Administration (HRSA) is tasked with ensuring the availability of services and providers to care offorBS-screened patients, administering the Advisory Committee on Heritable Disorders in Newborns and Children (Advisory Committee on Heritable Disorders in Newborns and Children, 2016a), funding NewSTEPs and supporting state adoption pilots. 3) The CDC operates the Newborn Screening Quality Assurance Program (NSQAP), a national program that provides training and assesses the performance of state laboratories conducting screening (Centers for Disease Control and Prevention, 2020 NSQAP).

Conditions are considered candidates for NBS based on the RUSP nomination criteria, which includes an assessment of whether early identification and intervention results in improved health outcomes. **Figure 1** describes the different stages of NBS expansion from research pilots to nationwide implementation. As shown in the figure, an important step in understanding whether a condition is a candidate for NBS is to conduct research pilots of the entire screening process, including the screening test, diagnostic testing, clinical referral, and treatment, to assess the feasibility and potential benefits of early identification and intervention. Prospective or retrospective studies designed to assess the analytical and clinical validity of screening methods are often undertaken as an initial step. These studies or research pilots are typically a collaboration of multiple state NBS programs, working alone or with researchers, clinicians, and/or industry (diagnostics, medical device, and/or drugs), and they capture the initial performance of the screening test (Elliott et al., 2016). The second step is the implementation pilot. The NBSSLA authorized the Hunter Kelly Newborn Screening Research Program to conduct

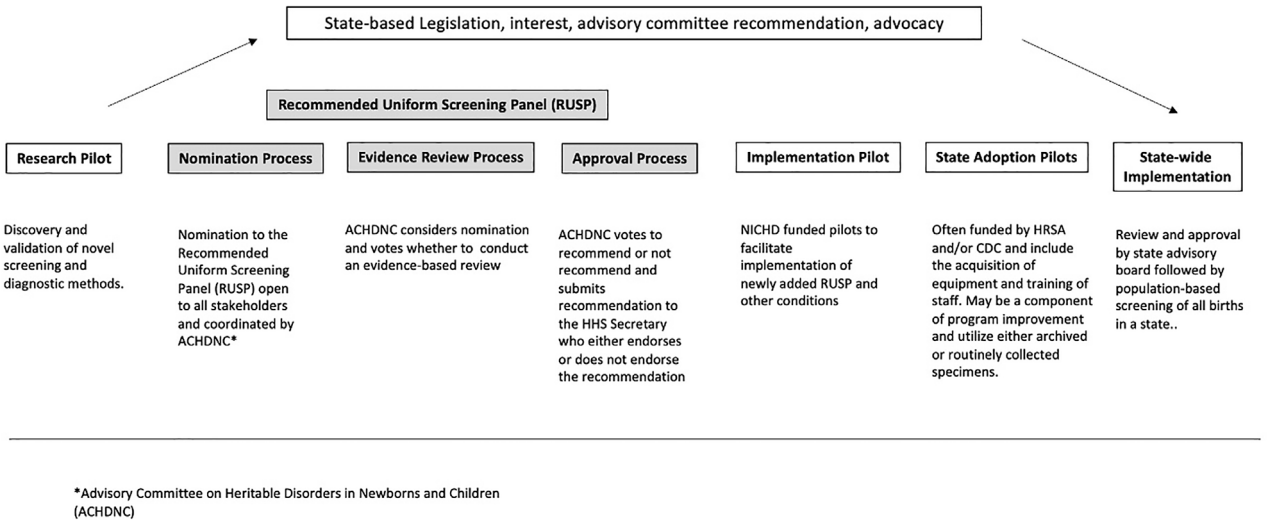

FIGURE 1 | Pathway of candidate conditions.

implementation pilot studies on conditions recommended by the (Advisory Committee on Heritable Disorders in Newborns and Children, 2016b) ACHDNC to "...ensure that screenings are ready for nationwide implementation."

In response, in 2016, NICHD created a pool of three states to conduct NBS pilots to facilitate the implementation of conditions recently recommended to the RUSP by the Health and Human Services (HHS) Secretary, and utilizing the coordinating infrastructure of the NBSTRN (Puryear et al., 2019). NBSTRN is a resource for investigators engaged in NBS-related research, led by the American College of Medical Genetics and Genomics (ACMG) and funded by a contract from NICHD. While these implementation pilots generate valuable information and data to accelerate and support the adoption of screening by state NBS programs, each state usually conducts state adoption pilots to demonstrate that they can meet the analytical standards established during the research and/or implementation pilots (Hall et al., 2020). Research pilots differ from implementation pilots, both of which differ from state adoption pilots (Vogel et al., 2015). However, all three types of pilots focus on the analytical validity of screening and diagnostic methods. All kinds of pilots are supported and funded through different mechanisms. Research pilots are supported by various stakeholders, including the Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, 2011), the National Institutes of Health (NIH, usually NICHD), industry, and advocacy groups. Implementation pilots are funded by NICHD and utilize a task order for each pilot available to a pool of three states, currently New York, Georgia, and North Carolina. State adoption pilots are funded by the Health Resources and Services Administration (HRSA) and CDC and include the acquisition of equipment and training of staff. Enrollment in prospective research and implementation pilots occurs in birthing facilities and may require informed consent from parents. Prospective state adoption pilots are typically conducted as a component of program improvement and utilize either archived or routinely collected specimens.

Over the past decade, the NBSTRN coordinated pilot studies and worked with several researchers and disease advocacy organizations to compile data and review the scientific literature to facilitate the nomination of conditions to the ACHDNC in addition to the RUSP. To check current practices, identify expansion challenges, and propose strategies to evaluate changes and improvements to NBS expansion, NBSTRN designed and conducted the NBS Expansion Study. The study included an in-person workshop, a review of state Practices, completed Pilots, and efforts of the ACHDNC, and an expert opinion survey on the readiness of candidate conditions for NBS pilot studies.

2 MATERIALS AND METHODS

2.1 NBS Expansion Study Workshop

Eighteen individuals participated in a 2 day workshop organized and hosted by NBSTRN staff. Attendees were selected based on their content knowledge of NBS, technology development and research, and involvement in NBS programs and pilots. Overviews of research, implementation, and state adoption pilots and expansion efforts were given by individuals from the NICHD pilot states, state NBS programs, and the HRSA-funded APHL NewSTEPs. The conference was recorded and transcribed. NBSTRN staff analyzed the transcripts and developed themes. These were presented to attendees for review, editing, and synthesis into a final report that was submitted to NICHD for consideration. The NBSTRN Steering Committee, a twelve-person group that guides NBSTRN activities, reviewed the workshop findings along with NICHD feedback and recommended NBSTRN survey state programs to assess their activities in the longitudinal follow-up of newborns

confirmed with a diagnosis and conduct an expert opinion survey to compile and rank the growing pipeline of conditions that are candidates for NBS pilots and eventual RUSP nomination.

2.2 Review of NBS and Expansion Efforts to Date

The online resources, including the NewSTEPs and NBSTRN online repositories, were reviewed to gather information and data describing state screening panels and practices. State NBS program websites were searched to identify legislation that mandates screening for non-RUSP conditions and identify results of long-term follow-up of screen-positive cases. Publications and/or summary reports provided by pilot sites were reviewed to analyze the number of sites; screened, referred, and diagnosed newborns; and pilot duration for Severe Combined Immune Deficiency (SCID), Pompe Disease, Mucopolysaccharidosis Type I (MPS I), and/or X-Linked Adrenoleukodystrophy (X-ALD). The ACHDNC website, meeting transcripts, reports, and letters were reviewed to summarize information related to nominated conditions.

2.3 Expert Opinion Survey on Readiness of Candidate Conditions for NBS Pilot Studies

NBSTRN staff compiled a list of 46 candidate conditions and developed a questionnaire that provided the name of the condition, RUSP status (included, nominated), and listed informative biomarkers, analytical method, second-tier test, and available treatment(s). A five-point Likert scale ranging from "No" (1) to "Yes" (5) was used to rate each condition for three criteria that are key to an ACHDNC nomination: 1) Understanding of the Condition (severity/urgency); 2) Test Efficacy; and 3) Treatment Efficacy. Criteria could be ranked as "0" when the respondent had "no opinion" about the condition/criteria (**Supplementary Tables S1, S2**).

The first criteria relate to whether there is sufficient understanding of the condition in question. This is especially important because NBS expansion has revealed considerable clinical variability and incidence differences compared to predictions from the evidence review. With implementation, the clinical variability inherent in nearly all screened conditions becomes evident, uncovering in some cases variability that is striking.

The second criteria address the availability of a high-throughput, sensitive, and specific screening algorithm, including 1st and 2nd tier tests, performed either on dried blood spots (DBS) or *via* physiologic assessment at the bedside. While the ability of MS/MS to screen for multiple inborn errors of metabolism (IEMs) simultaneously on a single sample facilitated rapid NBS expansion since the early 2000s, it also further complicated screening because conditions that did not meet the evidence threshold for inclusion in NBS could be detected while screening for those conditions that did meet the evidence. Similarly, genome or exome sequencing has the potential to identify multiple disease-associated pathogenic gene variants in a single assay and redefines assessment from that of a single test for a single disease to the identification of numerous disease risks. Metabolomics, proteomics, and other-omics are expected to further complicate this assessment. The third concept relates to the availability of treatments and interventions. The modality, urgency, efficacy, effectiveness, and availability of proposed therapies are important components in considering a condition for NBS.

Subject matter experts from the NBSTRN expert workgroups who did not attend the workshop contributed to the survey's design. The survey (**Supplementary Table S1**) administered *via* REDCap was distributed to 633 individuals, including 595 medical geneticists, metabolic disease experts, and laboratorians *via* the Society for Inherited Metabolic Disease (SIMD) email list and 38 NBSTRN users and researchers who conduct NBS pilots. The survey was open for 8 weeks, and two reminders to complete the survey were sent at weeks three and six. Likert scale responses were extracted from the survey, and the mean score for each criterion across respondents was computed. No opinion ratings were recorded as "0" and were excluded from mean score calculations. Based on consensus and review of the survey data from NBSTRN Steering Committee members, mean scores above or equal to 3.5, corresponding to the 70th percentile, were interpreted as a "yes" for the criteria ("Yes, this condition has a screening test," "Yes this condition is severe/urgent," "Yes this condition has a treatment"). Mean scores below the 70th percentile were interpreted as a "no" for the criteria ("No, this condition does not have a treatment"). Standard errors for each mean were calculated, and conditions were organized into groups based on the 70th percentile cut-off. A condition was deemed ready for pilot testing for NBS inclusion if the mean score for all three criteria (test, condition, and treatment) was ≥70%.

3 RESULTS

The NBS Expansion Study utilized a workshop of NBS experts, a survey of clinicians, a literature review, and a review of online resources and key efforts (e.g., ACHDNC, HRSA, CDC, and NICHD activities) to understand NBS expansion in the US. The findings are summarized below and organized by topic and data source.

3.1 Literature, Online Resources, and Key Effort Review Findings

3.1.1 NBS Expansion in the United States

In the US, 53 state-and territory-based programs conduct NBS. Before 2002, the number of screened conditions varied considerably from state to state ranging between 3 and 43 conditions. To address these differences, in 2002, the ACMG led a multi-year effort to survey experts and review the medical literature to assess the availability and characteristics of screening tests, the availability and complexity of diagnostic services, and the availability and efficacy of treatments for 84 conditions considered candidates for NBS. In 2005, this effort led to the original RUSP, with 29 core and 25 secondary conditions (Watson et al., 2006). After 3 years,

TABLE 1 | NBS conditions screened in at least one state but not on RUSP.

Carbamoyl phosphate synthase (CPS) deficiency	Fabry disease	Hyperornithinemia with gyrate deficiency	Nonketotic hyperglycinemia
Congenital cytomegalovirus infection	Formiminoglutamic acidemia	Hyperornithinemia-hyperammonemiahomocitrullinemia syndrome	Ornithine transcarbamylase (OTC) deficiency
Congenital human immunodeficiency virus infection	GAMT deficiency	Krabbe Disease	Prolinemia Type I/Type II
Congenital toxoplasmosis infection	Gaucher disease	Mucopolysaccharidosis Type II	Pyroglutamic acidemia
Ethylmalonic encephalopathy	Glucose-6-phosphate dehydrogenase deficiency	Niemann Pick disease	Zellweger syndrome

all but one NBS program reported screening for all core conditions. This move to uniformity was achieved in a short timeframe because 80% (23/29) of the core conditions could be screened using a common multiplex technology, tandem mass spectrometry (MS/MS).

Using the ACMG effort as a model, the ACHDNC developed a nomination and evidence review system that is open to all stakeholders (Green et al., 2007). Since 2007, 13 conditions have been nominated and reviewed, and six were recommended for screening by the ACHDNC and, ultimately, the HHS secretary. Nomination to the RUSP is open to all stakeholders, and nominated conditions follow a standard process of consideration, including an evidence review. Conditions are usually reviewed one by one, and the review must be completed within 9 months. While the system in place to amend the RUSP encourages uniformity across the US by recommending conditions for screening, state programs are not obligated to follow those recommendations, and each state decides on the makeup of its state's screening panel.

3.1.2 Composition of NBS Panels

A review of current state panels in 2021 using online resources found that screening for up to 20 non-RUSP conditions is mandated legislatively in 23 states, representing deviations from the goal of the RUSP, which is uniformity based on evidence review (**Table 1**). These 23 states account for the screening of 54% (2,116,299/3,883,107) of US newborns (ACHDNC RUSP). Thirty-five percent (7/20) of the conditions have been nominated to the RUSP in the past (ACHDNC RUSP), and 8/20 (40%) are included in a completed or current pilot (ScreenPlus, 2022). Since our review, Mucopolysaccharidosis Type II (MPS II) was recommended to the RUSP in February 2022. The current status of state NBS panels can be found on the individual state websites, as well as the NewSTEPs Repository and the NBSTRN data tool called the NBS Conditions Resource (NBSTRN NBS-CR, 2022). The Newborn Screening Conditions Resource (NBS-CR) provides a centralized resource of facts and statistics on both screened and candidate conditions. The NBS-CR is designed to be an interactive resource for researchers, clinicians, parents, and families to learn more about these disorders and links to National Library of Medicine (NLM) resources, including the National Center for Biotechnology Information (NCBI). The NBS programs report several reasons for screening for conditions that are not on the RUSP, including state legislation, state advisory committee recommendation, and advocacy (The Brack Bills, 2016; Justia US Law, 2019; Connecticut General Assembly, 2020).

3.1.3 NBS Pilots

Pilots of conditions newly recommended to the RUSP are conducted in conjunction with at least one state-based NBS program to assess the analytical and clinical validity of the screening technology. A review of five of these pilots, shown in **Table 2**, found that the average duration of screening (which can include multiple state programs) was 8.8 months; the number of newborns screened ranged from 12,065 to 420,000; each pilot found at least one case; the screening technology and the follow-up algorithms used by each state varied; there was no coordination of data analysis or consensus developed by the participating states; not all states participated in every pilot; most pilot findings were either presented at scientific meetings or published within 3 years.

There are no standardized requirements or endpoints for NBS pilot studies, and the choice of outcomes and the development of robust statistical endpoints may be complicated because NBS conditions are rare and may have variable penetrance, age of onset, and severity. The endpoint for enrollment for some pilot studies is a defined period of time or population size. In contrast, others end once a single newborn with the targeted condition has been identified and the diagnosis confirmed. As a consequence of the design of both research and implementation pilots coupled with the rarity of most diseases, an assessment of the treatment and long-term health outcomes of NBS-identified individuals is not feasible. This makes it difficult to assess the utility of screening with regard to long-term outcomes, which has only occurred, at best, after population-based screening has been implemented. Additionally, there are currently no systematic approaches for assessing the ethical, social, or behavioral impact of screening for particular conditions on newborns and their families.

The collection of longitudinal health information from clinicians, educators, and others that care for these individuals is critical but very challenging given the variety of health care systems that hold relevant information on outcomes and the non-reimbursed effort currently required by care providers to enter follow-up data into systems created for long-term follow-up. Long-term follow-up is defined by each program based on state policies and legislation but usually involves collecting health information beyond diagnosis, treatment, and referral to clinical care. To make the collection of long-term follow-up

TABLE 2 | NBS pilots after HHS endorsement for RUSP.

Condition	RUSP addition (month/ Year)	Number of sites	Number of newborns screened	Screening start	Screening duration (months)	Number referred	Number diagnosed	Publication date (mont h/year)	Link to publication
SCID	2/2010	4[a]	167,509 420,000 32,000 34,544	10/2010	8	247 43 8 9	24 1 7 4 8	8/2014	https://pubmed.ncbi.nlm.nih.gov/32003821/
Pom pe	3/2015	2	59,332 108,862	1/2017 NA	5.5	310 NA	4 13	1/2020 NA[b]	https://pubmed.ncbi.nlm.nih.gov/32003821/ NA
MPS I	2/2016	2	59,332 62,734	1/2017 8/2016	5.5 7	17 1 9	11 1 4	1/2020 8/2019	https://pubmed.ncbi.nlm.nih.gov/32003821/
X- AL D	2/2016	2	51,081 52,301	7/2017 3/2018	5 4	12 1 2	4 8	NA 1/2020	NA https://pubmed.ncbi.nlm.nih.gov/32003821/
SMA	7/2018	2	146,749 12,065	2/2019; 10/2018	12 15	23 2	11 1	NA 3/2021	NA https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8006221/

[a]*NY, CA, WI, conducted screening* via *courier for Louisiana; MA conducted screening* via *courier for Puerto Rico.*
[b]*NA, designates not published.*

TABLE 3 | Implementation status of new RUSP conditions (4/21).

Condition[a]	HHS recommendation to RUSP	Status	Years
SCID	2010	100% (53/53)	10
CCHD	2011	100% (53/53)	9
Pompe	2015	43% (23/53)	5+
MPS I	2016	39% (21/53)	4+
X-ALD	2016	34% (18/53)	4+
SMA	2018	43% (23/53)	2+

[a]*SCID, Severe Combined Immunodeficiency; CCHD, Critical Congenital Heart Disease; MPS I, Mucopolysaccharidosis Type I; X-ALD, X-Linked Adrenoleukodystrophy; SMA, Spinal Muscular Atrophy.*

data more streamlined, the NBSTRN developed the Longitudinal Pediatric Data Resource (LPDR), which includes common data elements (CDEs) developed by clinical experts and electronic case report forms for use by state NBS programs, researchers, and other stakeholders. NBSTRN aggregates the follow-up data in the LPDR and makes de-identified summaries publicly available (NBSTRN SCID).

3.1.4 Length of Time to Implement a New RUSP Condition

A review of the implementation status from the NewSTEPs Data Repository (APHL NewSTEPs) found that the time to achieve screening across all 53 programs for the first condition added to the RUSP, SCID, was 10 years. This multi-year adoption process has been repeated for the other five conditions recommended to the RUSP, as shown in **Table 3**. The length of time for implementing a new condition led the ACHDNC to add an assessment of state readiness to the evidence review process. This assessment enables a better understanding of the capacity of states to expand screening and the resources required to support expansion. An assessment of the capacity of the health care system, including subspecialties, to confirm diagnoses in screen-positive infants and manage diagnosed infants would be informative and facilitate state adoption but is not part of the current process. As the number of conditions that would benefit from early identification and treatment through NBS increases, workshop participants noted that a failure to address resources for follow-up and long-term care would continue to negatively impact NBS as a system.

3.2 Expert Opinion Survey

The survey was delivered electronically to 633 experts *via* the SIMD list serve, 55 logged into the survey, and 65% (36/55) completed the survey (**Supplementary Table S1**). Forty-six conditions were scored for three concepts, totaling 138 possible scores for each respondent. The number of respondents who ranked the three concepts for each condition varied because the survey allowed a response of "0" for "no opinion," and this resulted in an average of 27 respondents per condition with a range of 13–36. Mean scores and standard errors were calculated for each concept and condition (**Supplementary Table S2**). Two conditions, congenital HIV and guanidinoacetate methyltransferase deficiency (GAMT), ranked above 80% (Likert rank 4) for all three criteria. An additional 13 conditions ranked equal to or above 70% (Likert ranked 3.5). Using 70% as a cut-off for each criterion resulted in 15 conditions ranked as ready for NBS pilots based on condition understanding, available test, and

TABLE 4 | Conditions meeting the 70% threshold across concepts to identify readiness for NBS pilots.

Condition, test and treatment> 3.5(n = 15)	Condition and test> 3.5(n = 8)	Condition and treatment> 3.5(n = 8)	Condition > 3.5(n = 12)	All concepts <3.5(n = 3)
Acute neonatal bilirubin encephalopathy	Duchenne muscular dystrophy	BCKDK deficiency	Cerebrotendinous xanthomatosis	3-phosphoglycerate DH deficiency
AGAT deficiency	Fragile X	Brown vialetto van laere syndrome	Chr. 22 Deletion q11.2	Adenine phosphoribosyltransferase deficiency
Arginase deficiency	MPS IVA	CPS deficiency	Congenital toxoplasmosis	Pyruvate DH lipoic acid synthetase deficiency
Cbl C, D deficiency	MTHFR deficiency	Familial hypercholesterolemia	Creatine transporter deficiency	
Congenital HIV	NCL2 neuronal ceroid lipofuscinosis	NAGS deficiency	Cytomegalovirus	
CPT1A Deficiency	Niemann Pick A/B disease	OTC Deficiency	Friedreich Ataxia	
Fabry	MPS IIIA	Wilson Disease	Krabbe Disease	
G6PD	Smith lemli opitz syndrome	Wolman Disease	Menkes Disease	
GAMT deficiency			Metachromatic Leukodystrophy	
Gaucher			Molybdenum cofactor Deficiency	
Hemoglobin H disease			Niemann Pick C Disease	
MPS II			Pyruvate carboxylase deficiency	
MPS VI				
MPS VII				
Pyridoxine responsive epilepsy				

available treatment. Eight conditions lacked a therapy, an additional eight conditions lacked a screening test, 12 conditions had understanding but lacked treatment and test, and three conditions were ranked below the cut-off for all three criteria (**Table 4**).

4 DISCUSSION

The NBS Expansion Study explored the addition of conditions to nationwide NBS, surveyed experts to assess the readiness of conditions for NBS pilots, and described factors that delay and/or complicate expansion. Although the number of clinical experts who completed the survey was low, the individuals who completed the survey are involved in caring for newborns diagnosed with a condition through NBS. The pool of potential survey respondents was based on the SIMD list-serve, and the majority of these individuals may not be involved in NBS efforts. Future surveys of clinical experts may benefit from a targeted messaging campaign to encourage involvement.

The Study identified four factors that delay and/or complicate NBS expansion.

4.1 Variability in Screening Panels Persists

A review of individual state NBS screening panels found growing variation in state NBS panels and shows that the number of conditions screened ranges from a low of 32 core conditions to a high of 71 core, secondary, and non-RUSP conditions combined. A total of 81 different conditions are screened across the US. The makeup of screening panels is determined by each state's NBS program, and each program develops its own screening and follow-up algorithms. Non-RUSP conditions are added to state NBS panels through the efforts of advocates and legislation. Over one-third of the non-RUSP conditions have been submitted for evidence review to the ACHDNC, and 40% are part of current or past pilots. Therefore, state panels may inform the content of future NBS expansions. Although the CDC and NewSTEPs organize training and funding to facilitate state adoption, there is no formal dissemination plan to share data from pilot studies; thus, the current pilot system fails to capitalize on opportunities to disseminate findings from individual state efforts.

4.2 The Short Duration of Pilots Limits Information About Interventions and Health Outcomes

While pilot sites are usually able to describe the diagnosis and initial disposition of the referred cases, the short duration of pilots often limits the description of health outcomes after treatment. This results in several missed opportunities, including the ability to: 1) advance understanding of the genetic disease; 2) connect the screening for a defined biomarker with improved outcomes; 3) identify gaps in evidence to be filled to support the nomination to the RUSP; 4) plan for the medical system impact of adding a condition to screening; and 5) document the effectiveness of early identification through NBS.

4.3 Recent RUSP Additions Expand the Definition of NBS

While NBS aims to identify infants with conditions that benefit from the intervention before the onset of symptoms

and during the newborn period, recent RUSP additions have variable onset and/or defined late-onset forms manifesting far beyond the newborn period, if at all (e.g., Pompe, heterozygous X-ALD). A tool should be developed to assess the ethical, social, and behavioral impact of NBS for such disorders on newborns and families to identify and mitigate any potential harms to maximize the net benefit of screening prior to the addition of the condition to the RUSP.

4.4 The RUSP Nomination and Evidence Review Process has Capacity Constraints

The number of conditions candidates for NBS pilots and nationwide screening continues to increase. The approach of one-by-one nomination, review, implementation, and state adoption applied to this pipeline of candidates equates to decades of pilots designed to assess only the analytical part of the screening and the short-term follow-up aspect of a complex, multi-component system.

Although NBS has the potential to revolutionize genomic medicine through the population-based use of genomics to screen, diagnose and treat individuals with a genetic disease, current NBS expansion practices limit the realization of this promise. Findings from the NBS Expansion Study support the conclusion that the current approach to the expansion of NBS (i.e., one-by-one nomination, evidence review and HHS recommendation, implementation pilots, and state adoption) does not easily accommodate the hundreds of rare genetic disorders that could potentially benefit from NBS. The four factors identified in our study highlight weaknesses and gaps in the current system. Addressing these challenges will require innovative solutions so that the NBS system can be modernized and become responsive to the rapid advances in screening and diagnostic technologies, the emergence of novel therapies, and the expectations of the public (or families/advocates). Our companion paper, "Using Models to Address Challenges in Newborn Screening Expansion Study Part Two," builds upon these findings, suggests and prioritizes solutions using some case studies and models, and outlines a potential future course for NBS in the US.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/ **Supplementary Material.**

AUTHOR CONTRIBUTIONS

Conceptualization: AB, KC, MIW; Data Curation: AB, KC; Formal Analysis: AB, KC, MAW; Funding Acquisition: AB; Investigation: AB, KC; Methodology: AB, KC, MAW, RC, SB, PR, MIW; Project Administration: AB; Resources: AB, KC; Supervision: AB; Validation; AB, KC; Visualization: AB, KC; Writing-original Draft: AB, KC; Writing-review and editing: AB, KC, MAW, SB, RC, RP, MC, AG, WW, RS, IH, DM, JT, JO, LB, KS, AG, CS, MEW, RH, JA, OB, JC, ME, CF, NT, RL, SV, and MIW.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.867337/full#supplementary-material

REFERENCES

Advisory Committee on Heritable Disorders in Newborns and Children. (2016a). Heritable Disorders– About the Committee. Available at: https://www.hrsa.gov/advisory-committees/heritable-disorders/about/index.html [Accessed January 20, 2022]

Advisory Committee on Heritable Disorders in Newborns and Children. (2016b). Recommended Uniform Screening Panel. Available at : https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/recommendedpanel/index.html [Accessed January 20, 2022]

Advisory Committee on Heritable Disorders in Newborns and Children. (2011). Report on Newborn Screening for Severe Combined Immunodeficiency. Available at:https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/reports/newborn-screening-scid-report.pdf. [Accessed January 20, 2022]

Advisory Committee on Heritable Disorders in Newborns and Children. (2010) The Addition of SCID to the Uniform Panel and Related T-Cell Lymphocyte Deficiencies to the List of Secondary Targets as a Comprehensive Entity. Available at:https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/reports-recommendations/letter-to-sec-immune-deficiency.pdf [Accessed January 20, 2022]

Alexander, D. (2003). The National Institute of Child Health and Human Development and Phenylketonuria. *Pediatrics* 112, 1514–1515. doi:10.1542/peds.112.s4.1514

Association of Public Health Laboratories Newborn Screening (2020). Technical Assistance and Evaluation Program (NewSTEPs). Newborn Screening Status for All Disorders. Available at: https://www.newsteps.org/about-us. [Accessed January 20, 2022].

Centers for Disease Control and Prevention (CDC). (2011). Ten Great Public Health Achievements—The United States, 2001-2010. Morbidity and Mortality Weekly Report (MMWR), 60, 619–623.Available at: from http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6019a5.htm. [Accessed August 9, 2020].

Centers for Disease Control and Prevention. (2020). NSQAP: Newborn Screening Quality Assurance Program. Available at: https://www.cdc.gov/labstandards/nsqap.html [Accessed August 9, 2020]

Connecticut General Assembly. (2020). AIDS Testing and Medical Information. Available at: https://www.cga.ct.gov/current/pub/chap_368x.htm [Accessed August 9, 2020]

Dabbous, B., Maru, J. P., Jansen, J. P., Lorenzi, M., Cloutier, M., Guérin, A., et al. (2019). Survival, Motor Function, and Motor Milestones: Comparison of AVXS-101 Relative to Nusinersen for the Treatment of Infants with Spinal Muscular Atrophy Type 1. *Adv. Ther.* 36 (5), 1164–1176. doi:10.1007/s12325-019-00923-8

De Vivo, D. C., Bertini, E., Swoboda, K. J., Hwu, W.-L., Crawford, T. O., Finkel, R. S., et al. (2019). Nusinersen Initiated in Infants during the Presymptomatic Stage of Spinal Muscular Atrophy: Interim Efficacy and Safety Results from the Phase 2 NURTURE Study. *Neuromuscul. Disord.* 29 (11), 842–856. doi:10.1016/j.nmd.2019.09.007

Elliott, S., Buroker, N., Cournoyer, J. J., Potier, A. M., Trometer, J. D., Elbin, C., et al. (2016). Dataset and Standard Operating Procedure for Newborn Screening of Six Lysosomal Storage Diseases: By Tandem Mass Spectrometry. *Data Brief* 8 (4), 915–924. doi:10.1016/j.dib.2016.06.052

Farrell, P. M., Rock, M. J., and Baker, M. W. (2020). The Impact of the CFTR Gene Discovery on Cystic Fibrosis Diagnosis, Counseling, and Preventive Therapy. *Genes* 11 (4), 401. doi:10.3390/genes11040401

Green, N. S., Rinaldo, P., Brower, A., Boyle, C., Dougherty, D., Lloyd-Puryear, M., et al. (2007). Committee Report: Advancing the Current Recommended Panel of Conditions for Newborn Screening. *Genet. Med.* 9 (11), 792–796. doi:10.1097/gim.0b013e318159a38e

Hall, P. L., Sanchez, R., Hagar, A. F., Jerris, S. C., Wittenauer, A., and Wilcox, W. R. (2020). Two-Tiered Newborn Screening with Post-Analytical Tools for Pompe Disease and Mucopolysaccharidosis Type I Results in Performance Improvement and Future Direction. *Int. J. Neonatal Screen* 6 (1), 2. doi:10.3390/ijns6010002

Justia US Law. (2019). 2019 New Jersey Revised Statutes Title 26 - Health and Vital Statistics.

Martin, G. R., Ewer, A. K., Gaviglio, A., Hom, L. A., Saarinen, A., Sontag, M., et al. (2020). Updated Strategies for Pulse Oximetry Screening for Critical Congenital Heart Disease. *Pediatrics* 146 (1), e20191650. doi:10.1542/peds.2019-1650

NBSTRN NBS-CR. (2022) Newborn Screening Conditions Resource. Available at: https://nbstrn.org/tools/nbs-cr [Accessed May 22, 2022]

Newborn Screening Translational Research Network. (2011). National SCID Pilot Study. Available at : https://nbstrn-admin.nbstrn.org/sites/default/files/2020-12/National%20SCID%20Pilot%20Study%20Report.pdf [Accessed January 9, 2022]

Ombrone, D., Giocaliere, E., Forni, G., Malvagia, S., and la Marca, G. (2016). Expanded Newborn Screening by Mass Spectrometry: New Tests, Future Perspectives. *Mass Spec. Rev.* 35 (1), 71–84. doi:10.1002/mas.21463

Puck, J. M. (2019). Newborn Screening for Severe Combined Immunodeficiency and T-Cell Lymphopenia. *Immunol. Rev.* 287 (1), 241–252. doi:10.1111/imr.12729

Puryear, M., Brower, A., Berry, S. A., Brosco, J. P., Bowdish, B., and Watson, M. S. (2019). Foundation of the Newborn Screening Translational Research Network and its Tools for Research. *Genet. Med.* 21 (6), 1271–1279. doi:10.1038/s41436-018-0334-8

Screenplus 2022. What Is ScreenPlus? Retrieved April 6, 2022, from: https://einsteinmed.edu/research/screenplus/.

Senate of the United States. (2019) H.R.2507 -Newborn Screening Saves Lives Reauthorization Act of 2019. Available at : https://www.congress.gov/bill/116th-congress/house-bill/2507/text?q=%7B%22search%22%3A%5B%22newborn+screening+saves+lives%22%5D%7D&r=1&s=1. [Accessed January 10, 2022].

Sontag, M. K., Yusuf, C., Grosse, S. D., Edelman, S., Miller, J. I., McKasson, S., et al. (2020). Infants with Congenital Disorders Identified Through Newborn Screening - United States, 2015-2017. *MMWR Morb. Mortal. Wkly. Rep.* 69, 1265–1268. Retrieved August 3, 2021, from: https://www.cdc.gov/mmwr/volumes/69/wr/mm6936a6.htm#suggestedcitation. doi:10.15585/mmwr.mm6936a6

The Brack Bills. (2016). Update on the Implementation of Hannah's Law. , Retrieved from https://thebrackbills.com/2016/02/19/update-on-the-implementation-of-hannahs-law/[Accessed August 9, 2020]

Vogel, B. H., Bradley, S. E., Adams, D. J., D'Aco, K., Erbe, R. W., Fong, C., et al. (2015). Newborn Screening for X-Linked Adrenoleukodystrophy in New York State: Diagnostic Protocol, Surveillance Protocol and Treatment Guidelines. *Mol. Genet. Metabolism* 114 (4), 599–603. doi:10.1016/j.ymgme.2015.02.002

Watson, M. S., Mann, M. Y., Lloyd-Puryear, M. A., Rinaldo, P., and Howell, R. R.; American College of Medical Genetics Newborn Screening Expert Group (2006). Newborn Screening: Toward a Uniform Screening Panel and System –Executive Summary. *Pediatrics* 117 (Suppl. 3), S296–S307. doi:10.1542/peds.2005-2633i

Wilson, J. M., and Jungner, Y. G. (1968). Principles and Practice of Mass Screening for Disease. *Bol. Oficina Sanit. Panam.* 65, 281–393.

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Public Interest in Population Genetic Screening for Cancer Risk

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An emerging role for DNA sequencing is to identify people at risk for an inherited cancer syndrome in order to prevent or ameliorate the manifestation of symptoms. Two cancer syndromes, Hereditary Breast and Ovarian Cancer and Lynch Syndrome meet the "Tier 1" evidence threshold established by the Centers for Disease Control and Prevention (CDC) for routine testing of patients with a personal or family history of cancer. Advancements in genomic medicine have accelerated public health pilot programs for these highly medically actionable conditions. In this brief report, we provide descriptive statistics from a survey of 746 US respondents from a Qualtrics panel about the public's awareness of genetic testing, interest in learning about their cancer risk, and likelihood of participating in a population genetic screening (PGS) test. Approximately of half the respondents were aware of genetic testing for inherited cancer risk (n = 377/745, 50.6%) and would choose to learn about their cancer risk (n-309/635, 48.7%). Characteristics of those interested in learning about their cancer risk differed by educational attainment, age, income, insurance status, having a primary care doctor, being aware of genetic testing, and likelihood of sharing information with family ($p < 0.05$). A sizeable majority of the respondents who were interested in about learning their cancer risk also said that they were likely to participate in a PGS test that involved a clinical appointment and blood draw, but no out-of-pocket cost (n = 255/309, 82.5%). Reasons for not wanting to participate included not finding test results interesting or important, concerns about costs, and feeling afraid to know the results. Overall, our results suggest that engaging and educating the general population about the benefits of learning about an inherited cancer predisposition may be an important strategy to address recruitment barriers to PGS.

Keywords: population genetic screening, cancer, public awareness, DNA sequencing, barriers

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INTRODUCTION

DNA-based screening of healthy individuals has enormous, yet untapped potential to improve cancer-related health outcomes through early detection and cancer prevention before symptoms manifest. Multidisciplinary research supporting the clinical utility and validity of DNA-based population screening for certain medically actionable conditions is increasing. (Adams et al., 2016; Hunter et al., 2016; Milko et al., 2019; Zhang et al., 2019; Hendricks- Sturrup et al., 2020; Roman et al., 2020). A point of consensus for DNA-based screening is that the benefit to harm ratio

can be maximized by screening for pathogenic genomic variants in well-understood causative genes for conditions with effective, evidence-based clinical interventions. (Jarvik et al., 2014; Berg et al., 2016; Green et al., 2019; Hendricks- Sturrup et al., 2020; Murray et al., 2020; Bean et al., 2021; Murray et al., 2021).

The US Centers for Disease Control and Prevention (CDC) has defined two hereditary cancer syndromes as "Tier 1" based on their clinical actionability: Lynch syndrome (LS) and Hereditary Breast and Ovarian Cancer (HBOC). Evidence indicates that population screening could significantly reduce morbidity and mortality for millions of Americans each year. (Green et al., 2019; Bean et al., 2021; Murray et al., 2021). Cost-effectiveness analyses demonstrate that screening in the general population yields good value for money and even potential cost savings for health care systems, especially when cascade screening (i.e., family testing) is considered. (Manchanda et al., 2018; Zhang et al., 2019).

The National Academies of Sciences, Engineering and Medicine's Genomics and Public Health Action Collaborative has endorsed "an accelerated implementation science agenda" (Khoury et al., 2018) for the Tier 1 conditions, including LS, HBOC, and familial hypercholesterolemia (FH), to understand the potential impact of population genomic screening in healthy adults. Increasingly, these three conditions and eleven associated genes are being adopted for Population Genetic Screening (PGS) pilot programs to investigate clinical and implementation outcomes in various health care settings around the country. (Brown-Johnson et al., 2021; Christensen et al., 2021; East et al., 2021).

Though the capacity for clinical PGS programs to transform personalized public health in the United States is widely acknowledged (Evans et al., 2013; Green et al., 2020), current public interest in participating in PGS is an essential yet understudied aspect of equitable implementation. Several studies examining the public's interest in population genetic screening have shown that awareness about genetic screening for certain types of cancer is associated with being non-Hispanic White (Hay et al., 2018; Rubinsak et al., 2019), willingness to pay for testing, having a family history of cancer, and higher educational attainment. (Shen et al., 2022). Other population characteristics such as access to a primary care provider, rurality, income, insurance, sexual orientation, and gender have been shown to be related to genetic services use; however little is understood about their association with interested in and likelihood to participate in PGS. To this end, we conducted a survey to more comprehensively understand the characteristics of those who are interested in participating in PGS for learning about cancer risk. The results of this study may inform strategies to increase awareness and participation in PGS programs among diverse populations.

METHODS

Population

In December 2020, the UNC Lineberger Cancer Prevention and Control Program recruited an online convenience sample of US adults through the Qualtrics Online Panel platform (n = 746, Qualtrics, Seattle WA). Participants were eligible if they were over the age of 18 and resided in the US. Qualtrics panel members are recruited from multiple sources including but not limited to, targeted email lists, gaming sites, customer loyalty web portals, and social media. Panel members were sent an email invitation or were prompted on the survey platform to respond to the online survey for a specific compensation amount. Because panel members can be reimbursed in different ways (e.g., gather points, donate funds, etc.), incentive amount for this study is estimated to be $2.50 per person. Interested respondents clicked on the survey link provided. The University of North Carolina Institutional Review Board approved this study (#20–2338).

Measures

Primary outcomes of interest were adapted from existing surveys and included:

(1) awareness about genetic tests (i.e., *Genetic tests that analyze your DNA for potential cancer risks are currently available. Have you heard or read about these genetic tests? Yes/no*) (HINTS, 2022);
(2) receipt of genetic testing (among those aware of genetic testing: *Have you ever had a genetic test to determine if you have an increased risk of developing cancer? Yes/no*) (HINTS, 2022);
(3) interest in learning genetic risk (among those who have not received genetic testing: *How interested would you be in learning whether you have a genetic risk factor for cancer that can be prevented or treated? Likert 1–5*) (Peterson et al., 2022);
(4) likelihood of getting a PGS test (among those who were interested in learning genetic risk: *To learn whether you have a genetic risk factor for cancer, you would need to make an appointment at a local clinic, get your blood drawn, and set up an online account to access your test results. Assuming there is no cost to you, how likely would you be to get this test?* Likert 1–5); and
(4a) reasons why you selected "unlikely/very unlikely" or "neither likely or unlikely" or "likely/very likely" (open-ended response). (See **Supplementary Figure S1**).

Given that cost is a known barrier to genetic testing among patients (Steffen et al., 2017), we asked specifically about interest in a screening test that would be at no-cost to patients. Participants were also asked to explain how they arrived at their answer about their likelihood of getting a PGS test in an open field question (question 4a above).

Because we were interested in understanding which subpopulations are aware of, engaged in or interested in engaging in PGS programs, we collected sociodemographic information that has been associated with awareness about or use of genetic services in prior studies. These characteristics included: gender (women/men) (Sanderson et al., 2004; Childers et al., 2018), ethnicity (Hispanic, non-Hispanic) (Childers et al., 2018; Salloum et al., 2018), race (white, black, other) (Salloum et al., 2018; Chapman-Davis et al., 2021), education (less than HS/HS/GED, some college/technical

school, AD, BS, graduate/professional degree) (Sanderson et al., 2004; Armstrong et al., 2005; Childers et al., 2018), age (<25, 25–49, 50–74, 75+) (Sanderson et al., 2004; Orlando et al., 2019), income ($0–34,999, $35,000–99,999, $100K+) (Armstrong et al., 2005), insurance (Medicare/Medical Assistance/any kind of government-assistance plan for those with low incomes or a disability, Employer-based, any Medicaid, and other) (The National Academies Collection: Reports funded by National Institutes of Health, 2018), sexual orientation (straight, gay or lesbian, bisexual, prefer to self-describe) (Nathan et al., 2019), and rurality (urban, suburban, rural). (Salloum et al., 2018). We also included several additional variables: having a primary care doctor (yes/no), (Armstrong et al., 2005), perceived comparative cancer risk (5 point Likert scale) (Chopra and Kelly, 2017), and intentions to share results with family (8 point Likert scale) (Chopra and Kelly, 2017). These variables were included as conversations with primary care providers, (Armstrong et al., 2005), having higher perceived cancer risk (often due to family or personal cancer history) (Chopra and Kelly, 2017), and intentions to share results with family members have been associated with increased genetic services use (Chopra and Kelly, 2017).

Analysis

We calculated descriptive statistics to examine whether there were differences between the characteristics of respondents according to our primary outcomes. We used chi-square tests to examine differences between those who were 1) aware of genetic tests versus not aware, 2) previously tested versus not tested, 3) interested (very interested, interested) in PGS versus not interested (neutral, uninterested, very uninterested), and 4) likely to participate in PGS versus not likely (neutral, unlikely, very unlikely).

We used thematic analysis to understand respondents free text responses to their likelihood of participating in PGS (question 4a above). We report the top five themes among those who were likely, unlikely, and neutral about getting a PGS test (MCR and LVM). Independently coders reviewed open-ended responses and identified emergent themes for each response category (unlikely: unlikely/very unlikely; neutral: neither likely or unlikely; likely: likely/very likely) and applied them to 10% of responses in each category. Coders compared themes and their application, modified the list of themes, and then independently applied the codes to 20% of responses (n = 60). We repeated this process until we achieved 100% agreement (in one round), and then we independently coded the remaining responses. We calculated the level of agreement between coders (87.6%). Conflicts were then reconciled through discussion. We reported the major themes and exemplar quotes.

RESULTS

Of the overall sample of respondents, 377 (50.6%) were aware of genetic tests. Among those who were aware of genetic tests, a higher proportion were non-Hispanic, in the middle age categories, as well as had higher educational attainment, Medicare or other insurance, a primary care doctor and higher perceived comparative cancer risk. No significant differences between gender, race, income, rurality, and sexual orientation were identified (**Table 1**).

Among those aware of genetic tests, 110 respondents (29.2%) had received a genetic test for an inherited cancer risk in the past. Compared to the 267 respondents who had not previously received a genetic test, the tested group had a higher proportion of men, higher educational attainment, higher income, had insurance coverage, lived in urban areas, were in the middle age categories, and identified as not straight (**Table 2**).

Of the 635 respondents who had not received genetic test, 309 (48.7%) would be interested in learning whether they had a genetic risk factor for cancer. Among those interested in learning about their risk, a higher proportion were aware of genetic tests, had higher income, had a primary care doctor, had insurance coverage, were in older age categories, had higher educational attainment, and would be more likely to share information with family (**Table 3**).

Finally, of 309 respondents interested in learning whether they had a genetic risk factor for cancer, a substantial majority, 255 respondents (82.5%), would be likely or highly likely to get a PGS test (**Table 4**). Within this group, a higher proportion were male, in middle age categories, and were more likely to share information with family. Major themes emerged for being likely to get a PGS test and they included 1) believing the test could inform their health and/or plan for the future (n = 51 of 255), 2) wanting to know their risk of cancer (n = 46 of 255), 3) finding the test "important" (n = 45 of 255), 4) finding the test easy/available/free (n = 35 of 255), 5) having a family history of cancer (n = 21 of 255), and 6) having a personal history of cancer or other risk factors for cancer (n = 11 of 255). Only 14 respondents (4.5%) were unlikely to get a PGS test, and the top reasons were 1) not being interested or finding the test important (n = 5), 2) concerns about costs (n = 2), and 3) not wanting to or being scared to know (n = 2). The 40 respondents who were neutral (12.9%) were not sure if they wanted the test yet (n = 8), concerned about logistics (n = 4), felt the test was not interesting or important for them (n = 4), among other less common reasons (See **Supplementary Table S1**).

DISCUSSION

Despite increasing availability of direct-to-consumer (DTC) testing and PGS programs, we found that awareness of genetic testing for cancer predisposition in the general population remains at around 50%. This aligns with prior research from 2017 from the National Cancer Institute (NCI) Health Information National Trends Survey in which 57% of respondents reported being aware of genetic tests used for health reasons. (Roberts et al., 2019). This percentage is higher than a decade ago, at which time awareness about DTC genetic testing was 38.1% (Apathy et al., 2018). Our results were also consistent with prior reports of the association between awareness of genetic testing and education level, (Sanderson

TABLE 1 | Overall descriptive statistics and by awareness about genetic tests.

Characteristics	Survey item: *Genetic tests that analyze your DNA for potential cancer risks are currently available. Have you heard or read about these genetic tests?*						
	Total		No		Yes		*p*
	N	%	N	%	n	%	
Overall	745[a]	—	368	49.4	377	50.6	—
Gender[b]	—	—	—	—	—	—	0.43
Women	436	58.52	216	58.70	220	58.36	—
Men	287	38.52	139	37.77	148	39.26	—
Ethnicity	—	—	—	—	—	—	**0.01**
non-Hispanic	644	86.44	306	83.15	338	89.66	—
Hispanic	101	13.56	62	16.85	39	10.34	—
Race	—	—	—	—	—	—	0.11
White	569	76.38	269	73.10	300	79.58	—
Black	78	10.47	43	11.68	35	9.28	—
Other	98	13.15	56	15.22	42	11.14	—
Education	—	—	—	—	—	—	**<0.01**
Less than HS *or HS/GED*	187	25.10	114	30.98	73	19.36	—
Some college/technical school	153	20.54	79	21.47	74	19.63	—
AD	85	11.41	31	8.42	54	14.32	—
BS	175	23.49	84	22.83	91	24.14	—
Graduate/professional degree	145	19.46	60	16.30	85	22.55	—
Age	—	—	—	—	—	—	**0.001**
<25	126	17.10	76	20.94	50	13.37	—
25–49	333	45.18	166	45.73	167	44.65	—
50–74	247	33.51	100	27.55	147	39.30	—
≥75	31	4.21	21	5.79	10	2.67	—
Income	—	—	—	—	—	—	0.08
0–34,999	310	41.67	168	45.78	142	37.67	—
35,000–99,999	267	36.16	123	33.51	146	38.73	—
100,000+	165	22.18	76	20.71	89	23.61	—
Insurance	—	—	—	—	—	—	**<0.001**
Any Medicaid/Aid	253	34.10	124	33.97	129	34.22	—
Medicare	185	24.93	73	20.00	112	29.71	—
Employer-based	130	17.52	74	20.27	56	14.85	—
Other[c]	81	10.92	34	9.32	47	12.47	—
No Insurance	93	12.53	60	16.44	33	8.75	—
Rurality	—	—	—	—	—	—	0.14
Urban	251	33.74	135	36.78	116	30.77	—
Suburban	342	45.97	166	45.23	176	46.68	—
Rural	151	20.30	66	17.98	85	22.55	—
Have a primary doctor?	—	—	—	—	—	—	**<0.001**
Yes	416	55.84	174	47.28	242	64.19	—
No	329	44.16	194	52.72	135	35.81	—
Sexual Orientation[b]	—	—	—	—	—	—	0.88
Straight	650	87.37	322	87.50	328	87.23	—
Gay or lesbian	34	4.57	17	4.62	17	4.52	—
Bisexual	47	6.32	24	6.52	23	6.12	—
Comparative Cancer Risk[d]	—	—	—	—	—	—	**<0.01**
Very unlikely	80	12.64	51	15.94	29	9.27	—
Unlikely	118	18.64	63	19.69	55	17.57	—
Neither likely or unlikely	276	43.60	138	43.13	138	44.09	—
Likely	109	17.22	53	16.56	56	17.89	—
Very likely	50	7.90	15	4.69	35	11.18	—

[a]*One survey respondent did not answer this item (n = 745); Because of missing data, not all column numbers add to 745 (n = 14, 0.2% missing data fields).*
[b]*Other categories were censored due to small cell size; column percentages will not sum to 100%.*
[c]*Other insurance (Tricare, VA, HIS, self-pay, other).*
[d]*Those who reported a personal history of cancer did not receive this item (total responses = 633).*
Bold indicates a p*-value of < 0.05.*

TABLE 2 | Descriptive characteristics of those how have and have not received a genetic test for cancer risk.

Characteristics	Survey item: [a]*Have you ever had a genetic test to determine if you have an increased risk of developing cancer?*				
	No		Yes		*p*
	n	%	N	%	
Overall	267	70.82	110	29.18	—
Gender[b]	—	—	—	—	**<0.01**
Women	171	64.04	49	44.55	—
Men	92	34.46	56	50.91	—
Ethnicity	—	—	—	—	0.55
non-Hispanic	241	90.26	97	88.18	—
Hispanic	26	9.74	13	11.82	—
Race	—	—	—	—	0.19
White	219	82.02	81	73.64	—
Black	22	8.24	13	11.82	—
Other	26	9.74	16	14.55	—
Education	—	—	—	—	**<0.001**
Less than HS or HS/GED	53	19.85	20	18.18	—
Some college/technical school	65	24.34	—	—	—
AD	43	16.10	11	10.00	—
BS	60	22.47	31	28.18	—
Graduate/professional degree	46	17.23	39	35.45	—
Age	—	—	—	—	**<0.001**
<25	32	12.08	18	16.51	—
25–49	96	36.23	71	65.14	—
50–74	127	47.92	20	18.35	—
≥75	10	3.77	—	—	—
Income	—	—	—	—	**<0.001**
0–34,999	109	40.82	33	30.00	—
35,000–99,999	115	43.07	31	28.18	—
100,000+	43	16.10	46	41.82	—
Insurance	—	—	—	—	**<0.01**
Any Medicaid	75	28.09	54	49.09	—
Medicare	83	31.09	29	26.36	—
Employer-based	45	16.85	11	10.00	—
Other[c]	35	13.11	12	10.91	—
No Insurance	29	10.86	—	—	—
Rurality	—	—	—	—	**<0.001**
Urban	64	23.97	52	47.27	—
Suburban	134	50.19	42	38.18	—
Rural	69	25.84	16	14.55	—
Have a primary doctor?	—	—	—	—	0.13
Yes	165	61.80	77	70.00	—
No	102	38.20	33	30.00	—
Sexual Orientation[b]	—	—	—	—	**<0.01**
Straight	241	90.60	87	79.09	—
Gay or lesbian	—	—	10	9.09	—
Bisexual	11	4.14	12	10.91	—
Comparative Cancer Risk[d]	—	—	—	—	0.21
Very unlikely	23	9.62	--	--	
Unlikely	40	16.74	15	20.27	
Neither likely or unlikely	113	47.28	25	33.78	
Likely	40	16.74	16	21.62	
Very likely	23	9.62	12	16.22	

[a]*Among survey respondents who were aware of genetic tests (n = 377); Because of missing data, not all column numbers add to 377 (n = 8, 0.2% missing data fields).*
[b]*Other categories were censored due to small cell size; column percentages will not sum to 100%.*
[c]*Other insurance (Tricare, VA, HIS, self-pay, other).*
[d]*Those who reported a personal history of cancer did not receive this item (total responses = 313).*
Cell sizes less than 10 are not reported. Bold indicates a p*-value of < 0.05.*

TABLE 3 | Descriptive characteristics among those with different levels of interest in learning about genetic cancer risks.

Characteristics	Survey item: *How interested would you be in learning whether you have a genetic risk factor for cancer that can be prevented or treated? (n = 635)* [a]						
	[b]not interested		Neutral		Interested		*P*
	n	%	n	%	n	%	
Overall	183	28.82	143	22.52	309	48.66	—
Gender[c]	—	—	—	—	—	—	0.16
Women	103	56.28	94	65.73	190	61.49	—
Men	74	40.44	43	30.07	114	36.89	—
Ethnicity	—	—	—	—	—	—	0.13
non-Hispanic	152	83.06	120	83.92	275	89.00	—
Hispanic	31	16.94	23	16.08	34	11.00	—
Race	—	—	—	—	—	—	0.21
White	135	73.77	105	73.43	248	80.26	—
Black	18	9.84	16	11.19	31	10.03	—
Other	30	16.39	22	15.38	30	9.71	—
Education	—	—	—	—	—	—	**0.04**
Less than HS or HS/GED	51	27.87	49	34.27	67	21.68	—
Some college/technical school	42	22.95	36	25.17	66	21.36	—
AD	19	10.38	15	10.49	40	12.94	—
BS	38	20.77	31	21.68	75	24.27	—
Graduate/professional degree	33	18.03	12	8.39	61	19.74	—
Age	—	—	—	—	—	—	**0.04**
<25	35	19.44	32	22.70	41	13.36	—
25–49	61	33.89	55	39.01	146	47.56	—
50–74	73	40.56	49	34.75	105	34.20	—
≥75	11	6.11	—	—	15	4.89	—
Income	—	—	—	—	—	—	**<0.001**
0–34,999	90	49.18	79	55.63	108	34.95	—
35,000–99,999	70	38.25	47	33.10	121	39.16	—
100,000+	23	12.57	16	11.27	80	25.89	—
Insurance	—	—	—	—	—	—	**<0.001**
Any Medicaid	49	26.78	40	28.37	110	35.71	—
Medicare	54	29.51	26	18.44	76	24.68	—
Employer-based	24	13.11	25	17.73	70	22.73	—
Other[d]	24	13.11	15	10.64	30	9.74	—
No Insurance	32	17.49	35	24.82	22	7.14	—
Rurality	—	—	—	—	—	—	0.19
Urban	53	28.96	36	25.35	110	35.60	
Suburban	90	49.18	76	53.52	134	43.37	
Rural	40	21.86	30	21.13	65	21.04	
Have a primary doctor?							**<0.001**
Yes	81	44.26	60	41.96	198	64.08	
No	102	55.74	83	58.04	111	35.92	
How likely to share with family	—	—	—	—	—	—	**<0.001**
Not at all likely	56	30.60	—	—	11	3.56	—
Not likely	16	8.74	—	—	—	—	—
Somewhat not likely	24	13.11	16	11.19	—	—	—
Neither likely or unlikely	27	14.75	78	54.55	25	8.09	—
Somewhat likely	23	12.57	23	16.08	59	19.09	—
Likely	14	7.65	11	7.69	66	21.36	—
Very likely	23	12.57	10	6.99	134	43.37	—
Aware of genetic tests	70	38.25	51	35.7	146	47.2	**0.03**

[a]*Among those who reported not receiving a genetic test; Because of missing data, not all column numbers add to 635 (n = 12, 0.2% missing data fields).*

[b]*Not interested = not at all interested, not interested, somewhat not interested; Neutral = neither interested or uninterested; Interested = very interested, interested, somewhat interested.*

[c]*We did not report "prefer not to say" for gender given small cell size, nor do we present sexual orientation.*

[d]*Other insurance (Tricare, VA, HIS, self-pay other).*

Cell sizes less than 10 are not reported.

Bold indicates a p*-value of < 0.05.*

TABLE 4 | Descriptive characteristics among those with different likelihoods of getting a population genetic screening test for cancer risk.

Characteristics	Survey item: [a]*To learn whether you have a genetic risk factor for cancer, you would need to make an appointment at a local clinic, get your blood drawn, and set up an online account to access your test results. Assuming there is no cost to you, how likely would you be to get this test? (n = 309)*						
	[b]unlikely to get Test		Neutral		Likely to get Test		*p*
	N	%	n	%	n	%	
Overall	14	4.53	40	12.94	255	82.52	—
Gender[c]	—	—	—	—	—	—	**<0.001**
Women	—	—	28	70.00	157	61.57	—
Men	—	—	12	30.00	97	38.04	—
Ethnicity	—	—	—	—	—	—	0.86
non-Hispanic	12	85.71	35	87.50	228	89.41	—
Hispanic	—	—	—	—	27	10.59	—
Race	—	—	—	—	—	—	0.09
White	10	71.43	30	75.00	208	81.57	
Black	—	—	—	—	26	10.20	—
Other	—	—	—	—	21	8.24	—
Education	—	—	—	—	—	—	0.09
Less than HS or HS/GED	—	—	14	35.00	48	18.82	—
Some college/technical school	—	—	10	25.00	51	20.00	—
AD	—	—	—	—	34	13.33	—
BS	—	—	—	—	66	25.88	—
Graduate/professional degree	—	—	—	—	56	21.96	—
Age	—	—	—	—	—	—	**0.001**
<25	—	—	12	30.00	25	9.88	—
25–49	—	—	14	35.00	130	51.38	—
50–74	—	—	10	25.00	89	35.18	—
≥75	—	—	—	—	—	—	—
Income	—	—	—	—	—	—	0.10
0–34,999	—	—	21	52.50	81	31.76	—
35,000–99,999	—	—	10	25.00	105	41.18	—
100,000+	—	—	—	—	69	27.06	—
Insurance	—	—	—	—	—	—	0.07
Any Medicaid	—	—	14	35.00	90	35.43	—
Medicare	—	—	10	25.00	61	24.02	—
Employer-based	—	—	—	—	66	25.98	—
Other[d]	—	—	—	—	22	8.66	—
No Insurance	—	—	—	—	15	5.91	—
Rurality	—	—	—	—	—	—	0.14
Urban	—	—	13	32.50	93	36.47	—
Suburban	—	—	22	55.00	108	42.35	—
Rural	—	—	—	—	54	21.18	—
Have a primary doctor?	—	—	—	—	—	—	0.23
Yes	—	—	27	67.50	165	64.71	—
No	—	—	13	32.50	90	35.29	—
How likely to share with family	—	—	—	—	—	—	**<0.01**
Not at all likely	—	—	—	—	—	—	—
Not likely	—	—	—	—	—	—	—
Somewhat not likely	—	—	—	—	—	—	—
Neither likely or unlikely	—	—	—	—	18	7.06	—
Somewhat likely	—	—	12	30.00	46	18.04	—
Likely	—	—	—	—	62	24.31	—
Very likely	—	—	13	32.50	113	44.31	—
Aware of genetic tests	—	—	16	40.00	124	48.63	0.56

[a]*Marked somewhat-very interested in "learning whether you have a genetic risk factor for cancer that can be prevented or treated (n = 309 of 635 who have not yet received genetic testing); Because of missing data, not all column numbers add to 309 (n = 3, 0.1% missing data fields).*

[b]*Unlikely to get test = very unlikely, unlikely; Neutral = neither likely nor unlikely; Likely to get test = very likely, likely.*

[c]*Other categories were censored due to small cell size; column percentages will not sum to 100%.*

[d]*Other insurance (Tricare, VA, HIS, self-pay, other).*

Cell sizes less than 10 are not reported.

Bold indicates a p-value of < 0.05.

et al., 2004; Armstrong et al., 2005; Childers et al., 2018), demonstrating a persistent need to reach individuals with lower educational attainment to prevent widening disparities in access to precision health care.

Though racial disparities in genetic testing utilization are well established in the literature, (Salloum et al., 2018; Chapman-Davis et al., 2021), we did not find statistically significant disparities in our data, likely because only individuals who reported being aware of genetic tests were asked about their genetic testing history. This aligns with data from the NCI using a similar measure about awareness of DTC genetic testing in which differences by race were not observed. (Agurs -Collins et al., 2015). We did find that people of Hispanic ethnicity were significantly less likely to be aware of testing, indicating that efforts to increase accessibility to precision health care should also include native Spanish speakers.

Among those aware of genetic testing who have not already had genetic testing, almost half would be interested in learning whether they had a genetic risk factor for cancer that can be prevented or treated, which is lower than what has been reported elsewhere in public samples. (Donovan and Tucker, 2000; Alvord et al., 2020). For example, in a 2020 study of public perception of predictive cancer genetic testing in Oregon, 87% of participants reported an interest in cancer genetic testing and receiving genetic information about themselves; however, it is important to note that 85% of individuals in this study had a personal or family diagnosis of cancer. As better understanding of family cancer risks is a known motivator for testing reported by participants in that study, this study also highlights an urgent need for more data from participants with no prior personal or family history of cancer. (HINTS, 2019). In our data we found that respondents who were likely to share their results with family were also more likely to be interested in learning whether they had a genetic risk factor for cancer. Deeper understanding about the reasons for overall disinterest in testing (e.g. uninformed about benefits vs mistrust of health system) will be important for developing strategies to engage the broader population in genetic screening. We also found socioeconomic factors (educational attainment, insurance, income), age, and having a primary care provider differed, such that larger proportions of those who are traditionally underserved and those without a primary care provider reported being uninterested in learning about their genetic risk for cancer. This aligns with prior work that has demonstrated potential disparities in genetic services use among these populations. (Shen et al., 2022; Sanderson et al., 2004; Childers et al., 2018; Armstrong et al., 2005; Orlando et al., 2019; The National Academies Collection: Reports funded by National Institutes of Health, 2018).

Among respondents who had not had any previous genetic testing, about half were interested in learning about a genetic risk for cancer predisposition. Furthermore, a large majority said they would be likely to participate in a PGS test in a clinical setting that required making an appointment, getting a blood draw, and creating an online account for a patient portal. All respondents provided contextual information about how and why they responded to this question and, interestingly, only one respondent mentioned mistrust or concerns about genetic discrimination, data privacy or security, which have been commonly reported in the literature. (Hann et al., 2017). This may be due to our small sample size of individuals who reported being very unlikely or unlikely to participate in the PGS (n = 14) and also that these concerns are reflected in the high proportion of respondents who were not interested in learning about a genetic risk for cancer predisposition. Overall, we found it telling that most survey respondents who were interested in learning their risk for developing an inherited cancer syndrome would also hypothetically be willing to commit the time and effort participate in a clinical offering that included a blood draw and a patient portal. Of note, cost was still a concern of respondents despite explicitly noting that the hypothetical clinical screening test would be at no-cost to patients. A deeper awareness about participants' downstream financial concerns is warranted and may help us better understand barriers related to follow-up medical costs or costs associated with taking time off to get a blood draw.

While these descriptive findings provide foundational data on public awareness, use and interest in genetic testing and screening, they should be interpreted within the context of several limitations. First, because of small sample size, we are unable to examine multivariable associations between key variables and certain outcomes (receipt of a genetic test, interest in learning genetic risk and likelihood of getting a PGS test). Further, while Qualtrics survey samples can provide a diverse sample, (Miller et al., 2020), respondents may not be representative of the general population. We used convenience sampling from a geographically diverse area in the US to rapidly gather data about the public's opinions and to generate hypotheses about potentially important factors related to stakeholder engagement around PGS. However, this sampling approach has several drawbacks including lack of generalizability, as well as selection, sampling, and positivity biases. Further, we are unable to determine the denominator required to calculate a response rate given the ways in which participants were invited to take the survey. Future work should include larger nationally representative samples to better understand the association between key sociodemographic variables and key outcomes which will be essential for ensuring equity in the implementation of population genetic screening program. In addition, we asked about individuals' *intentions* to learn about genetic risk and *likelihood of participating* in a PGS test. Intentions are associated with health behaviors, as are other factors, some of which are known, such as perceived control (data not collected) and others which are less certain. (Ajzen, 1991). Thus, it will be important for clinical PGS programs to collect data on actual uptake of PGS to understand how the public engages with PGS in real world settings. This work should be expanded to include other clinical contexts, such as familial hypercholesterolemia, which is also a CDC Tier One condition for which population genetic screening has the potential to improve precision public health. (CDC, 2021). Because we test multiple comparisons, our chances of having a type I error are higher; results should be interpreted in this light. Finally, the population genetic screening program described in the survey item mentioned that the test would be free, clinic-based, and require a blood draw, limiting the generalizability of our findings to PGS programs with different characteristics. Future studies to compare different PGS models will further inform the implementation of PGS models moving forward.

Our findings identified two key challenges for the implementation of population genetic screening: increasing awareness of the potential benefits of genetic testing and interest in learning one's genetic risk for cancer. This may be especially important for subpopulations with lower socioeconomic status and those without a primary source of care. Future work to better understand and develop strategies to overcome these challenges will be essential as PGS programs are increasingly implemented into clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This human subjects research study was reviewed and determined to be exempt by The University of North Carolina Institutional Review Board.

AUTHOR CONTRIBUTIONS

MR, KF, GH, SP, KS, KW, and LM contributed to the design of the study. MR conducted the data analysis and MR, KF, GH, SP, KS, KW, and LM all contributed to the interpretation of the study results. MR and LM wrote the manuscript and all authors MR, KF, GH, SP, KS, KW, and LM contributed revisions and approved this manuscript for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.886640/full#supplementary-material

Supplementary Figure S1 | Survey flow and primary measures of interest.

Supplementary Table S1 | Open-ended responses about reasons for respondents' perceived likelihood of getting a population genetic screening test.

REFERENCES

Adams, M. C., Evans, J. P., Henderson, G. E., and Berg, J. S. (2016). The Promise and Peril of Genomic Screening in the General Population. *Genet. Med.* 18 (6), 593–599. doi:10.1038/gim.2015.136

Agurs-Collins, T., Ferrer, R., Ottenbacher, A., Waters, E. A., O'Connell, M. E., and Hamilton, J. G. (2015). Public Awareness of Direct-To-Consumer Genetic Tests: Findings from the 2013 U.S. Health Information National Trends Survey. *J. Canc Educ.* 30 (4), 799–807. doi:10.1007/s13187-014-0784-x

Ajzen, I. (1991). The Theory of Planned Behavior. *Organ. Behav. Hum. Decis. Process.* 50 (2), 179–211. doi:10.1016/0749-5978(91)90020-T

Alvord, T. W., Marriott, L. K., Nguyen, P. T., Shafer, A., Brown, K., Stoller, W., et al. (2020). Public Perception of Predictive Cancer Genetic Testing and Research in Oregon. *Jrnl Gene Coun* 29 (2), 259–281. doi:10.1002/jgc4.1262

Apathy, N. C., Menser, T., Keeran, L. M., Ford, E. W., Harle, C. A., and Huerta, T. R. (2018). Trends and Gaps in Awareness of Direct-To-Consumer Genetic Tests from 2007 to 2014. *Am. J. Prev. Med.* 54 (6), 806–813. doi:10.1016/j.amepre.2018.02.013

Armstrong, K., Micco, E., Carney, A., Stopfer, J., and Putt, M. (2005). Racial Differences in the Use of BRCA1/2 Testing Among Women with a Family History of Breast or Ovarian Cancer. *JAMA* 293 (14), 1729–1736. doi:10.1001/jama.293.14.1729

Bean, L. J. H., Scheuner, M. T., Murray, M. F., Biesecker, L. G., Green, R. C., Monaghan, K. G., et al. (2021). DNA-based Screening and Personal Health: a Points to Consider Statement for Individuals and Health-Care Providers from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (6), 979–988. doi:10.1038/s41436-020-01083-9

Berg, J. S., Foreman, A. K. M., O'Daniel, J. M., Booker, J. K., Boshe, L., Carey, T., et al. (2016). A Semiquantitative Metric for Evaluating Clinical Actionability of Incidental or Secondary Findings from Genome-Scale Sequencing. *Genet. Med.* 18 (5), 467–475. doi:10.1038/gim.2015.104

Brown-Johnson, C. G., Safaeinili, N., Baratta, J., Palaniappan, L., Mahoney, M., Rosas, L. G., et al. (2021). Implementation Outcomes of Humanwide: Integrated Precision Health in Team-Based Family Practice Primary Care. *BMC Fam. Pract.* 22 (1), 28. doi:10.1186/s12875-021-01373-4

CDC (2021). Tier 1 Genomics Applications and Their Importance to Public Health | CDC. Published March 16. 2021Available at: https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm (Accessed February 14, 2022).

Chapman-Davis, E., Zhou, Z. N., Fields, J. C., Frey, M. K., Jordan, B., Sapra, K. J., et al. (2021). Racial and Ethnic Disparities in Genetic Testing at a Hereditary Breast and Ovarian Cancer Center. *J. Gen. Intern Med.* 36 (1), 35–42. doi:10.1007/s11606-020-06064-x

Childers, K. K., Maggard-Gibbons, M., Macinko, J., and Childers, C. P. (2018). National Distribution of Cancer Genetic Testing in the United States. *JAMA Oncol.* 4 (6), 876–879. doi:10.1001/jamaoncol.2018.0340

Chopra, I., and Kelly, K. M. (2017). Cancer Risk Information Sharing: The Experience of Individuals Receiving Genetic Counseling forBRCA1/2Mutations. *J. Health Commun.* 22 (2), 143–152. doi:10.1080/10810730.2016.1258743

Christensen, K. D., Bell, M., Zawatsky, C. L. B., Galbraith, L. N., Green, R. C., Hutchinson, A. M., et al. (2021). Precision Population Medicine in Primary Care: The Sanford Chip Experience. *Front. Genet.* 12, 626845. doi:10.3389/fgene.2021.626845

Donovan, K. A., and Tucker, D. C. (2000). Knowledge about Genetic Risk for Breast Cancer and Perceptions of Genetic Testing in a Sociodemographically Diverse Sample. *J. Behav. Med.* 23 (1), 15–36. doi:10.1023/a:1005416203239

East, K. M., Kelley, W. V., Cannon, A., Cochran, M. E., Moss, I. P., May, T., et al. (2021). A State-Based Approach to Genomics for Rare Disease and Population Screening. *Genet. Med.* 23 (4), 777–781. doi:10.1038/s41436-020-01034-4

Evans, J. P., Berg, J. S., Olshan, A. F., Magnuson, T., and Rimer, B. K. (2013). We Screen Newborns, Don't We?: Realizing the Promise of Public Health Genomics. *Genet. Med.* 15 (5), 332–334. doi:10.1038/gim.2013.11

Green, E. D., Gunter, C., Biesecker, L. G., Di Francesco, V., Easter, C. L., Feingold, E. A., et al. (2020). Strategic Vision for Improving Human Health at the

Forefront of Genomics. *Nature* 586 (7831), 683–692. doi:10.1038/s41586-020-2817-4

Green, R. F., Ari, M., Kolor, K., Dotson, W. D., Bowen, S., Habarta, N., et al. (2019). Evaluating the Role of Public Health in Implementation of Genomics-Related Recommendations: a Case Study of Hereditary Cancers Using the CDC Science Impact Framework. *Genet. Med.* 21 (1), 28–37. doi:10.1038/s41436-018-0028-2

Hann, K. E. J., Freeman, M., Freeman, M., Fraser, L., Waller, J., Sanderson, S. C., et al. (2017). Awareness, Knowledge, Perceptions, and Attitudes towards Genetic Testing for Cancer Risk Among Ethnic Minority Groups: a Systematic Review. *BMC Public Health* 17 (1), 503. doi:10.1186/s12889-017-4375-8

Hay, J. L., Zielaskowski, K., Meyer White, K., Kaphingst, K., Robers, E., Guest, D., et al. (2018). Interest and Uptake ofMC1RTesting for Melanoma Risk in a Diverse Primary Care Population. *JAMA Dermatol* 154 (6), 684–693. doi:10.1001/jamadermatol.2018.0592

Hendricks-Sturrup, R. M., Linsky, A., Lu, C. Y., and Vassy, J. L. (2020). Genomic Testing Is Best Integrated into Clinical Practice when it Is Actionable. *Pers. Med.* 17 (1), 5–8. doi:10.2217/pme-2019-0106

HINTS (2022). Survey Instruments | HINTS. Available at: https://hints.cancer.gov/data/survey-instruments.aspx (Accessed January 24, 2022).

HINTS (2019). View HINTS Questions | HINTS. Available at: https://hints.cancer.gov/view-questions-topics/all-hints-questions.aspx (Accessed February 14, 2022).

Hunter, J. E., Irving, S. A., Biesecker, L. G., Buchanan, A., Jensen, B., Lee, K., et al. (2016). A Standardized, Evidence-Based Protocol to Assess Clinical Actionability of Genetic Disorders Associated with Genomic Variation. *Genet. Med.* 18 (12), 1258–1268. doi:10.1038/gim.2016.40

Jarvik, G. P., Amendola, L. M., Berg, J. S., Brothers, K., Clayton, E. W., Chung, W., et al. (2014). Return of Genomic Results to Research Participants: the Floor, the Ceiling, and the Choices in between. *Am. J. Hum. Genet.* 94 (6), 818–826. doi:10.1016/j.ajhg.2014.04.009

Khoury, M. J., Feero, W. G., Chambers, D. A., Brody, L. C., Aziz, N., Green, R. C., et al. (2018). Correction: A Collaborative Translational Research Framework for Evaluating and Implementing the Appropriate Use of Human Genome Sequencing to Improve Health. *PLoS Med.* 15 (8), e1002650. doi:10.1371/journal.pmed.1002650

Manchanda, R., Patel, S., Gordeev, V. S., Antoniou, A. C., Smith, S., Lee, A., et al. (2018). Cost-effectiveness of Population-Based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 Mutation Testing in Unselected General Population Women. *J. Natl. Cancer Inst.* 110 (7), 714–725. doi:10.1093/jnci/djx265

Milko, L. V., O'Daniel, J. M., DeCristo, D. M., Crowley, S. B., Foreman, A. K. M., Wallace, K. E., et al. (2019). An Age-Based Framework for Evaluating Genome-Scale Sequencing Results in Newborn Screening. *J. Pediatr.* 209, 68–76. doi:10.1016/j.jpeds.2018.12.027

Miller, C. A., Guidry, J. P. D., Dahman, B., and Thomson, M. D. (2020). A Tale of Two Diverse Qualtrics Samples: Information for Online Survey Researchers. *Cancer Epidemiol. Biomarkers Prev.* 29 (4), 731–735. doi:10.1158/1055-9965.EPI-19-0846

Murray, M. F., Evans, J. P., and Khoury, M. J. (2020). DNA-based Population Screening. *JAMA* 323 (4), 307–308. doi:10.1001/jama.2019.18640

Murray, M. F., Giovanni, M. A., Doyle, D. L., Harrison, S. M., Lyon, E., Manickam, K., et al. (2021). DNA-based Screening and Population Health: a Points to Consider Statement for Programs and Sponsoring Organizations from the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* 23 (6), 989–995. doi:10.1038/s41436-020-01082-w

Nathan, M. L., Ormond, K. E., Dial, C. M., Gamma, A., and Lunn, M. R. (2019). Genetic Counselors' and Genetic Counseling Students' Implicit and Explicit Attitudes toward Homosexuality. *J. Genet. Couns.* 28 (1), 91–101. doi:10.1007/s10897-018-0295-8

Orlando, L. A., Voils, C., Horowitz, C. R., Myers, R. A., Arwood, M. J., Cicali, E. J., et al. (2019). IGNITE Network: Response of Patients to Genomic Medicine Interventions. *Mol. Genet. Genomic Med.* 7 (5), e636. doi:10.1002/mgg3.636

Peterson, E. B., Taber, J. M., and Klein, W. M. P. (2022). Information Avoidance, Self-Affirmation, and Intentions to Receive Genomic Sequencing Results Among Members of an African Descent Cohort. *Ann. Behav. Med.* 56 (2), 205–211. doi:10.1093/abm/kaab042

Roberts, M. C., Turbitt, E., and Klein, W. M. P. (2019). Psychosocial, Attitudinal, and Demographic Correlates of Cancer-Related Germline Genetic Testing in the 2017 Health Information National Trends Survey. *J. Community Genet.* 10 (4), 453–459. doi:10.1007/s12687-018-00405-4

Roman, T. S., Crowley, S. B., Roche, M. I., Foreman, A. K. M., O'Daniel, J. M., Seifert, B. A., et al. (2020). Genomic Sequencing for Newborn Screening: Results of the NC NEXUS Project. *Am. J. Hum. Genet.* 107 (4), 596–611. doi:10.1016/j.ajhg.2020.08.001

Rubinsak, L. A., Kleinman, A., Quillin, J., Gordon, S. W., Sullivan, S. A., Sutton, A. L., et al. (2019). Awareness and Acceptability of Population-Based Screening for Pathogenic BRCA Variants: Do Race and Ethnicity Matter? *Gynecol. Oncol.* 154 (2), 383–387. doi:10.1016/j.ygyno.2019.06.009

Salloum, R. G., George, T. J., Silver, N., Markham, M.-J., Hall, J. M., Guo, Y., et al. (2018). Rural-urban and Racial-Ethnic Differences in Awareness of Direct-To-Consumer Genetic Testing. *BMC Public Health* 18 (1), 277. doi:10.1186/s12889-018-5190-6

Sanderson, S. C., Wardle, J., Jarvis, M. J., and Humphries, S. E. (2004). Public Interest in Genetic Testing for Susceptibility to Heart Disease and Cancer: a Population-Based Survey in the UK. *Prev. Med.* 39 (3), 458–464. doi:10.1016/j.ypmed.2004.04.051

Shen, E. C., Sriniva, S., Passero, L. E., Allen, C. G., Dixon, M., Foss, K., et al. (2022). Barriers and Facilitators for Population Genetic Screening in Healthy Populations: A Systematic Review. Published online. doi:10.21203/rs.3.rs-1315303/v1

Steffen, L. E., Du, R., Gammon, A., Mandelblatt, J. S., Kohlmann, W. K., Lee, J.-H., et al. (2017). Genetic Testing in a Population-Based Sample of Breast and Ovarian Cancer Survivors from the REACH Randomized Trial: Cost Barriers and Moderators of Counseling Mode. *Cancer Epidemiol. Biomarkers Prev.* 26 (12), 1772–1780. doi:10.1158/1055-9965.EPI-17-0389

The National Academies Collection: Reports funded by National Institutes of Health(2018). *Exploring the Barriers to Accessing Genomic and Genetic Services*. (US): National Academies Press. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538442/(Accessed April 25, 2022).

Zhang, L., Bao, Y., Riaz, M., Tiller, J., Liew, D., Zhuang, X., et al. (2019). Correction: Population Genomic Screening of All Young Adults in a Health-Care System: a Cost-Effectiveness Analysis. *Genet. Med.* 21 (9), 2162–2163. doi:10.1038/s41436-019-0515-0

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REVIEW
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Incomplete Penetrance and Variable Expressivity: From Clinical Studies to Population Cohorts

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The same genetic variant found in different individuals can cause a range of diverse phenotypes, from no discernible clinical phenotype to severe disease, even among related individuals. Such variants can be said to display incomplete penetrance, a binary phenomenon where the genotype either causes the expected clinical phenotype or it does not, or they can be said to display variable expressivity, in which the same genotype can cause a wide range of clinical symptoms across a spectrum. Both incomplete penetrance and variable expressivity are thought to be caused by a range of factors, including common variants, variants in regulatory regions, epigenetics, environmental factors, and lifestyle. Many thousands of genetic variants have been identified as the cause of monogenic disorders, mostly determined through small clinical studies, and thus, the penetrance and expressivity of these variants may be overestimated when compared to their effect on the general population. With the wealth of population cohort data currently available, the penetrance and expressivity of such genetic variants can be investigated across a much wider contingent, potentially helping to reclassify variants that were previously thought to be completely penetrant. Research into the penetrance and expressivity of such genetic variants is important for clinical classification, both for determining causative mechanisms of disease in the affected population and for providing accurate risk information through genetic counseling. A genotype-based definition of the causes of rare diseases incorporating information from population cohorts and clinical studies is critical for our understanding of incomplete penetrance and variable expressivity. This review examines our current knowledge of the penetrance and expressivity of genetic variants in rare disease and across populations, as well as looking into the potential causes of the variation seen, including genetic modifiers, mosaicism, and polygenic factors, among others. We also considered the challenges that come with investigating penetrance and expressivity.

Keywords: penetrance, expressivity, variant intepretation, genomic sequencing, rare disease

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INTRODUCTION

Approximately 72% (Nguengang Wakap et al., 2020) of all rare diseases are genetic in origin, and most of these are thought to be monogenic in nature (Haendel et al., 2020). Rare, deleterious variants are known to cause thousands of different genetic disorders in humans (Boycott et al., 2017; Rahit and Tarailo-Graovac, 2020), and while the molecular basis of over 6,000 monogenic diseases has been uncovered (OMIM,

2022), with more than 200,000 pathogenic variants described (QIAGEN, 2022; Stenson et al., 2017), the genetic basis of most rare disorders remains to be determined. With advances in next-generation sequencing (NGS) and the increasing availability of whole exome/genome sequencing (WES/WGS), the study of genotype–phenotype relationships has become more widespread as determining how the genotype causes a phenotype is a fundamental step toward understanding disease pathology (Stephanou et al., 2019). Protein-coding variants that are associated with disease phenotypes directly link DNA variation to altered protein function or dosage and to the phenotypic outcome, and so much of what we know about the genotype–phenotype relationship is based on the study of rare variants that cause monogenic disease (Chong et al., 2015). Monogenic genotypes can be highly predictive for specific individual disorders, but sometimes this relationship can be complicated, with some damaging dominant monogenic variants not following the expected Mendelian inheritance patterns (Schacherer, 2016). Individuals with the same genotype can display distinctly different clinical phenotypes (McDermott et al., 2017; Kumar et al., 2019; Crawford et al., 2021), including being clinically asymptomatic. Currently, there are gaps in translating how the individual genomic variation affects phenotypic presentation and how genetic variants exert their functional impact to cause disease.

The study of genetic disease has often been divided into rare monogenic forms of disease and more common polygenic complex disorders (Claussnitzer et al., 2020). Current evidence suggests that these groups may be more overlapping than previously thought as the genetic variation present across the genome highlights the complexity underlying the phenotypic presentation. There are both rare variants in individual genes that cause monogenic forms of complex disease (Vuckovic et al., 2020; Muse et al., 2021) and common variants that affect the severity of monogenic disease (Niemi et al., 2018; Goodrich et al., 2021). Such complexity makes investigating the genotype–phenotype relationships more complicated, which is only exacerbated by erroneous variant associations due to study design problems (Wright et al., 2019a). Human genetic diversity displays considerable variability, with individual genomes differing from the reference at 4.1–5 million sites (Auton et al., 2015). Although most variation is common and predicted to be functionally neutral (Ng et al., 2008), each individual has on average 85 heterozygous and 35 homozygous protein-truncating variants (PTVs) (Lek et al., 2016). Population cohort studies have shown that the average genome contains around 200 very rare variants per person (Gudmundsson et al., 2021) and 54 variants previously reported as disease-causing, including 7.6 rare non-synonymous coding variants in monogenic disease genes (Lek et al., 2016; Walsh et al., 2017). Variant interpretation is an ongoing challenge within diagnostic medicine, making understanding the phenotypic consequences of underlying genetic variation a key aim of genomics research.

Incomplete Penetrance and Variable Expressivity

A deleterious genotype should be no more prevalent in the population than the disease that it causes (Minikel et al., 2016). However, the same genetic variant can result in different disease presentations in different people, from clinically asymptomatic to severely affected, even among members of the same family (Mahat et al., 2021). The proportion of individuals who possess a particular genotype and exhibit the expected clinical symptoms is defined as the penetrance of that genotype (Cooper et al., 2013; Shawky, 2014). If everyone with the genotype presents with clinical symptoms by a particular age, then it is said to be fully penetrant, whereas if it falls below this, it is said to exhibit reduced or incomplete penetrance. Genotypes can also display variable expressivity, where the severity of the phenotype caused by the genotype can vary among affected individuals (Shawky, 2014) (**Table 1**); this differs from pleiotropy, where different variants in the same gene can cause different, potentially unrelated phenotypes that may even be categorized as different diseases (Ittisoponpisan et al., 2017) (**Figure 1**). Although penetrance, expressivity, and pleiotropy are three distinct concepts, biological reality means that their overall effects often overlap, especially in population cohorts where it is difficult to identify the cause of the phenotypic diversity. Multiple distinct phenotypes, in aggregate, could either be classified as a single more severe phenotype or different disease subtypes. As these three are likely to be caused by overlapping or similar mechanisms (Gruber and Bogunovic, 2020), especially in genetically heterogenous conditions, we will discuss them together in this review.

Incomplete penetrance can be observed in both dominant and recessive conditions. However, the cause of variability in genotype–phenotype correlations can be difficult to elucidate; phenotypic variation has been observed in mice with identical environmental and genetic backgrounds, including variability in lethality for gene knockouts despite the introduction of identical variants (Dickinson et al., 2016). Establishing that a identified variant is the sole (or primary) cause of an individual's clinical phenotype can be difficult (Shieh, 2019), which is an important concern when it comes to diagnosis and providing accurate genetic counseling, and such difficulties can lead to incorrect or delayed diagnosis (Maroilley and Tarailo-Graovac, 2019). The widespread presence of incomplete penetrance and variable expressivity through many overlapping mechanisms (**Figure 2**) can explain why apparently unaffected parents can pass on pathogenic variants to affected offspring (McDermott et al., 2017) and why seemingly healthy individuals' genomes can contain a large number of putatively damaging variants and yet not suffer any obvious adverse effects (Xue et al., 2012).

Although databases of clinically identified variants in affected individuals are useful for assessing pathogenicity (van Rooij et al., 2020), population-based datasets that include WES/WGS alongside phenotypic and medical information are increasingly important for investigating the penetrance and expressivity of these variants. Large population cohort studies have shown the occurrence of apparently pathogenic variants is much higher than previously estimated through small clinical or familial cohort studies (Wright et al., 2019a; Lacaze et al., 2020;

TABLE 1 | Examples of variable expressivity in monogenic diseases. Deleterious variants in these genes are known to cause a spectrum of phenotypes, from severe disease to mild subclinical effects.

Causal gene	Severe phenotype	Milder phenotype
HOXD13	Synpolydactyly (extra fused digits) (Ibrahim et al., 2016)	Short digits (Johnston et al., 2015; Zhang et al., 2020b)
KCNQ4	Deafness (Li et al., 2021a)	Mild hearing loss (Johnston et al., 2015)
SGCE	Myoclonus dystonia (Raymond et al., 1993)	Dystonia/Writer's cramp (Gerrits et al., 2009; Johnston et al., 2015)
KRT16	Pachyonychia congenita (Smith et al., 1993)	Blistered feet (Johnston et al., 2015; Li et al., 2021b)
FLCN	Birt-Hogg-Dube syndrome (Schmidt and Linehan, 2018)	Mild fibrofolliculomas (Johnston et al., 2015)
SFTPC	Lung disease (Nathan et al., 20201983)	Abnormal lung diffusion capacity (Somaschini et al., 2005; Johnston et al., 2015)
FBN1	Severe Marfan syndrome (Díaz de Bustamante et al., 2012; Aubart et al., 2018)	Mild Marfan phenotypes (tall, thin, slender fingers) (Dietz et al., 1993)
ERCC4	Xeroderma pigmentosum (Kraemer et al., 1993)	Higher likelihood of sunburn (Wright et al., 2019a)
FLG	Ichthyosis vulgaris (Akiyama, 2010)	Eczema (Wright et al., 2019a)
POLG	Childhood onset Alpers-Huttenlocher syndrome (Kammenga, 2017)	Deterioration of eye muscles (Neeve et al., 2012)

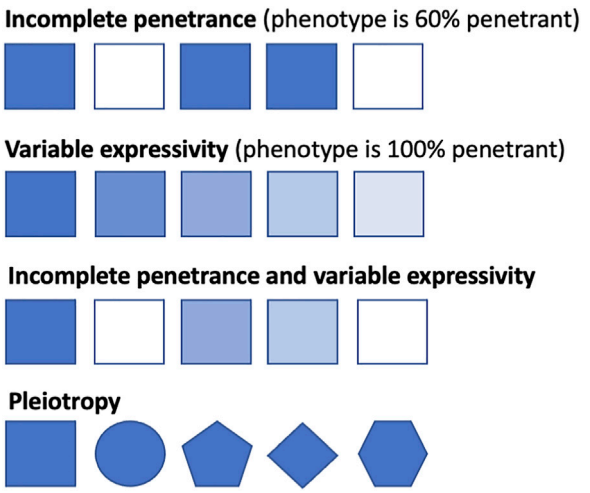

FIGURE 1 | Conceptual representation of penetrance, expressivity, and pleiotropy. Squares represent individuals with the same genotype, with shaded squares indicating the individual displays the related phenotype and non-shaded squares indicating the individual does not display the related disease phenotype. Line one shows incomplete penetrance, where 60% of the individuals display the related phenotype. Line two shows that all individuals display the related phenotype, from severe manifestations to milder presentations. Line three shows incomplete penetrance and variable expressivity, where the genotype varies both in the severity of presentation and in penetrance across the population. Line four shows pleiotropy, whereby different phenotypes are caused by variants (represented by different shapes) in one gene.

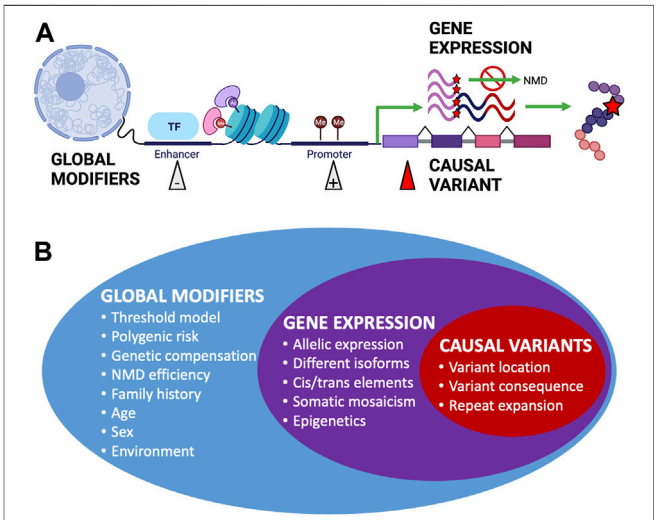

FIGURE 2 | Factors affecting penetrance and expressivity. **(A)** Examples of different biological mechanisms that can affect the overall penetrance and expressivity of monogenic disease-causing genetic variants. Figure created using BioRender.com. **(B)** Summary of factors affecting penetrance and expressivity across the genome, from global modifiers that can have wide-ranging overall effects to expression of the gene containing causal variants and to specific causal variants that have more distinctive effects.

van Rooij et al., 2020), and their frequency highlights either the incomplete penetrance, variable expressivity, or misclassification of such variants. The existence of PTVs in dosage-sensitive genes in healthy individuals also remains problematic when it comes to determining pathogenicity (Cummings et al., 2020). The potential for genomic technologies and WGS to detect individuals at risk of genetic disease is enormous, but incomplete penetrance and variable expressivity present a challenge for clinicians, especially when an incidental finding occurs without any prior clinical indication, leading to uncertainty over whether a clinical phenotype will develop, and if so, when. This problem is highlighted when testing unselected population cohorts, who may or may not have phenotypes of relevance to genomic findings at the point of testing. To understand how genetic disorders develop, we need to consider how deleterious variants interact with the rest of the variation in the genome and how variation can affect phenotypic presentation. This may also identify targets that help prevent disease progression (Downs et al., 2019). The presence of putatively pathogenic variants in asymptomatic adults also highlights the possibility that there are disease resistance mechanisms we can identify through the sequencing of general population cohorts.

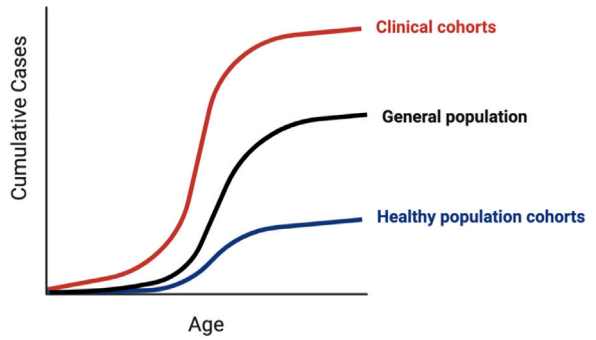

FIGURE 3 | Penetrance in clinical versus population cohorts.
Penetrance of genetic variants identified in clinical cohorts tends to be higher than the same variants identified in population cohorts, which can manifest as earlier disease onset, less severe disease, or a larger proportion of affected individuals. Due to inherent ascertainment biases in both types of cohorts, the penetrance of variants in the general unselected population is likely to lie somewhere in-between.

Clinical Versus Population Cohorts

Traditionally, rare pathogenic variants were identified in small phenotypically enriched clinical cohorts of individuals and families with similar monogenic disease. Population cohorts allow us to utilize the information from small clinical studies to investigate the penetrance of variants in the general "healthy" population, where such severe monogenic phenotypes are likely to be depleted, and the potential to identify the causes of clinical heterogeneity. Ascertainment bias can occur with any study design, with volunteer population cohorts tending to be healthier than the average individual (Fry et al., 2017) and clinical cohorts tending to have more severe phenotypes. Estimates of the maximum and minimum variant effect sizes across different ascertainment contexts are needed to avoid falsely predicting that a significant proportion of the healthy population is at risk for a monogenic condition (Flannick et al., 2013). The proportion of individuals affected and the average age of onset (i.e., age-dependent penetrance) can vary depending on the ascertainment context (**Figure 3**). For example, individuals with putatively pathogenic variants in *HNF1A* and *HNF4A*, known for causing maturity-onset diabetes of the young (MODY), develop diabetes significantly later or not at all when tested outside of the context of clinical referrals for the suspected MODY (Mirshahi et al., 2021).

For almost all human genetic diseases, individual variability in the phenotype is influenced by background variation in the genome. As genetic testing has become more widely available, both through healthcare systems, direct-to-consumer testing (Stoeklé et al., 2016), our understanding of how genomic variation affects disease progression and prevalence has become significantly more important, both for clinical utility (Shieh, 2019) and for our functional understanding of the disease (Tarailo-Graovac et al., 2017). Variation in the genome can predispose individuals to disease through traditional monogenic variants that disrupt physiological pathways and exert a large effect on the phenotype, or through the accumulation of polygenic effects that involve many variants of small effect sizes in different pathways (Fahed et al., 2020), or as is increasingly becoming clear, through their combined effect.

Within population cohorts, penetrance estimates for monogenic variant carriers average 60% or lower for most conditions (Goodrich et al., 2021), illustrating that many individuals have highly penetrant, pathogenic variants in known monogenic disease-causing genes who never develop the corresponding phenotype (Chen et al., 2016). Generally, 70% of the "Wellderly" healthy aging cohort, all of whom reached 80 without any chronic diseases, had one heterozygous deleterious variant in genes listed in the American College of Medical Genetics and Genomics (ACMG) secondary findings (Erikson et al., 2016). Similarly, one in 75 (1.3%) of healthy elderly individuals in the APSREE trial carried a previously identified pathogenic variant, including in Lynch syndrome and familial hypercholesterolemia genes, without having the associated phenotype (Lacaze et al., 2020). These cases demonstrate that carrying such pathogenic variants does not always cause the associated disease and that other mechanisms may contribute to the protection of human health, including genetic modifiers that 'rescue' individuals from a disease phenotype.

CAUSAL VARIANTS

Variant Location and Consequence

For genetically heterogenous monogenic diseases, the penetrance and expressivity can vary between different genes or variants, with the same phenotype potentially caused by numerous different variants across multiple genes (Wright et al., 2018). Even within the same gene, some deleterious variants in known monogenic disease genes may exhibit complete penetrance, while others show incomplete or low penetrance. Variation can be due to functional redundancy of genes, or the location and type of variant, with missense and PTVs in the same gene often causing different phenotypes. For example, hereditary angioedema can show great phenotypic diversity, even among members of the same family, and individuals with missense variants in *SERPING1* typically display a milder and later onset of disease than patients with PTVs (Speletas et al., 2015). In contrast, missense variants in *BMPR2* cause earlier and more severe pulmonary hypertension than PTVs in the same gene (Austin et al., 2009).

Pathogenic PTVs typically cause disease through loss of function (LoF) due to degradation of the RNA by nonsense-mediated decay (NMD) (Lu and Krebber, 2021). NMD is an mRNA surveillance pathway that recognizes and degrades damaged mRNA transcripts that would produce misfolded or shortened proteins that can accumulate in the cell and initiate the endoplasmic reticulum (ER) stress response (Haeri and Knox, 2012). However, the production of a variant protein can either exacerbate disease severity through the accumulation of toxic proteins in the cell (Nguyen et al., 2014) or alleviate it through providing a residual function that protects against haploinsufficiency-mediated disease in the heterozygous state (van Leeuwen et al., 2017; Coban-Akdemir et al., 2018;

Kennedy et al., 2019), meaning the occurrence of NMD can affect phenotypic severity depending on the mechanism of disease. PTVs may also cause LoF through aberrant splicing (Cummings et al., 2020), which is also regulated by NMD (Lareau and Brenner, 2015). In some cases, the location of NMD boundaries at the 5′ and 3′ ends of genes containing causal variants can explain phenotypic variation between individuals with different PTVs in the same gene (Nagy and Maquat, 1998; Lindeboom et al., 2016). For example, PTVs located outside of the region that triggers NMD in *SOX10* escape NMD and produce proteins that have dominant-negative activity, causing the severe complex neurological disorder PCWH, whereas PTVs located within the NMD region produce transcripts that are recognized by NMD and removed, causing the relatively milder WS4 syndrome *via* haploinsufficiency (Inoue et al., 2004; Miller and Pearce, 2014). This variability in penetrance or expressivity could potentially be classed as distinct subtypes of disease, with different variants causing disease through different mechanisms and producing distinct syndromes. Pathogenic variants in *KAT6B* show a similar disease manifestation, with two distinct syndromes depending on whether NMD is triggered or not (Zhang et al., 2020a). Variants in *KAT6A* cause severe intellectual disability (ID) and neurodevelopmental disorders (NDD), with late PTVs more likely to cause a severe phenotype, compared to 60% of early PTVs which conferred a mild phenotype (Kennedy et al., 2019), potentially due to whether NMD is activated or not. The position of the PTV within the gene has also been seen to modulate the severity of clinical phenotypes in Marfan syndrome (Taniguchi et al., 2021) and Charcot-Marie-Tooth disease (Pipis et al., 2022). Disease due to *SFTPB* variants typically presents in neonates as respiratory distress syndrome, resulting in death within the first few months; variants that allow partial production of the SP-B protein confer longer survival times and later onset of disease, whereas the variants that cause complete deficiency of SP-B due to NMD cause fatal neonatal respiratory distress syndrome (van Moorsel et al., 2021).

Missense variants can also result in LoF due to substantially reduced protein function or stability (Høie et al., 2022). Although many missense variants have little or no effect, they can result in conformational changes, increased protein misfolding, and aberrant protein trafficking, which can lead to intracellular retention or accumulation, increased ER stress, activation of the unfolded protein response, or increased pro-apoptotic signaling and apoptosis (van Moorsel et al., 2021). Some missense variants, small insertions/deletions, and gene duplications can also result in gain of function (GoF) effects due to increased activity (Niday and Tzingounis, 2018), increased protein production (Stefl et al., 2013), or *via* protein products that gain a new damaging function (Li and Babu, 2018). Some GoF variants can exhibit a more severe phenotype than LoF variants in the same gene; for example, GoF variants in *KCNA2* were associated with more severe epilepsy phenotypes than LoF variants (Syrbe et al., 2015). Where in a gene a variant is located can affect the mechanism of disease, as well as penetrance and expressivity through molecular subregional effects (Platzer et al., 2017); the impact of a variant depends on whether it is located at sites that undergo post-translational modification, within sites that are critical for tertiary and quaternary structure, at protein–protein interaction interfaces or ligand binding sites, or inside versus outside of functional domains (Faure et al., 2022). For example, missense variants in *GRIN2A* located in transmembrane or linker domains were more frequently associated with severe developmental phenotypes than those located elsewhere, such as within amino-terminal or ligand-binding domains (Liu et al., 2021), with a wide range of phenotypes observed from normal to mild epilepsy, to severe developmental phenotypes and epileptic encephalopathy (Strehlow et al., 2019); similarly, GoF variants in highly conserved regions of the potassium channel of *KCNA2* were associated with more severe epileptic encephalopathy than variants located elsewhere (Masnada et al., 2017). An improved understanding of the protein structure and the functionality of interacting domains will help elucidate specific variant effects on the resulting phenotypic presentation (Ittisoponpisan et al., 2021).

Finally, there are a small but increasing number of pathogenic non-coding variants that have been identified as causes of monogenic diseases. These variants can operate either through LoF or GoF mechanisms by altering the gene or isoform expression (Ellingford et al., 2021). For example, biallelic variants in the *PTF1A* enhancer are a well-established cause of recessive pancreatic agenesis through tissue-specific LoF (Weedon et al., 2014); *de novo* LoF variants in the 5′ untranslated region (UTR) of *MEF2C* have been shown to account for around a quarter of developmental disorder diagnoses in this gene (Wright et al., 2021); and a single GoF variant that creates a novel promoter has been shown to cause α-thalassemia (Bozhilov et al., 2021). However, establishing the pathogenicity of non-coding variants is often much more challenging than coding variants, and thus, studies of penetrance and expressivity of these variants are likely to lag behind.

Size of Repeat Expansions

Repeat expansion disorders are caused by genomic expansions of short tandem repeat (STR) sequences that either affect the gene expression or protein sequence (Paulson, 2018), with the penetrance and expressivity affected by the number of repeats (**Table 2**). Anticipation is often observed in families due to molecular instability around the repeats; in each generation, the repeat length can increase, resulting in the earlier onset of disease and increased severity. For example, Fragile X syndrome is caused by the expansion of over 200 repeats in the CGG motif in the 5′UTR of *FMR1* on the X chromosome, resulting in hypermethylation of the promoter, silencing the gene (Hagerman et al., 2017). Fragile X exhibits incomplete penetrance and reduced expressivity, with 100% of males and 60% of females presenting with ID and 50–60% of males and 20% of females diagnosed with autism spectrum disorder (ASD) (Payán-Gómez et al., 2021). Wild type (WT) alleles contain <44 CGG repeats, while full mutations in affected individuals typically have >200 repeats. Those with premutation alleles of 55–200 repeats have milder phenotypes

TABLE 2 | Trinucleotide repeat disorders with varying penetrance depending on the number of repeats present.

Disease	Gene	STR	Non-penetrant	Intermediate penetrance	Full penetrance
Spinocerebellar ataxia 8	*ATXN8OS/ATXN8* (Perez et al., 2021)	CTG/CAG	<91	92–106	>107
Spinal muscular atrophy	*SNM1* (Laskaratos et al., 2021)	CAG	<34	35–46	>47
Fragile X	*FMR1* (Hagerman et al., 2017)	CGG	<44	45–200	>200
Huntington's	*HTT* (Kay et al., 2016)	CAG	<36	37–39	>40
ALS	*C9orf72* (DeJesus-Hernandez et al., 2011)	GGGGCC	<23	24+	>700
Friedrich's Ataxia	*FXN* (Kim et al., 2011)	GAA	<34	35–99	>100

than full mutation carriers, although they have an increased risk of Fragile X-associated tremor/ataxia syndrome (Cabal-Herrera et al., 2020) and primary ovarian insufficiency prior to age 40 (Fink et al., 2018) compared to WT. Monotonic dystrophy shows a similar mechanism, with unaffected individuals having 5–37 CTG repeats in the 3′UTR of *DMPK* and fully affected individuals having >80 repeats (although repeats of >1,000 have been seen in congenitally affected children (Morales et al., 2016)), with an number of repeats correlating with the earlier age of onset.

Although the number of repeats accounts for a large proportion of variable expressivity, there are still missing genetic factors accounting for differences in the age of onset. For example, in Huntington's disease, a lower number of N-terminal CAG repeats in *HTT* is associated with reduction in penetrance and later onset of clinical symptoms (Kay et al., 2016), but while the number of repeats is inversely correlated with the age of onset of motor symptoms, they only account for 70% of the variability (Holmans et al., 2017). The remaining unexplained variance displays a high degree of heritability, suggesting further genetic modifiers (Arning, 2016). Additional genetic variants in the DNA mismatch repair pathway have been linked with anticipation and overall severity of disease, and functional studies showing the knockout of base-excision repair or transcription-coupled repair pathways in animal and cellular models of nucleotide repeat disorders can inhibit the expansion and reduce the phenotypic severity (Goula and Merienne, 2013; Massey and Jones, 2018). Variants in the DNA repair gene *MSH3* have also been linked with differences in disease severity through somatic instability (Flower et al., 2019). As non-penetrant individuals will not necessarily come to clinical attention and large triplet repeats are hard to genotype accurately using NGS (Bahlo et al., 2018), it is suspected that individuals with fewer than 41 CAG repeats in *HTT* may exist at a higher frequency than previously expected in the general asymptomatic population (Kay et al., 2016).

GENE EXPRESSION

Variation in Allelic Expression

It has been hypothesized that the differential expression of alternative alleles in the gene containing causal variants could affect the presentation of phenotypic traits in individuals with identical genotypes. This mechanism has been proposed primarily for dominantly inherited conditions where haploinsufficiency is the cause of the disease (Ahluwalia et al., 2009; Jordan et al., 2019), including Lynch syndrome (Hesson et al., 2015) and hypertrophic cardiomyopathy (HCM) (Glazier et al., 2019), where an allelic imbalance could cause either higher expression of the WT allele, thus compensating for the haploinsufficiency and resulting in reduced penetrance, or lower expression of the WT allele, thus exacerbating the haploinsufficiency and resulting in higher penetrance. Significant allelic imbalance has been observed in up to 88% of genes in human tissues, potentially caused by genetic modifiers or stochastic factors (Aguet et al., 2017), and has been identified as both tissue-specific and genome-wide in mouse models (Pinter et al., 2015). Structural variants such as duplications that are in *trans* with a pathogenic LoF variant can alleviate the potential clinical phenotype when disease would be caused by haploinsufficiency, by providing an additional WT copy of a gene, thus resulting in a normal level of gene expression (Servetti et al., 2021), as has been observed in DiGeorge syndrome (Carelle-Calmels et al., 2009). Additional variants in the untranslated regions of mRNA can also affect the translational efficiency and gene expression can also vary widely across tissues, highlighting the importance of sequencing disease-relevant tissue in the interpretation of genetic variation (Cummings et al., 2017; Mignone et al., 2002). Compared to synonymous variants, rare missense variants show a significant reduction in allelic expression across many tissues in proportion to their predicted pathogenicity, suggesting deleterious variants are depleted from highly expressed haplotypes (Castel et al., 2018). Some highly differentially expressed genes have been shown to contain fewer disease-associated variants (Chen et al., 2008), which are less likely to accumulate on haplotypes that are highly expressed, or in high-penetrance combinations (Castel et al., 2018). For example, genetically heterogenous monogenic eye disorders display both incomplete penetrance and variable expressivity and also display significant variability in gene expression levels throughout the population (Green et al., 2020). The differential expression of alleles has also been shown to play a role in the variable expressivity of Marfan's syndrome (Aubart et al., 2015).

The differential expression of alleles can also potentially cause recessive conditions to present in a dominant fashion. For example, Zellweger spectrum disorder (ZSD) is an autosomal recessive disorder caused by deleterious variants in any of 13 PEX genes, with the most common cause being variants in *PEX1* or

PEX6. Affected heterozygous carriers have been identified with ZSD despite lacking a second pathogenic allele, with all affected heterozygotes presenting with the allelic overexpression of the variant allele compared to WT, and a common polymorphism has been linked to this allelic overexpression (Falkenberg et al., 2017). In HCM, the proportion of sarcomeric proteins produced by variant alleles can vary with the allelic expression, and 30–80% of the sarcomere structure can be made up of proteins with reduced function (Marian and Braunwald, 2017; de Marvao et al., 2021), causing variation in overall phenotypic severity.

Stochastic variation within normal cellular and developmental processes can potentially be amplified by disease-causing variants and thus play a role in incomplete penetrance and variable expressivity (Binder et al., 2015). Random monoallelic expression (RME) is the transcription of only one allele from a homologous pair and can be constitutive, with all cells expressing the same allele throughout (as seen in imprinted genes), or somatic, with individual cells showing variation in expression levels (Eckersley-Maslin and Spector, 2014). Overall levels of RNA in cell populations tend to be stable, but dynamic allelic fluctuation through RME can present variability in the gene expression. Genes that show little RME are mostly housekeeping genes that have higher expression levels (Eckersley-Maslin and Spector, 2014). Although no variation in the disease trait has yet been definitively linked to somatic RME, conceptually it could explain the phenotypic variation either through alteration of gene dosage or the higher expression of a variant allele. RME during embryonic development has been tentatively linked with variation in developmental disorders such as Holt-Oram syndrome (Gui et al., 2017). Model organism research has suggested stochastic variation in the gene expression can affect the expressivity of variant genotypes, with 20% of genes causing variation in phenotypes in two different isolates with defined genetic backgrounds in *C. elegans* (Vu et al., 2015). Phenotypic variability has also been observed in inbred mice with a defined genetic background (Dickinson et al., 2016), as well as in monozygotic (MZ) twins (Baranzini et al., 2010), suggesting the influence of stochastic molecular events in variable expressivity.

Variation in Isoform Expression

Production of different transcripts of genes may also lead to the differential expression of traits and explain why potentially deleterious variants in haploinsufficient genes are found in population cohorts. Annotations based on transcription levels of different isoforms in haploinsufficient genes identified that 23% of LoF variants are in under-expressed exons and had similar effect sizes to synonymous variants (Cummings et al., 2020). In monogenic cardiomyopathies caused by LoF variants in the giant muscle protein titin, studies of *TTN* expression levels indicate that LoF variants found in unaffected population cohorts occur predominantly in exons that are absent from the most highly expressed transcripts and thus do not cause the phenotypic effect associated with deleterious variants (Begay et al., 2015; Akinrinade et al., 2019). Similarly, haploinsufficiency of *TCF4* causes the highly penetrant Pitt-Hopkins syndrome (Kharbanda et al., 2016; Sirp et al., 2021), PTVs identified in these gene in unaffected individuals were all found to be located in minimally expressed exons (Aguet et al., 2017), suggesting that functional protein can be made in the presence of these variants. The expression of tissue-specific isoforms can also affect the penetrance of a genotype, potentially resulting in distinct disease subtypes. For example, *CACNA1C* has two clinically important isoforms with mutually exclusive exons that explain two different forms of Timothy syndrome; pathogenic variants across the widely expressed transcript produce a multi-system disorder (type 1), while pathogenic variants in the alternative exon of a transcript predominantly expressed in the heart are much rarer and result in more severe cardiac-specific defects and fewer syndromic phenotypes (type 2) (Dick et al., 2016). Further examples are likely to be uncovered through large-scale analysis of isoform expression in different tissues and at different times.

Cis- and *Trans*-Acting Genetic Modifiers

Variants in regulatory regions can affect the phenotypic presentation of disease by altering the gene expression and through modulation of deleterious genetic variants found in associated protein-coding regions (Scacheri and Scacheri, 2015), potentially affecting the penetrance and expressivity of the monogenic variant. *Cis*-acting elements are DNA sequences located on the same haplotype as the gene they affect, whereas *trans*-acting factors are proteins or elements that bind to the *cis*-acting sequences to affect the gene expression. Variants in these non-coding regions can have multiple downstream effects, through interactions with other genetic features or through effects on monogenic variants (van der Lee et al., 2020). Small changes within transcription factor binding or expression can lead to dysregulation that affects multiple genes within the same regulatory network (van der Lee et al., 2020) and therefore could potentially alter the final phenotypic presentation. *Cis*-regulatory variants have been identified that modify the penetrance of coding variants and therefore contribute to disease risk or presentation. Pathogenic coding variants are depleted from higher-expressed haplotypes with *cis*-regulatory variants in the general population (Castel et al., 2018), suggesting that individuals who present with a disease phenotype may have an enrichment of *cis*-regulatory variants that increase the expression of the pathogenic allele, compared to individuals who are asymptomatic who have an enrichment of 'protective' regulatory variants that decrease the expression and, therefore, penetrance of the pathogenic allele (Castel et al., 2018).

Upstream open reading frames (uORFs) are tissue-specific *cis*-regulators of protein translation found in the 5′UTR region of protein-coding genes, and variants that alter uORFs can affect whether a deleterious protein-coding variant causes a disease phenotype or not and may alter the phenotypic presentation of the disease (Silva et al., 2019). Active translation of a uORF can reduce downstream protein levels by up to 80% *via* several mechanisms, including the production of a peptide that stalls the translating ribosome (Young et al., 2016) and termination at a uORF stop codon that can trigger NMD (Lee et al., 2021a). Variation that either introduces or removes uORF start or stop codons can, therefore, affect the phenotypic presentation, and uORF variants may also have a role in disease pathology (Whiffin

et al., 2020). Variants in the downstream 3′UTR region may also play a role in regulation of the gene expression through altering the mRNA stability or translational efficiency (Jansen, 2001; Mignone et al., 2002; Steri et al., 2018). For example, a common single nucleotide polymorphism (SNP) downstream of *GATA6* has been shown to reduce its expression, potentially resulting in a more severe pancreatic agenesis phenotype when found in *trans* with a LoF variant in the same gene (Kishore et al., 2020). Similarly, polymorphisms in the 3′UTR region of *KCNQ1* have been suggested to alter the expression of the *cis* allele, either increasing the severity of the disease or reducing it through an uneven expression of WT or variant alleles (Amin et al., 2012). However, an attempt to replicate this in a diverse group of population cohorts found no association between the identified polymorphisms and the severity of disease (Kolder et al., 2015), highlighting the difficulties with trying to identify non-coding modifiers of rare disease, both in clinical cohorts and population studies.

Approximately 400,000 candidate enhancer regions have been identified in the human genome, with an average of around 20 enhancers per gene (The ENCODE Project Consortium, 2012; Yokoshi et al., 2020). Non-coding variants within enhancer regions can be a cause of phenotypic diversity through alterations in gene expression, therefore affecting overall disease phenotype presentation (Sun et al., 2018). Although identifying non-coding variants that affect disease presentation can be very difficult, there are some notable examples. A large study identified an SNP in an intronic enhancer of *RET* that appeared to increase the penetrance of Hirschsprung disease in patients with rare *RET*/coding variants (Emison et al., 2010). Intronic variants have also been suggested to affect the penetrance of coding variants in patients with Stargardt disease, where a deep intronic variant has been shown to be a major *cis*-acting modifier of the most common pathogenic variant in *ABCA4* (Zernant et al., 2018; Lee et al., 2021b). A small study also suggested that SNPs in promoter regions affect the severity of arrhythmias among individuals with LoF variants in *SCN5A* (Park et al., 2012). Variants that create novel binding sites for transcription factors have been implicated in affecting penetrance through altering the gene expression, including a common non-coding polymorphism that alters the hepatic expression of *SORT1* (Musunuru et al., 2010), contributing to myocardial infarction. Further WGS research is needed to identify non-coding variants that affect gene expression levels.

Genes are often associated with multiple *cis*-regulatory elements through topologically associated domains (TADs) (Delaneau et al., 2019). These domains are thought to affect the gene expression and mediate the effects of *cis*- and *trans*-regulatory factors through the 3D conformation of chromatin, and therefore, variants in these domains can affect penetrance and expressivity of genotypes (Galupa and Heard, 2017; McArthur and Capra, 2021). Although the expression of some genes has been shown to be unaffected by changes in TADs (Williamson et al., 2019), the creation of new TADs has been implicated in the pathogenicity of rare duplications (Franke et al., 2016). Alterations to the 3D chromatin structure within and between TADs can lead to mis-alignment of genes, enhancers, and silencers, affecting transcriptional control of the gene expression (Boltsis et al., 2021). Variants in TAD loops may have no effect on healthy individuals but could affect disease presentation in those with an underlying monogenic variant (Lu et al., 2020). Common genetic variants in *cis*-regulatory domains can affect the gene expression, and rare variants have been identified that disrupt the structure of the domain (Epstein, 2009; van der Lee et al., 2020), and both could contribute to varying phenotypic expressivity of identical protein-coding sequences by causing changes in upstream mechanisms of gene regulation. Structural changes that affect transcription factor binding can lead to functional gene expression changes (McArthur and Capra, 2021), as seen in the *EPHA4* locus, where deletions or duplications that overlap the TAD boundary can cause severe limb malformations (Lupiáñez et al., 2015), while deletion of the entire locus does not (Helmbacher et al., 2000), which is thought to be due to differential gene enhancer associations.

Somatic Mosaicism

Postzygotic *de novo* mutations that occur during cell division can result in somatic genetic variation that differs between cells, leading to mosaicism (Biesecker and Spinner, 2013). Monogenic disease is usually less severe in mosaic individuals than those who have the same variant expressed constitutively and depending upon which cells or tissues contain the pathogenic variant, mosaicism can result in non-penetrance or reduced expressivity (Hervé et al., 2015). Somatic mosaicism is suspected to be more widespread than is usually detected, especially when testing only a single tissue sample that may or may not contain the clinically relevant variant(s), although NGS is making it easier to identify lower-level genetic changes (Domogala et al., 2021; Chen et al., 2022).

Mosaic somatic variants have been suggested to be more representative than germline variants of the true diversity and range of potential variation in human disease as genotypes that are lethal in the constitutive form can be identified when present as mosaic (Bickley et al., 2014; Alswied et al., 2021). These include variants that cause osteogenesis imperfecta, where a mosaic father presented with mild symptoms, but the constitutive form was incompatible with life (Wallis et al., 1990), Proteus syndrome (Cohen, 2014) and CLOVES syndrome (Ferreira et al., 2021), two overgrowth disorders that are lethal in the constitutive form, and various mosaic aneuploidies (Leon et al., 2011). Alternatively, mosaic individuals can display different or milder phenotypes than those with germline variants in the same gene. For example, mosaic individuals with a variant in *HRAS* present with benign keratinocytic epidermal nevi ("woolly hair") (Honda et al., 2017), whereas those with the same constitutive variant have the more severe Costello syndrome (Gripp et al., 1993). Other diseases that have been demonstrated to show a milder phenotype when caused by somatic mosaicism include telangiectasis (Tørring et al., 2017) and polycystic kidney disease (Hopp et al., 2020). Mosaic genotypes can also display varying phenotypes that include segmental forms of the constitutive disease, such as segmental neurofibromatosis type 1, where clinical manifestations are only shown in certain parts of the body

(Jindal et al., 2019). In addition to presenting with variable expressivity, mosaic variants can also be incompletely penetrant. In individuals with primary immunodeficiencies, 80% of mosaic individuals were clinically asymptomatic, with the remaining 20% exhibiting partial clinical symptoms (Mensa-Vilaró et al., 2019; Gruber and Bogunovic, 2020). Similarly, mosaic chromosomal aneuploidy has been shown to be incompletely penetrant in population cohorts, with women who had 45,X/46,XX mosaicism presenting with normal reproductive lifespan and birth-rate and no cardiovascular complications, compared to those with the non-mosaic genotype (Tuke et al., 2019). Unaffected parents with mosaic pathogenic variants can pass their genotype onto their offspring as a constitutive germline variant, so an incompletely penetrant or milder disease in one generation can cause a completely penetrant disease in the next (Campbell et al., 2014; Acuna-Hidalgo et al., 2015; Lauritsen et al., 2017; Wright et al., 2019b; Mastromoro et al., 2020).

Somatic mosaicism can also rescue an individual from disease, through cellular reversion that reduces the expressivity of a phenotype. For example, somatic reversions have been observed in several cell lineages from individuals with immunodeficiency caused by biallelic variants in *DOCK8*, including variants that correct or remove germline PTVs, and recombination events that attenuate or remove the deleterious variant from one allele. These somatic reversions improve overall survival time, but they are unable to completely eliminate the disease phenotype (Jing et al., 2014). Somatic reversion has been observed in other primary immunodeficiencies (Hou et al., 2021; Miyazawa and Wada, 2021) and may partially explain incomplete penetrance (Gruber and Bogunovic, 2020). Reversion of the clinical phenotype in individuals with recessive dystrophic epidermolysis (Pasmooij et al., 2010) and Fanconi anemia (Gross et al., 2002; Nicoletti et al., 2020) has also been identified. Remarkably, long-term remission from WHIM syndrome, caused by GoF variants in *CXCR4*, was seen in an adult who had undergone chromothripsis of chromosome 2 resulting in deletion of the disease allele in a single hematopoietic stem cell, leading to the repopulation of the bone marrow with the haploinsufficient CXCR4 cells (McDermott et al., 2015; Heusinkveld et al., 2017).

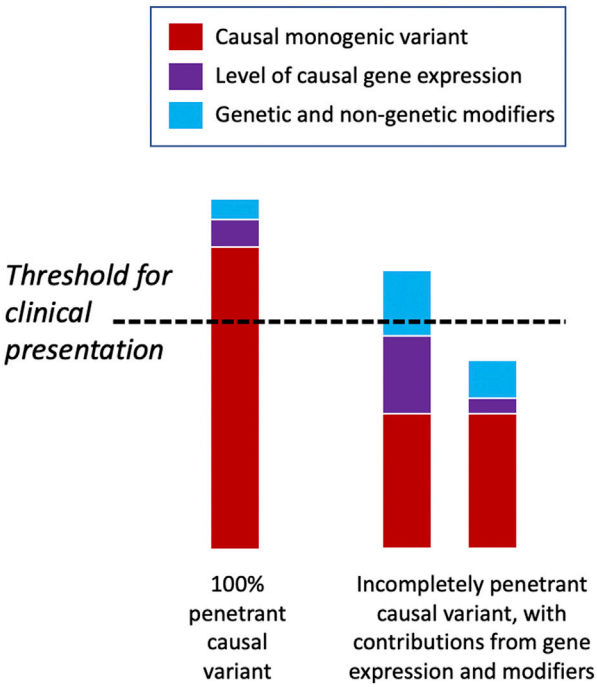

FIGURE 4 | Threshold model of disease. Some deleterious monogenic variants are sufficient to cause the disease alone and do not need any genetic modifiers to cause the disease phenotype. Other monogenic variants may be incompletely penetrant and only display a disease phenotype when accompanied by other genetic or non-genetic factors that raise them above the clinical threshold for disease presentation. In the latter scenario, individuals may have the same underlying causal variant but have very different phenotypic presentations depending upon their modifying factors.

Epigenetics

Epigenetic modifications are molecularly heritable changes that alter gene expression without altering the DNA sequence itself, including DNA methylation, histone modifications, and microRNA (miRNA) expression (Weinhold, 2006). Differential epigenetic modifications between individuals carrying the same pathogenic genotype can potentially account for incomplete penetrance and variable expressivity of the phenotype. DNA methylation is important in the control of tissue-specific gene expression, alternative splicing, prevention of cryptic initiation of transcription from alternative promoters, and X chromosome inactivation, all of which have been shown to affect the progression of disease (Velasco and Francastel, 2019). Studies of MZ twins that are discordant for disease phenotypes have highlighted how epigenetic mechanisms could affect the penetrance or expressivity of disease (Castillo-Fernandez et al., 2014). For example, MZ twins with neurofibromatosis, caused by variants in *NF1*, showed significant discordance in the presence of tumors and severity of scoliosis, suggesting that additional non-hereditary factors were modifying their phenotypes (Rieley et al., 2011). Similarly, one MZ twin with a pathogenic homozygous variant in *GBA* was diagnosed with Gaucher disease, while the other was clinically asymptomatic (Lachmann et al., 2004; Biegstraaten et al., 2011), and differences in their epigenome were posited as a mechanism to explain this discordance. However, epigenetic studies are generally more challenging than genetic studies as variation may be both tissue and time-specific, making it harder to elucidate how epigenetic mechanisms affect the penetrance of such genotypes. One suggested mechanism is that epigenetics may compensate for the presence of a deleterious variant, and segregate through several generations without any ill effects until the epigenetic modifications are no longer functional (Tolmacheva et al., 2020). This has been seen in Xq24 microdeletions that are inherited from mothers with extremely skewed X-chromosome inactivation, which modifies the

TABLE 3 | Examples of monogenic conditions affected by a putative second genetic locus that modifies the phenotypic expression.

Disease	Causal gene	Modifier gene/locus	Phenotypic effect
Cystic fibrosis	*CFTR*	*TGFB1* (Racanelli et al., 2018) *IFRD1* (Gu et al., 2009) *DCTN4* (Emond et al., 2012; Viel et al., 2016)	Increased severity of lung disease Earlier age of the onset of chronic infection
Sickle cell disease	*HBB*	*BCL11A* (Bae et al., 2012) *HBS1L-MYB* (Bae et al., 2012; Steinberg and Sebastiani, 2012; Chang et al., 2018; Allard et al., 2021) *CLCN6* (Wonkam et al., 2020) *OGHDL* (Wonkam et al., 2020)	Prolonged production of fetal hemoglobin and reduced disease severity Decrease in disease severity
Long QT syndrome	*KCNQ1* *KCHN2* *SCN5A*	*NOS1AP* (Crotti et al., 2009)	Modulate the risk of arrythmias
X-linked retinitis pigmentosa	*RPGR*	*IQCB1* (Fahim et al., 2012) *RPGRIP1L* (Khanna et al., 2009) *CEP290* (Kammenga, 2017)	Increase in disease severity
Bardet-Biedl syndrome	*BBS10*	*CCDC28B* (Cardenas-Rodriguez et al., 2013)	Increase in disease severity
Spinal muscular atrophy	*SMN1*	*PLS3* (Oprea et al., 2008) *SNM2* (Calucho et al., 2018)	Reduction in disease severity
Fragile X syndrome	*FMR1*	*COMT* (Crawford et al., 2021)	Reduction in disease severity
Spinocerebellar ataxia 17	*TBP*	*STUB1* (Magri et al., 2022)	Changes from non-penetrant to penetrant
Phenylketonuria	*PKU*	*SHANK* gene family (Klaassen et al., 2021)	Protective effect on cognitive development in untreated patients

penetrance (Tolmacheva et al., 2020). Skewed X inactivation is also suggested to be a cause behind the clinical heterogeneity in Klinefelter syndrome (Skakkebaek et al., 2020). Epigenetic mechanisms have also been suggested to partially compensate for deletions in healthy carriers of *IMMP2L* deletions, which cause ID and NDD, as reduced DNA methylation levels were seen in healthy carriers but not in affected offspring (Vasilyev et al., 2021).

Another mechanism by which epigenetic changes may affect the penetrance of monogenic diseases is *via* miRNAs, small non-coding RNAs that regulate the gene expression (Catalanotto et al., 2016). One miRNA can influence multiple genes, and a gene can be affected by several miRNAs, potentially highlighting how variants in one miRNA may lead to multiple downstream phenotypic effects (Wallace et al., 2020). Differential miRNA expressions can be caused by genetic variation, and variants within miRNA could, thus, affect the allelic expression and modify the penetrance or expressivity of monogenic diseases (Cammaerts et al., 2015). The expression of numerous miRNAs may affect the penetrance and expressivity in hereditary breast and ovarian cancer (HBOC) (Tommasi et al., 2021); incomplete and age-dependent penetrance is common in carriers of pathogenic variants in *BRCA1* and *BRCA2,* and variation in several miRNAs that bind the 3′UTRs and downregulate the expression of both genes have been linked with an increased risk of earlier onset cancer (Chen and Parmigiani, 2007; Chang et al., 2011; Moskwa et al., 2011; Sun et al., 2013; Tommasi et al., 2021).

GLOBAL MODIFIERS

Threshold Model of Disease

There may be a threshold that has to be met for the manifestation of a clinical disease phenotype, and genetic and other factors may vary in their relative contribution to meeting this threshold for different diseases and in different individuals (**Figure 4**) (Walsh et al., 2020). Some highly penetrant monogenic disease variants may always be sufficient to push the genetic burden above the threshold of the disease, although secondary variants may still contribute to severity (Pizzo et al., 2019). For example, Dravet syndrome (DS) is a highly penetrant and devastating form of childhood epilepsy caused by *de novo* LoF variants in *SCN1A* (Ding et al., 2021). Although DS displays considerable clinical heterogeneity within families and severity may relate to background genetic variation (Hammer et al., 2017), there are no known modifiers that protect against the effects of the primary causal variant; the LoF variant alone is sufficient to push the individual above the threshold for disease and other variants can only change the severity of the phenotype above this point.

Individuals with monogenic variants that are causative of disease alone and, thus, are already above the threshold for disease can be further modulated by secondary monogenic variants in related genes that also cause the same phenotype, and the accumulation of these PTVs is associated with a more severe phenotype as the burden is pushed way beyond the threshold (Bertolini et al., 2020). For example, in monogenic polycystic kidney disease, individuals with PTVs in each of the causative genes, *PKD1* and *PKD2*, present with a much more severe disease than those with just one PTV (Arora et al., 2020). Many monogenic disease-causing variants have been found to have secondary genes or loci that affect the severity of their related clinical phenotypes (Posey et al., 2017; Pizzo et al., 2019) (**Table 3**).

In contrast, some monogenic disease-causing variants may be partially tolerated and transmitted through unaffected generations unnoticed, until they surpass the threshold for causing disease in the presence of other contributory factors. For example, large copy number variants (CNVs) are well-known causes of NDDs, but some—such as recurrent 16p12.1 deletions (Hanson et al., 2015)—have been widely observed to be inherited from unaffected parents. In this case, the penetrance of a phenotype that is severe enough to present clinically requires an additional variant that modulates the primary genetic variant (Servetti et al., 2021) supporting a "two-hit" model of NDDs (Girirajan et al., 2010). Similarly, deleterious variants in *CNTNAP2* and *LRRC4C* are insufficient to cause the disease alone but together may impair the development and function of synapses (Maussion et al., 2017; Um and Ko, 2017), suggesting a possible digenic mechanism for modulation of phenotypes (Poot, 2015). In many cases, however, there are likely to be numerous factors that affect whether an individual lies above or below the disease threshold, including the overall deleteriousness of the primary causal variant(s), the level of expression of the causal gene or isoform, and other genetic and non-genetic modifiers (**Figure 4**). Global modifiers that might affect penetrance and expressivity include polygenic risk, genetic compensation, variation in the NMD efficiency, family history, age, sex, and environmental factors.

Polygenic Risk

The penetrance and expressivity of genotypes can be altered through the accumulated impact of many common genetic variants throughout the genome. The "omnigenic" model proposes that due to their interconnected nature, variants in gene-regulatory networks that are expressed in disease-relevant cells or tissues may affect the functioning of "core" disease-related genes due to effects on genes outside of the core pathways (Boyle et al., 2017), suggesting that many unrelated variants contribute to the presentation of a phenotype. Proposed as a factor in the inheritance of complex traits, this polygenic architecture could potentially also affect the presentation of monogenic conditions in a similar way, through non-coding variation that affects overall gene regulation, and many loci have been shown to additively affect expressivity and penetrance of monogenic variants in model organisms (Schell et al., 2022).

Genome-wide association studies (GWAS) have uncovered thousands of susceptibility loci for hundreds of diseases (Buniello et al., 2019), suggesting that the polygenic background can either predispose (Fahed et al., 2020) or protect individuals from diseases (Chami et al., 2020). Polygenic background can be quantified into a polygenic risk score (PRS) (Oetjens et al., 2019; Lewis and Vassos, 2020) and potentially used as a tool for the prediction of the overall disease risk in both monogenic and polygenic disorders (Khera et al., 2018). PRS associations highlight the additional risk of polygenic components in affecting the severity of monogenic disease, with the polygenic risk being shared across monogenic variant carriers and the general population (Kuchenbaecker et al., 2017). The effect of PRS has been widely explored to improve clinical interpretation of the penetrance of pathogenic variants across a range of monogenic conditions, including numerous familial cancer syndromes (Huyghe et al., 2019). The penetrance estimates for individuals with a pathogenic *BRCA1* or *BRCA2* variant range from 45 to 85% for breast cancer and from 10 to 65% for ovarian cancer (Petrucelli et al., 1993; van der Kolk et al., 2010), some of which can be explained by a polygenic background (Kuchenbaecker et al., 2017; Lee et al., 2019; Gallagher et al., 2020). Using a PRS generated from breast cancer GWAS, it has been shown that individual carriers of monogenic variants have risk differences of over 10% between the top and bottom PRS deciles (Kuchenbaecker et al., 2017). Interestingly, the majority of the SNPs identified as polygenic risk variants in breast cancer are common non-coding variants within regulatory regions, the target genes of which overlap with other known somatic cancer driver genes (Michailidou et al., 2017). Polygenic risk can also have a large effect on phenotypic diversity, even within individuals who have a known monogenic variant, illustrating that the genetic architecture for many diseases can be viewed as a spectrum rather than a binary classification of clinically symptomatic versus asymptomatic (Walsh et al., 2020). Although the overall polygenic contribution to the disease phenotype can be weaker in individuals with a monogenic variant (Harper et al., 2021), it can be useful in predicting overall penetrance and risk stratification.

Genetic Compensation

The phenomenon of genetic compensation (or genetic buffering), where another gene or genes in a network can functionally compensate for LoF variants, has been shown in model organisms (Leopold et al., 2021) and hypothesized to play a role in incomplete penetrance in humans (Buglo et al., 2020). The upregulation of related genes or pathways or the differential expression of compensating alleles can help suppress a disease phenotype (Jordan et al., 2015), either through a small number of compensatory mechanisms or *via* a global shift in the gene expression. The functional redundancy of genes and rewiring of affected genetic networks may affect the penetrance and expressivity of corresponding phenotypes, and the consequence of a pathogenic variant may be influenced by variation across the genome (Payne and Wagner, 2015) and explain why certain LoF variants are tolerated by some individuals but

not others (Subaran et al., 2015; Sulem et al., 2015). Haploinsufficiency can influence the expression of other genes in the same network, to maintain homeostasis or suppression of disease phenotypes (El-Brolosy and Stainier, 2017). The functional loss of one gene can be compensated for through functional redundancy (Chen et al., 2013). Genes that contain high numbers of PTVs in general population cohorts and thus are less likely to cause adverse phenotypes were found to belong to larger gene families than genes that contain known pathogenic PTVs (Ng et al., 2008), suggesting functional redundancy as a mechanism affecting penetrance (Hunter, 2022). Further research is needed to find robust evidence of this mechanism in humans.

Nonsense-Mediated Decay Efficiency

The efficiency of NMD varies between individuals (Huang and Wilkinson, 2012), which could act as a potential modifier of penetrance and expressivity of PTVs targeted by NMD, irrespective of the specific causal variant(s) (Sarri et al., 2017). The variation in the NMD efficiency across codons, genes, cells, and tissues can affect disease pathology (Miller and Pearce, 2014; Sarkar et al., 2019; Sato and Singer, 2021). In studies of model organisms, the variant alleles that caused milder phenotypes were those that exhibited more NMD, with reduction in NMD being correlated with a more severe phenotype (El-Brolosy and Stainier, 2017). In this case, NMD could either help trigger a compensatory response, or haploinsufficiency could produce a milder phenotype than accumulation of truncated proteins. Variants in genes that encode the NMD machinery, or that either downregulate or remove NMD activity, have been linked to several NDD and ID syndromes, including variants in *UPF2* (Hildebrand et al., 2020), *UPF3A* (Nguyen et al., 2012), *EIF4A3* (Miller et al., 2017), *SMG8* (Alzahrani et al., 2020), and *RNPS1* (Nguyen et al., 2013), highlighting its importance in development and phenotypic expression. Common polymorphisms within the NMD pathway have been suggested to cause differences in NMD efficiency (Khajavi et al., 2006; Dyle et al., 2020), which could help explain differences in the expressivity of diseases caused by haploinsufficiency, with severity linked to whether they trigger NMD or not. Interindividual variability in NMD efficiency has the ability to alter the expressivity of genetic variants, by converting the cause of the disease phenotype from dominant-negative to haploinsufficiency, or vice versa (Supek et al., 2021). For example, two patients with the same PTV in the *DMD* gene displayed different clinical phenotypes, with one diagnosed with Duchenne muscular dystrophy, and the other with the milder Becker muscular dystrophy; here, the difference in the phenotype was suspected to be caused by weaker NMD efficiency in the less severely affected patient, which resulted in the production of the damaged but still partially functional DMD protein (Kerr et al., 2001; Torella et al., 2020).

Family History

Family history can be seen as a crude but effective proxy for the combined effect of many shared genetic and environmental modifiers of disease phenotypes. In many cases, the pathogenicity and penetrance of variants in monogenic diseases have only been determined through studies of large families with multiple affected individuals, which can make it difficult to disentangle the relative contribution of different modifiers. Family history is a well-known major risk factor for hereditary cancer syndromes, and the number of affected relatives increases the risk of a pathogenic variant carrier developing cancer (Brewer et al., 2017). Although the evidence base for estimating penetrance in individuals without a family history is currently very limited (Turner and Jackson, 2020), individuals identified with a pathogenic variant for a heritable monogenic disease but without a family history of that disease may have a lower penetrance than those with a family history (Moreno-De-Luca et al., 2015; Wright et al., 2019a, Jackson et al., 2022).

Evaluating genetic differences between affected and unaffected carriers in the same family—such as *de novo* variants or unique combinations of modifiers—can be informative for understanding penetrance. It has been shown that children with monogenic NDDs have an excess of other damaging genetic variants compared to their either mildly clinically affected or asymptomatic carrier parents, with the extra genetic burden being enriched in genes that are highly expressed within the brain and in neurodevelopmental pathways (Pizzo et al., 2019). Similarly, children with 22q11.2 deletion syndrome display a wide variability in IQ scores that is highly correlated with the scores of their immediate relatives (Olszewski et al., 2014). The IQ of individuals affected by 22q11.2 deletion syndrome follows a normal distribution curve, similar to that of the general population, only 30 points lower (De Smedt et al., 2007). The significant association seen between parental and proband IQ (Klaassen et al., 2016; Davies et al., 2020) suggests that inherited genetic variants associated with intelligence may alleviate some of the deleterious impact of the 22q11.2 deletion on phenotypic presentation. The heritability of intelligence may be driven either by the cumulative effect of many common small-effect variants, similar to the heritability within population cohorts (Davies et al., 2011), or by a small number of rare high-effect variants. Similarly, individuals carrying 16p11.2 deletions present with variable phenotypic diversities (Moreno-De-Luca et al., 2015; Fetit et al., 2020) and are frequently present in "healthy" general population cohorts (Rosenfeld et al., 2013), albeit with a range of cognitive and neuropsychiatric difficulties despite none of them reaching traditional clinical diagnosis threshold levels (Stefansson et al., 2014). Within these carrier individuals, the best overall predictor of the phenotype was that of the average of their parental phenotype for the traits of interest, with individuals displaying deleterious effects relative to their phenotypic family background (Polyak et al., 2015; Evans and Uljarević, 2018).

Age

It can be argued that penetrance is an almost meaningless concept without specifying an age threshold as many diseases do not present until later in life. As we age, gene expression and chromatin structure across the genome change, which can increase the penetrance or expressivity of disease (Brookes and Shi, 2014; Bashkeel et al., 2019). Expression of certain genes can

cause change in a predictable way throughout life, with some only being expressed in the foetus or during early childhood, and others only after this developmental period. For example, the relative proportion of two protein subunits in the NMDA receptor alters with age due to the varying expression levels of the two genes, *GRIN2A* and *GRIN2B*, which can alter phenotypic expression of deleterious variants in these genes; prenatally expressed *GRIN2B* is linked with severe cognitive defects from birth, while postnatally expressed *GRIN2A* is linked with epilepsies in childhood and schizophrenia in adults (Strehlow et al., 2019). Studies of individuals who are below the age-penetrant threshold for known age-dependent diseases could explain why some pathogenic variants are found in apparently asymptomatic population cohorts. Classical examples of conditions where penetrance increases with age include cancer predisposition syndromes such as Li-Fraumeni (Correa, 2016), Lynch Syndrome (Biller et al., 2019), and HBOC (Chen and Parmigiani, 2007), where penetrance is affected by the accumulation of DNA damage over time (White et al., 2014). Meta-analysis studies have shown that the cumulative breast cancer risks for *BRCA1* and *BRCA2* pathogenic variant carriers by age 70 are 57–65% and 45–49%, respectively (Antoniou et al., 2003; Chen and Parmigiani, 2007), highlighting the difficulties with predicting the course of disease even in known pathogenic variant carriers and the importance of considering family history as well as other genetic and environmental factors (Lee et al., 2019). Age-dependent penetrance of cognitive phenotypes is also seen in diseases caused by the slow accumulation of aberrant proteins, where variation can affect the rate at which the protein accumulates (Chiti and Dobson, 2017). For example, retinitis pigmentosa (RP) has been suggested to be caused by retention of misfolded proteins, which leads to upregulation of genes that encode for proapoptotic machinery, and leads to apoptosis of photoreceptor cells, accumulating damage over time and eventually reaching the disease threshold and causing penetrant disease (Rose and Bhattacharya, 2016). Age-dependent penetrance may also be caused through gradual loss of neurons, causing the associated disease phenotype when the number of surviving cells drops below a certain threshold or overcomes brain plasticity (Magrinelli et al., 2021). For example, progressive and late occurring neurological manifestations in patients with *DNMT1* variants may originate from the gradual loss of DNA methylation over time, affecting adult neurogenesis (Velasco and Francastel, 2019).

The penetrance of age-dependent variants, present a diagnostic and prognostic challenge for individuals with such genotypes (Kalia et al., 2017). Previously, testing for many conditions early in life was not possible, and so little is known about long-term effects of mildly deleterious variants. Variants in *HFE* cause hereditary hemochromatosis, which can lead to iron overload in adulthood, and were previously thought to be an adult-onset condition. However, healthy cohort studies of children have shown that the effects of homozygous variants in *HFE* can be seen in childhood and that the cumulative effect of excess iron over a lifetime may affect the penetrance of numerous iron-related diseases (Kim and Connor, 2020). Recent population studies of adults have also shown substantially higher morbidity in homozygous *HFE* variant carriers with increasing age (Pilling et al., 2019). In this case early identification of individuals at risk can help with monitoring disease progression and introducing timely interventions (such as blood donation).

Sex

Sex can affect the penetrance and expressivity of some genetic disorders, most obviously when deleterious genetic variants occur on the X chromosome, with hemizygous males more phenotypically affected than heterozygous females. Although differences in the penetrance of inherited variants based on sex have been reported in a variety of disorders (Cooper et al., 2013), mechanisms behind sex-dependent penetrance outside those that occur on the X chromosome are mostly unknown. However, there are widespread sex-biased differences in gene expression (Oliva et al., 2020), so differences in penetrance of phenotypes are also likely to be common. Females are less likely to be diagnosed with neurodevelopmental disorders than males, with a fourfold increase in the number of males diagnosed with autism spectrum disorders (ASD) compared to females (Scott et al., 2002; Christensen et al., 2016), suggesting that there may be a female protective effect that affects the penetrance of such conditions (Jacquemont et al., 2014). Girls diagnosed with ASD have an increased number of CNVs compared to boys with the same diagnosis, and asymptomatic mothers with children diagnosed with NDDs or ASD had a higher genetic burden of deleterious variants than fathers (Polyak et al., 2015), suggesting there may be some other cause for the incomplete penetrance and variable expressivity in females compared to males. However, females are ascertained at a closer frequency to males when they are more severely affected, suggesting some bias in clinical ascertainment due to differing phenotypic presentations between the sexes (Ratto et al., 2018), supported by the fact that males were more likely to be referred for genetic testing than females carrying the same autosomal variant (Russell et al., 2011).

Environment

The environment can affect disease penetrance or expressivity in both a negative and positive manner and includes diet, drugs, alcohol intake, physical activity, ultraviolet light, *in utero* exposures, education, and socio-economic status, among many others factors. Epigenetic factors can provide a mechanistic link between the environment and gene expression (Dolinoy et al., 2007; Cavalli and Heard, 2019; Safi-Stibler and Gabory, 2020), and studies of the human microbiome can also explain some extreme variability in genotype–phenotype presentation (Sanna et al., 2019). However, although gene–environment interactions are likely to be widespread, they are often extremely hard to prove as the complete and systematic collection of an individual's environment is almost impossible, and detailed relevant exposure data are rarely available alongside genetic data.

Inborn errors of metabolism perhaps provide the simplest examples of monogenic diseases where both a pathogenic genotype and an environmental exposure are required to cause disease (van Karnebeek and Stockler, 2012). A clear example of the dietary impact on phenotypic variation is phenylketonuria, a

rare autosomal recessive disease that is usually detected through newborn screening, whereby individuals who have damaging biallelic variants in *PAH* can be put on a low phenylalanine diet to avoid serious disease progression (Flydal and Martinez, 2013; Al Hafid and Christodoulou, 2015). Later onset monogenic disease penetrance can also be affected by the environment, as seen in several cancer syndromes, including colorectal cancer, where inherited genetic variants interact with dietary variables and BMI to confer the overall risk (Lee et al., 2015). Cancer susceptibility can also be altered through gene–environment interactions such as smoking or sunburn, which can accelerate the accumulation of somatic variants that contribute toward tumorigenesis (Newcomb and Carbone, 1992; Wu et al., 2016). Similarly, environmental exposure to cigarette smoke, air pollution, and other airborne toxins can cause accumulation of unfolded or misfolded proteins and therefore affect the penetrance or expressivity of chronic lung disease (Wei et al., 2013). Individuals who carry a damaging monogenic variant may also be more susceptible to some environmental exposures, which can affect phenotypic severity (Tukker et al., 2021). For example, cystic fibrosis is characterized by progressive damage to the lungs, and non-genetic factors may account for up to 50% of the clinical variation seen (Collaco et al., 2010). Environmental factors such as smoking, air pollutants, temperature, and high-fat diets have all been shown to affect the severity and progression of disease (Collaco et al., 2010; Collaco et al., 2011; Schindler et al., 2015; Tukker et al., 2021), and the specific *CFTR* variant can also modulate how much environmental impact has on disease severity (Collaco and Cutting, 2008). Environmental factors can also affect the presentation of disease in primary atopic disorders, commonly seen as monogenic allergic disorders, where diet, microbiome at the epithelial-environment interface, presence/extent of infection, and psychological stress can all affect the penetrance or expressivity of the related phenotype (Sacco and Milner, 2019).

CHALLENGES WITHIN DETERMINING PENETRANCE AND EXPRESSIVITY

Incomplete Penetrance Challenges Definitions of Pathogenicity

Determining the penetrance and expressivity of a variant can be difficult because it is sensitive to ascertainment context, and many studies are designed to enable the discovery of causative pathogenic variants in clinically affected individuals rather than to analyze effect sizes in populations (Manrai et al., 2016). This has been demonstrated in recent studies that stress the importance of cohort background for the determination of penetrance (Goodrich et al., 2021; Mirshahi et al., 2021). Investigating clinically classified pathogenic variants in large population cohorts can provide additional information about penetrance and expressivity (Kingdom et al., 2022), or determine whether variants or genes have been misclassified (Wright et al., 2019a). However, finding low penetrance pathogenic variants in large numbers of asymptomatic individuals challenges the concept of pathogenicity, particularly in the absence of known modifiers. What does it mean to describe a genotype as pathogenic if it is frequently found in individuals without disease and no explanation as to why? Reclassification of previously reported pathogenic variants occurs frequently, with variants first classified prior to the release of large population datasets showing a higher rate of reclassification (Harrison and Rehm, 2019). A study reappraising pathogenic variants in Brugada syndrome showed that only one gene (*SCN5A*) out of 21 could be definitively identified as causal (Hosseini et al., 2018), and another study has raised doubt over the involvement of 11/58 genes thought to cause inherited monogenic retinal disease (Hanany and Sharon, 2019). Variants that show low penetrance or a wide range of expressivity can also be potentially classified as risk alleles rather than causative variants. Some *CFTR* variants have been classified this way, with variations in cystic fibrosis phenotypes from very mild to very severe, and over 1900 different genotypes have been reported (Collaco and Cutting, 2008; Guillot et al., 2014; Pereira et al., 2019). Many genotype–phenotype associations are only reported once, or they are reported several times but with inconsistent results due to differences in data collection, differences in methods, or differences in cohort ascertainment. Associations can also differ due to poor annotation of coding genes, lack of relevant functional information for non-coding regions, sequencing and annotation errors, and varying penetrance and expressivity, making a simple binary classification of many genetic variants very difficult.

Monogenic Versus Polygenic Disease

An overlapping genetic basis between complex traits and monogenic conditions is becoming increasingly apparent across the genome. Deleterious variants in genes causative of monogenic disease can be further dysregulated by non-coding variants that are associated with common traits, and monogenic forms of numerous common complex diseases have been identified (Peltonen et al., 2006; Chami et al., 2020; Hassanin et al., 2021). This overlap can cause considerable complexity when it comes to determining genotype–phenotype relationships (Freund et al., 2018). The prevalence of incomplete penetrance and variable expressivity raises questions as to what constitutes a disease state as opposed to extremes of normal phenotypic variation, especially within conditions that show significant clinical heterogeneity (Moreno-De-Luca et al., 2015), with many traits that constitute a clinical phenotype being the extreme end of either side of the bell curve of continuous distribution in the general population. Therefore, defining the penetrance of a genotype can be difficult, especially when there is ambiguity as to what defines the "disease state," particularly for disorders where clinical features are only identified when they reach above a certain threshold (Senol-Cosar et al., 2019).

Genetic Modifiers Are Hard to Identify

Relatively few studies have investigated low penetrant rare variants in detail or identified why such variants cause disease in one individual and not another. Despite increasing numbers of sequenced individuals, identification of genetic modifiers for monogenic conditions remains challenging. By definition, carriers of rare variants that cause monogenic conditions will be rare, with even fewer individuals having identical genetic modifiers that explain incomplete penetrance or variable expression. NGS approaches

involving bioinformatic algorithms, including pathogenicity score-based prioritizations, can produce conflicting results and often need manual curation to identify candidate variants. A computational approach that could comprehensively analyze and prioritize candidate variants and potential modifiers would be a great advantage. Even in large population cohorts genome-wide analysis of genetic interactions lacks statistical power and can be easily affected by confounders (Wei et al., 2014). Many genetic modifiers are likely to be located in non-coding regions, making it challenging to determine their direct functional effect on the gene expression, especially as much of the genome is found to be bound by at least one transcription factor, many of which have no known function yet (The ENCODE Project Consortium, 2012). Improved computational approaches to identify candidate modifier gene interactions across the genome are needed (Lee et al., 2010), as well as identification of functional non-coding regions and the genes that they affect (Petrovski et al., 2015), and machine learning approaches such as DeepSEA and Enformer (Avsec et al., 2021) could improve annotation of these regions (Zhou and Troyanskaya, 2015).

FUTURE PERSPECTIVES

Estimating Penetrance in Diverse Cohorts

Participants in population studies are usually investigated in a research-based environment rather than a clinical context, and despite rigorous phenotypic collection in some population studies, individuals involved may have subclinical manifestations of disease phenotypes that were unnoticed at the time of recruitment, or were not recorded in their medical histories (van Rooij et al., 2020). Lack of comprehensive phenotypic data can make using population cohorts to calculate the penetrance of genotypes very difficult but can at least provide a lower boundary of penetrance, with small clinical studies providing the upper boundary (Elfatih et al., 2021). Variant interpretation guidelines suggest that the penetrance of pathogenic variants in general population cohorts should be taken into account when calculating the overall penetrance of such variants (Kalia et al., 2017); however, even within healthy population cohorts there have been individuals identified with the associated phenotype but who have previously been described as unaffected (Chen et al., 2016), as well as individuals who display symptoms but are below the clinical threshold for classification. This is further complicated by conditions that are late-onset. In addition, genetic studies of human disease currently fail to capture the diversity that exists across the world, with most studies involving individuals of European descent (Lawson et al., 2020). This issue directly affects penetrance estimates, particularly as GWAS results and PRS may not be transferrable across diverse populations due to differing allele frequencies (Sirugo et al., 2019). Many deleterious variants may not be sufficient alone to cause disease, and therefore, estimates of penetrance need to consider the presence of other genetic variants and potential environmental effects (**Figure 4**). Calculating the etiological fraction of rare variants in specific conditions may provide a useful way to evaluate the probability that a variant detected in an individual with disease is causative (Walsh et al., 2017; Walsh et al., 2019), and disease-specific variant classifiers may also be of use (Zhang et al., 2021).

Screening of Unselected Populations

As WGS becomes more common, individuals at risk of genetic disease will be identified earlier in life, potentially even from birth (Holm et al., 2018) and often prior to the appearance of relevant phenotypes. This can have a positive impact on overall health, with individuals who have no family history but a previously unknown high risk of disease being identified, enabling preventative screening or early treatment interventions. However, it can also cause harm through overdiagnosis; As seen across a number of population cohort studies, healthy individuals can harbor many potentially deleterious variants without ever developing any clinical symptoms. The effective use of genomic data requires a comprehensive understanding of functional genotype–phenotype correlations, which goes beyond that of Mendelian inheritance patterns. The increased sequencing of unselected populations, linked with electronic health records or other longitudinal phenotypic data, gives us an unprecedented ability to identify and reclassify rare variants and calculate penetrance estimates for a wide range of diseases and genotypes. These large-scale studies are crucial to inform the development of genomic screening programs (Holm et al., 2018; Wojcik et al., 2021) and the management of incidental or secondary findings. Discovery estimates of secondary findings vary from 1–3% of the population, with the majority of identified variants being those that confer susceptibility to cancer (Hart et al., 2019; Gordon et al., 2020). Incidental findings are predicted to be detectable at an appreciable level in individuals in the general population, many of whom may never develop the corresponding disease, suggesting that more robust determinations of pathogenicity are needed, including penetrance estimates for those without a family history of the disease (Johnston et al., 2012).

CONCLUSION

Incomplete penetrance and variable expressivity are a significant concern for the correct interpretation of genetic variation and of diagnosing genetic disease. Correctly estimating penetrance and expressivity is challenging, with clinical cohorts and population studies both offering a different insight into its quantification. Although many monogenic disease-causing variants are fully penetrant, many are not, and improving our knowledge will involve WGS of population cohorts of increasing size and diversity, as well as functional studies of individual patients with specific clinical phenotypes. Achieving a mechanistic understanding of how incomplete penetrance and variable expressivity occur will help inform diagnostic and prognostic testing, clinical management, and accurate genetic counseling. To improve diagnostics and clinical interpretation of incompletely penetrant genotypes, a more sophisticated approach to disease genetics may be needed that integrates disease mechanism and specific variants with variation in levels of gene and tissue-specific isoform expressions and other genetic and non-genetic modifiers.

Improving our knowledge of how variants exert their effects on genes, cellular pathways, and overall phenotypes will improve our understanding of disease and facilitate the development of new therapeutic interventions.

AUTHOR CONTRIBUTIONS

RK: literature review and drafting of the article. CW: critical revision and additions.

REFERENCES

Acuna-Hidalgo, R., Bo, T., Kwint, M. P., van de Vorst, M., Pinelli, M., Veltman, J. A., et al. (2015). Post-zygotic Point Mutations Are an Underrecognized Source of De Novo Genomic Variation. *Am. J. Hum. Genet.* 97, 67–74. doi:10.1016/j.ajhg.2015.05.008

Aguet, F., Brown, A. A., Castel, S. E., Davis, J. R., He, Y., Jo, B., et al. (2017). Genetic Effects on Gene Expression across Human Tissues. *Nature* 550, 204–213.

Ahluwalia, J. K., Hariharan, M., Bargaje, R., Pillai, B., and Brahmachari, V. (2009). Incomplete Penetrance and Variable Expressivity: Is There a microRNA Connection? *BioEssays* 31, 981–992. doi:10.1002/bies.200900066

Akinrinade, O., Heliö, T., Lekanne Deprez, R. H., Jongbloed, J. D. H., Boven, L. G., van den Berg, M. P., et al. (2019). Relevance of Titin Missense and Non-frameshifting Insertions/Deletions Variants in Dilated Cardiomyopathy. *Sci. Rep.* 9, 4093. doi:10.1038/s41598-019-39911-x

Akiyama, M. (2010). FLG Mutations in Ichthyosis Vulgaris and Atopic Eczema: Spectrum of Mutations and Population Genetics. *Br. J. Dermatol.* 162, 472–477. doi:10.1111/j.1365-2133.2009.09582.x

Al Hafid, N., and Christodoulou, J. (2015). Phenylketonuria: a Review of Current and Future Treatments. *Transl. Pediatr.* 4, 304–317. doi:10.3978/j.issn.2224-4336.2015.10.07

Allard, P., Alhaj, N., Lobitz, S., Cario, H., Jarisch, A., Grosse, R., et al. (2021). Genetic Modifiers of Fetal Hemoglobin Affect the Course of Sickle Cell Disease in Patients Treated with Hydroxyurea. *Haematologica*.

Alswied, A., Rehman, A., Lai, L.-W., Duran, J., Sardar, M., and Proytcheva, M. A. (2021). Rare Monosomy 7 and Deletion 7p at Diagnosis of Chronic Myeloid Leukemia in Accelerated Phase. *Cancer Genet.* 252-253, 111–114. doi:10.1016/j.cancergen.2021.01.006

Alzahrani, F., Kuwahara, H., Long, Y., Al-Owain, M., Tohary, M., AlSayed, M., et al. (2020). Recessive, Deleterious Variants in SMG8 Expand the Role of Nonsense-Mediated Decay in Developmental Disorders in Humans. *Am. J. Hum. Genet.* 107, 1178–1185. doi:10.1016/j.ajhg.2020.11.007

Amin, A. S., Giudicessi, J. R., Tijsen, A. J., Spanjaart, A. M., Reckman, Y. J., Klemens, C. A., et al. (2012). Variants in the 3′ Untranslated Region of the KCNQ1-Encoded Kv7.1 Potassium Channel Modify Disease Severity in Patients with Type 1 Long QT Syndrome in an Allele-specific Manner. *Eur. Heart J.* 33, 714–723. doi:10.1093/eurheartj/ehr473

Antoniou, A., Pharoah, P. D. P., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., et al. (2003). Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies. *Am. J. Hum. Genet.* 72, 1117–1130. doi:10.1086/375033

Arning, L. (2016). The Search for Modifier Genes in Huntington Disease - Multifactorial Aspects of a Monogenic Disorder. *Mol. Cell. Probes* 30, 404–409. doi:10.1016/j.mcp.2016.06.006

Arora, V., Bijarnia-Mahay, S., Tiwari, V., Bansal, S., Gupta, P., Setia, N., et al. (2020). Co-inheritance of Pathogenic Variants in PKD1 and PKD2 Genes Presenting as Severe Antenatal Phenotype of Autosomal Dominant Polycystic Kidney Disease. *Eur. J. Med. Genet.* 63, 103734. doi:10.1016/j.ejmg.2019.103734

Aubart, M., Gazal, S., Arnaud, P., Benarroch, L., Gross, M.-S., Buratti, J., et al. (2018). Association of Modifiers and Other Genetic Factors Explain Marfan Syndrome Clinical Variability. *Eur. J. Hum. Genet.* 26, 1759–1772. doi:10.1038/s41431-018-0164-9

Aubart, M., Gross, M.-S., Hanna, N., Zabot, M.-T., Sznajder, M., Detaint, D., et al. (2015). The Clinical Presentation of Marfan Syndrome Is Modulated by Expression of Wild-type FBN1 Allele. *Hum. Mol. Genet.* 24, 2764–2770. doi:10.1093/hmg/ddv037

Austin, E. D., Phillips, J. A., Cogan, J. D., Hamid, R., Yu, C., Stanton, K. C., et al. (2009). Truncating and Missense BMPR2 Mutations Differentially Affect the Severity of Heritable Pulmonary Arterial Hypertension. *Respir. Res.* 10, 87. doi:10.1186/1465-9921-10-87

Auton, A., Auton, A., Brooks, L. D., Durbin, R. M., Garrison, E. P., Kang, H. M., et al. (2015). A Global Reference for Human Genetic Variation. *Nature* 526, 68–74. doi:10.1038/nature15393

Avsec, Ž., Agarwal, V., Visentin, D., Ledsam, J. R., Grabska-Barwinska, A., Taylor, K. R., et al. (2021). Effective Gene Expression Prediction from Sequence by Integrating Long-Range Interactions. *Nat. Methods* 18, 1196–1203. doi:10.1038/s41592-021-01252-x

Bae, H. T., Baldwin, C. T., Sebastiani, P., Telen, M. J., Ashley-Koch, A., Garrett, M., et al. (2012). Meta-analysis of 2040 Sickle Cell Anemia Patients: BCL11A and HBS1L-MYB Are the Major Modifiers of HbF in African Americans. *Blood* 120, 1961–1962. doi:10.1182/blood-2012-06-432849

Bahlo, M., Bennett, M. F., Degorski, P., Tankard, R. M., Delatycki, M. B., and Lockhart, P. J. (2018). Recent Advances in the Detection of Repeat Expansions with Short-Read Next-Generation Sequencing. *F1000Res* 7, F1000. doi:10.12688/f1000research.13980.1

Baranzini, S. E., Mudge, J., van Velkinburgh, J. C., Khankhanian, P., Khrebtukova, I., Miller, N. A., et al. (2010). Genome, Epigenome and RNA Sequences of Monozygotic Twins Discordant for Multiple Sclerosis. *Nature* 464, 1351–1356. doi:10.1038/nature08990

Bashkeel, N., Perkins, T. J., Kærn, M., and Lee, J. M. (2019). Human Gene Expression Variability and its Dependence on Methylation and Aging. *BMC Genomics* 20, 941. doi:10.1186/s12864-019-6308-7

Begay, R. L., Graw, S., Sinagra, G., Merlo, M., Slavov, D., Gowan, K., et al. (2015). Role of Titin Missense Variants in Dilated Cardiomyopathy. *J. Am. Heart Assoc.* 4, e002645. doi:10.1161/JAHA.115.002645

Bertolini, S., Calandra, S., Arca, M., Averna, M., Catapano, A. L., Tarugi, P., et al. (2020). Homozygous Familial Hypercholesterolemia in Italy: Clinical and Molecular Features. *Atherosclerosis* 312, 72–78. doi:10.1016/j.atherosclerosis.2020.08.027

Bickley, V. M., Parker, E. M., Taylor, J. C., Watt, J. E., Robertson, M. D., Doudney, K. W. E., et al. (2014). Rare Complete and Partial Monosomy 7 Mosaicism Detected in a Case with FTT and Borderline Motor Delay, Subsequently Diagnosed with Juvenile MDS: An Exposition of This Case and Other Interesting Mosaic Cancer Case Studies. *Cancer Genet.* 207, 286. doi:10.1016/j.cancergen.2014.06.009

Biegstraaten, M., van Schaik, I. N., Aerts, J. M. F. G., Langeveld, M., Mannens, M. M. A. M., Bour, L. J., et al. (2011). A Monozygotic Twin Pair with Highly Discordant Gaucher Phenotypes. *Blood Cells, Mol. Dis.* 46, 39–41. doi:10.1016/j.bcmd.2010.10.007

Biesecker, L. G., and Spinner, N. B. (2013). A Genomic View of Mosaicism and Human Disease. *Nat. Rev. Genet.* 14, 307–320. doi:10.1038/nrg3424

Biller, L. H., Syngal, S., and Yurgelun, M. B. (2019). Recent Advances in Lynch Syndrome. *Fam. Cancer* 18, 211–219. doi:10.1007/s10689-018-00117-1

Binder, B. J., Landman, K. A., Newgreen, D. F., and Ross, J. V. (2015). Incomplete Penetrance: The Role of Stochasticity in Developmental Cell Colonization. *J. Theor. Biol.* 380, 309–314. doi:10.1016/j.jtbi.2015.05.028

Boltsis, I., Grosveld, F., Giraud, G., and Kolovos, P. (2021). Chromatin Conformation in Development and Disease. *Front. Cell. Dev. Biol.* 9, 723859. doi:10.3389/fcell.2021.723859

Boycott, K. M., Rath, A., Chong, J. X., Hartley, T., Alkuraya, F. S., Baynam, G., et al. (2017). International Cooperation to Enable the Diagnosis of All Rare Genetic Diseases. *Am. J. Hum. Genet.* 100, 695–705. doi:10.1016/j.ajhg.2017.04.003

Boyle, E. A., Li, Y. I., and Pritchard, J. K. (2017). An Expanded View of Complex Traits: From Polygenic to Omnigenic. *Cell.* 169, 1177–1186. doi:10.1016/j.cell.2017.05.038

Bozhilov, Y. K., Downes, D. J., Telenius, J., Marieke Oudelaar, A., Olivier, E. N., Mountford, J. C., et al. (2021). A Gain-Of-Function Single Nucleotide Variant Creates a New Promoter Which Acts as an Orientation-dependent Enhancer-Blocker. *Nat. Commun.* 12, 3806. doi:10.1038/s41467-021-23980-6

Brewer, H. R., Jones, M. E., Schoemaker, M. J., Ashworth, A., and Swerdlow, A. J. (2017). Family History and Risk of Breast Cancer: an Analysis Accounting for Family Structure. *Breast Cancer Res. Treat.* 165, 193–200. doi:10.1007/s10549-017-4325-2

Brookes, E., and Shi, Y. (2014). Diverse Epigenetic Mechanisms of Human Disease. *Annu. Rev. Genet.* 48, 237–268. doi:10.1146/annurev-genet-120213-092518

Buglo, E., Sarmiento, E., Martuscelli, N. B., Sant, D. W., Danzi, M. C., Abrams, A. J., et al. (2020). Genetic Compensation in a Stable Slc25a46 Mutant Zebrafish: A Case for Using F0 CRISPR Mutagenesis to Study Phenotypes Caused by Inherited Disease. *PLoS ONE* 15, e0230566. doi:10.1371/journal.pone.0230566

Buniello, A., MacArthur, J. A. L., Cerezo, M., Harris, L. W., Hayhurst, J., Malangone, C., et al. (2019). The NHGRI-EBI GWAS Catalog of Published Genome-wide Association Studies, Targeted Arrays and Summary Statistics 2019. *Nucleic Acids Res.* 47, D1005–D1012. doi:10.1093/nar/gky1120

Cabal-Herrera, A. M., Tassanakijpanich, N., Salcedo-Arellano, M. J., and Hagerman, R. J. (2020). Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS): Pathophysiology and Clinical Implications. *Int. J. Mol. Sci.* 21, E4391. doi:10.3390/ijms21124391

Calucho, M., Bernal, S., Alías, L., March, F., Venceslá, A., Rodríguez-Álvarez, F. J., et al. (2018). Correlation between SMA Type and SMN2 Copy Number Revisited: An Analysis of 625 Unrelated Spanish Patients and a Compilation of 2834 Reported Cases. *Neuromuscul. Disord.* 28, 208–215. doi:10.1016/j.nmd.2018.01.003

Cammaerts, S., Strazisar, M., De Rijk, P., and Del Favero, J. (2015). Genetic Variants in microRNA Genes: Impact on microRNA Expression, Function, and Disease. *Front. Genet.* 6, 186. doi:10.3389/fgene.2015.00186

Campbell, I. M., Yuan, B., Robberecht, C., Pfundt, R., Szafranski, P., McEntagart, M. E., et al. (2014). Parental Somatic Mosaicism Is Underrecognized and Influences Recurrence Risk of Genomic Disorders. *Am. J. Hum. Genet.* 95, 173–182. doi:10.1016/j.ajhg.2014.07.003

Cardenas-Rodriguez, M., Osborn, D. P. S., Irigoín, F., Graña, M., Romero, H., Beales, P. L., et al. (2013). Characterization of CCDC28B Reveals its Role in Ciliogenesis and Provides Insight to Understand its Modifier Effect on Bardet-Biedl Syndrome. *Hum. Genet.* 132, 91–105. doi:10.1007/s00439-012-1228-5

Carelle-Calmels, N., Saugier-Veber, P., Girard-Lemaire, F., Rudolf, G., Doray, B., Guérin, E., et al. (2009). Genetic Compensation in a Human Genomic Disorder. *N. Engl. J. Med.* 360, 1211–1216. doi:10.1056/nejmoa0806544

Castel, S. E., Cervera, A., Mohammadi, P., Aguet, F., Reverter, F., Wolman, A., et al. (2018). Modified Penetrance of Coding Variants by Cis-Regulatory Variation Contributes to Disease Risk. *Nat. Genet.* 50, 1327–1334. doi:10.1038/s41588-018-0192-y

Castillo-Fernandez, J. E., Spector, T. D., and Bell, J. T. (2014). Epigenetics of Discordant Monozygotic Twins: Implications for Disease. *Genome Med.* 6, 60. doi:10.1186/s13073-014-0060-z

Catalanotto, C., Cogoni, C., and Zardo, G. (2016). MicroRNA in Control of Gene Expression: An Overview of Nuclear Functions. *Ijms* 17, 1712. doi:10.3390/ijms17101712

Cavalli, G., and Heard, E. (2019). Advances in Epigenetics Link Genetics to the Environment and Disease. *Nature* 571, 489–499. doi:10.1038/s41586-019-1411-0

Chami, N., Preuss, M., Walker, R. W., Moscati, A., and Loos, R. J. F. (2020). The Role of Polygenic Susceptibility to Obesity Among Carriers of Pathogenic Mutations in MC4R in the UK Biobank Population. *PLOS Med.* 17, e1003196. doi:10.1371/journal.pmed.1003196

Chang, A. K., Ginter Summarell, C. C., Birdie, P. T., and Sheehan, V. A. (2018). Genetic Modifiers of Severity in Sickle Cell Disease. *Chem.* 68, 147–164. doi:10.3233/ch-189004

Chang, S., Wang, R.-H., Wang, R.-H., Akagi, K., Kim, K.-A., Martin, B. K., et al. (2011). Tumor Suppressor BRCA1 Epigenetically Controls Oncogenic microRNA-155. *Nat. Med.* 17, 1275–1282. doi:10.1038/nm.2459

Chen, D., Xu, Y., Ding, C., Wang, Y., Fu, Y., Cai, B., et al. (2022). The Inconsistency between Two Major Aneuploidy-Screening Platforms-Single-Nucleotide Polymorphism Array and Next-Generation Sequencing-In the Detection of Embryo Mosaicism. *BMC Genomics* 23, 62. doi:10.1186/s12864-022-08294-1

Chen, R., Morgan, A. A., Dudley, J., Deshpande, T., Li, L., Kodama, K., et al. (2008). FitSNPs: Highly Differentially Expressed Genes Are More Likely to Have Variants Associated with Disease. *Genome Biol.* 9, R170. doi:10.1186/gb-2008-9-12-r170

Chen, R., Shi, L., Hakenberg, J., Naughton, B., Sklar, P., Zhang, J., et al. (2016). Analysis of 589,306 Genomes Identifies Individuals Resilient to Severe Mendelian Childhood Diseases. *Nat. Biotechnol.* 34, 531–538. doi:10.1038/nbt.3514

Chen, S., and Parmigiani, G. (2007). Meta-Analysis of BRCA1 and BRCA2 Penetrance. *Jco* 25, 1329–1333. doi:10.1200/jco.2006.09.1066

Chen, W.-H., Zhao, X.-M., van Noort, V., and Bork, P. (2013). Human Monogenic Disease Genes Have Frequently Functionally Redundant Paralogs. *PLoS Comput. Biol.* 9, e1003073. doi:10.1371/journal.pcbi.1003073

Chiti, F., and Dobson, C. M. (2017). Protein Misfolding, Amyloid Formation, and Human Disease: A Summary of Progress over the Last Decade. *Annu. Rev. Biochem.* 86, 27–68. doi:10.1146/annurev-biochem-061516-045115

Chong, J. X., Buckingham, K. J., Jhangiani, S. N., Boehm, C., Sobreira, N., Smith, J. D., et al. (2015). The Genetic Basis of Mendelian Phenotypes: Discoveries, Challenges, and Opportunities. *Am. J. Hum. Genet.* 97, 199–215. doi:10.1016/j.ajhg.2015.06.009

Christensen, D. L., Baio, J., Braun, K. V. N., Bilder, D., Charles, J., Constantino, J. N., et al. (2016). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *MMWR Surveill. Summ.* 65, 1–23. doi:10.15585/mmwr.ss6503a1

Claussnitzer, M., Cho, J. H., Collins, R., Cox, N. J., Dermitzakis, E. T., Hurles, M. E., et al. (2020). A Brief History of Human Disease Genetics. *Nature* 577, 179–189. doi:10.1038/s41586-019-1879-7

Coban-Akdemir, Z., White, J. J., Song, X., Jhangiani, S. N., Fatih, J. M., Gambin, T., et al. (2018). Identifying Genes Whose Mutant Transcripts Cause Dominant Disease Traits by Potential Gain-Of-Function Alleles. *Am. J. Hum. Genet.* 103, 171–187. doi:10.1016/j.ajhg.2018.06.009

Cohen, M. M. (2014). Proteus Syndrome Review: Molecular, Clinical, and Pathologic Features. *Clin. Genet.* 85, 111–119. doi:10.1111/cge.12266

Collaco, J. M., Blackman, S. M., McGready, J., Naughton, K. M., and Cutting, G. R. (2010). Quantification of the Relative Contribution of Environmental and Genetic Factors to Variation in Cystic Fibrosis Lung Function. *J. Pediatr.* 157, 802–807. doi:10.1016/j.jpeds.2010.05.018

Collaco, J. M., and Cutting, G. R. (2008). Update on Gene Modifiers in Cystic Fibrosis. *Curr. Opin. Pulm. Med.* 14, 559–566. doi:10.1097/mcp.0b013e3283121cdc

Collaco, J. M., McGready, J., Green, D. M., Naughton, K. M., Watson, C. P., Shields, T., et al. (2011). Effect of Temperature on Cystic Fibrosis Lung Disease and Infections: a Replicated Cohort Study. *PloS One* 6, e27784. doi:10.1371/journal.pone.0027784

Cooper, D. N., Krawczak, M., Polychronakos, C., Tyler-Smith, C., and Kehrer-Sawatzki, H. (2013). Where Genotype Is Not Predictive of Phenotype: towards an Understanding of the Molecular Basis of Reduced Penetrance in Human Inherited Disease. *Hum. Genet.* 132, 1077–1130. doi:10.1007/s00439-013-1331-2

Correa, H. (2016). Li-Fraumeni Syndrome. *J. Pediatr. Genet.* 5, 84–88. doi:10.1055/s-0036-1579759

Crawford, H., Scerif, G., Wilde, L., Beggs, A., Stockton, J., Sandhu, P., et al. (2021). Genetic Modifiers in Rare Disorders: the Case of Fragile X Syndrome. *Eur. J. Hum. Genet.* 29, 173–183. doi:10.1038/s41431-020-00711-x

Crotti, L., Monti, M. C., Insolia, R., Peljto, A., Goosen, A., Brink, P. A., et al. (2009). NOS1AP Is a Genetic Modifier of the Long-QT Syndrome. *Circulation* 120, 1657–1663. doi:10.1161/circulationaha.109.879643

Cummings, B. B., Karczewski, K. J., Kosmicki, J. A., Seaby, E. G., Watts, N. A., Singer-Berk, M., et al. (2020). Transcript Expression-Aware Annotation Improves Rare Variant Interpretation. *Nature* 581, 452–458. doi:10.1038/s41586-020-2329-2

Cummings, B. B., Marshall, J. L., Tukiainen, T., Lek, M., Donkervoort, S., Foley, A. R., et al. (2017). Improving Genetic Diagnosis in Mendelian Disease with Transcriptome Sequencing. *Sci. Transl. Med.* 9, eaal5209. doi:10.1126/scitranslmed.aal5209

Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S. E., Liewald, D., et al. (2011). Genome-wide Association Studies Establish that Human Intelligence Is Highly Heritable and Polygenic. *Mol. Psychiatry* 16, 996–1005. doi:10.1038/mp.2011.85

Davies, R. W., Fiksinski, A. M., Fiksinski, A. M., Breetvelt, E. J., Williams, N. M., Hooper, S. R., et al. (2020). Using Common Genetic Variation to Examine

Phenotypic Expression and Risk Prediction in 22q11.2 Deletion Syndrome. *Nat. Med.* 26, 1912–1918. doi:10.1038/s41591-020-1103-1

de Marvao, A., McGurk, K. A., Zheng, S. L., Thanaj, M., Bai, W., Duan, J., et al. (2021). Phenotypic Expression and Outcomes in Individuals with Rare Genetic Variants of Hypertrophic Cardiomyopathy. *J. Am. Coll. Cardiol.* 78, 1097–1110. doi:10.1016/j.jacc.2021.07.017

De Smedt, B., Devriendt, K., Fryns, J.-P., Vogels, A., Gewillig, M., and Swillen, A. (2007). Intellectual Abilities in a Large Sample of Children with Velo?Cardio? Facial Syndrome: an Update. *J. Intellect. Disabil. Res.* 51, 666–670. doi:10.1111/j.1365-2788.2007.00955.x

DeJesus-Hernandez, M., Mackenzie, I. R., Boeve, B. F., Boxer, A. L., Baker, M., Rutherford, N. J., et al. (2011). Expanded GGGGCC Hexanucleotide Repeat in Noncoding Region of C9ORF72 Causes Chromosome 9p-Linked FTD and ALS. *Neuron* 72, 245–256. doi:10.1016/j.neuron.2011.09.011

Delaneau, O., Zazhytska, M., Borel, C., Giannuzzi, G., Rey, G., Howald, C., et al. (2019). Chromatin Three-Dimensional Interactions Mediate Genetic Effects on Gene Expression. *Science* 364, eaat8266. doi:10.1126/science.aat8266

Díaz de Bustamante, A., Ruiz-Casares, E., Darnaude, M. T., Perucho, T., and Martínez-Quesada, G. (2012). Phenotypic Variability in Marfan Syndrome in a Family with a Novel Nonsense FBN1 Gene Mutation. *Rev. Esp. Cardiol. Engl. Ed.* 65, 380–381. doi:10.1016/j.recesp.2011.05.027

Dick, I. E., Joshi-Mukherjee, R., Yang, W., and Yue, D. T. (2016). Arrhythmogenesis in Timothy Syndrome Is Associated with Defects in Ca2+-dependent Inactivation. *Nat. Commun.* 7, 10370. doi:10.1038/ncomms10370

Dickinson, M. E., Flenniken, A. M., Flenniken, A. M., Ji, X., Teboul, L., Wong, M. D., et al. (2016). High-throughput Discovery of Novel Developmental Phenotypes. *Nature* 537, 508–514. doi:10.1038/nature19356

Dietz, H. (1993). "FBN1-Related Marfan Syndrome," in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, et al. (Seattle, WA: University of Washington, Seattle).

Ding, J., Li, X., Tian, H., Wang, L., Guo, B., Wang, Y., et al. (2021). SCN1A Mutation-Beyond Dravet Syndrome: A Systematic Review and Narrative Synthesis. *Front. Neurol.* 12, 743726. doi:10.3389/fneur.2021.743726

Dolinoy, D., Weidman, J., and Jirtle, R. (2007). Epigenetic Gene Regulation: Linking Early Developmental Environment to Adult Disease. *Reprod. Toxicol.* 23, 297–307. doi:10.1016/j.reprotox.2006.08.012

Domogala, D. D., Gambin, T., Zemet, R., Wu, C. W., Schulze, K. V., Yang, Y., et al. (2021). Detection of Low-Level Parental Somatic Mosaicism for Clinically Relevant SNVs and Indels Identified in a Large Exome Sequencing Dataset. *Hum. Genomics* 15, 72. doi:10.1186/s40246-021-00369-6

Downs, B., Sherman, S., Cui, J., Kim, Y. C., Snyder, C., Christensen, M., et al. (2019). Common Genetic Variants Contribute to Incomplete Penetrance: Evidence from Cancer-free BRCA1 Mutation Carriers. *Eur. J. Cancer* 107, 68–78. doi:10.1016/j.ejca.2018.10.022

Dyle, M. C., Kolakada, D., Cortazar, M. A., and Jagannathan, S. (2020). How to Get Away with Nonsense: Mechanisms and Consequences of Escape from Nonsense-Mediated RNA Decay. *Wiley Interdiscip. Rev. RNA* 11, e1560. doi:10.1002/wrna.1560

Eckersley-Maslin, M. A., and Spector, D. L. (2014). Random Monoallelic Expression: Regulating Gene Expression One Allele at a Time. *Trends Genet.* 30, 237–244. doi:10.1016/j.tig.2014.03.003

El-Brolosy, M. A., and Stainier, D. Y. R. (2017). Genetic Compensation: A Phenomenon in Search of Mechanisms. *PLOS Genet.* 13, e1006780. doi:10.1371/journal.pgen.1006780

Elfatih, A., Mohammed, I., Abdelrahman, D., and Mifsud, B. (2021). Frequency and Management of Medically Actionable Incidental Findings from Genome and Exome Sequencing Data: a Systematic Review. *Physiol. Genomics* 53, 373–384. doi:10.1152/physiolgenomics.00025.2021

Ellingford, J. M., Ahn, J. W., Bagnall, R. D., Baralle, D., Barton, S., Campbell, C., et al. (2021). Recommendations for Clinical Interpretation of Variants Found in Non-coding Regions of the Genome. *Search life-sciences lit.* 12 (28), 21267792.

Emison, E. S., Garcia-Barcelo, M., Grice, E. A., Lantieri, F., Amiel, J., Burzynski, G., et al. (2010). Differential Contributions of Rare and Common, Coding and Noncoding Ret Mutations to Multifactorial Hirschsprung Disease Liability. *Am. J. Hum. Genet.* 87, 60–74. doi:10.1016/j.ajhg.2010.06.007

Emond, M. J., Louie, T., Louie, T., Emerson, J., Zhao, W., Mathias, R. A., et al. (2012). Exome Sequencing of Extreme Phenotypes Identifies DCTN4 as a Modifier of Chronic *Pseudomonas aeruginosa* Infection in Cystic Fibrosis. *Nat. Genet.* 44, 886–889. doi:10.1038/ng.2344

Epstein, D. J. (2009). Cis-regulatory Mutations in Human Disease. *Briefings Funct. Genomics Proteomics* 8, 310–316. doi:10.1093/bfgp/elp021

Erikson, G. A., Bodian, D. L., Rueda, M., Molparia, B., Scott, E. R., Scott-Van Zeeland, A. A., et al. (2016). Whole-Genome Sequencing of a Healthy Aging Cohort. *Cell.* 165, 1002–1011. doi:10.1016/j.cell.2016.03.022

Evans, D. W., and Uljarević, M. (2018). Parental Education Accounts for Variability in the IQs of Probands with Down Syndrome: A Longitudinal Study. *Am. J. Med. Genet.* 176, 29–33. doi:10.1002/ajmg.a.38519

Fahed, A. C., Wang, M., Homburger, J. R., Patel, A. P., Bick, A. G., Neben, C. L., et al. (2020). Polygenic Background Modifies Penetrance of Monogenic Variants for Tier 1 Genomic Conditions. *Nat. Commun.* 11, 3635. doi:10.1038/s41467-020-17374-3

Fahim, A. T., Bowne, S. J., Sullivan, L. S., Webb, K. D., Williams, J. T., Wheaton, D. K., et al. (2012). Polymorphic Variation of RPGRIP1L and IQCB1 as Modifiers of X-Linked Retinitis Pigmentosa Caused by Mutations in RPGR. *Adv. Exp. Med. Biol.* 723, 313–320. doi:10.1007/978-1-4614-0631-0_41

Falkenberg, K. D., Braverman, N. E., Moser, A. B., Steinberg, S. J., Klouwer, F. C. C., Schlüter, A., et al. (2017). Allelic Expression Imbalance Promoting a Mutant PEX6 Allele Causes Zellweger Spectrum Disorder. *Am. J. Hum. Genet.* 101, 965–976. doi:10.1016/j.ajhg.2017.11.007

Faure, A. J., Domingo, J., Schmiedel, J. M., Hidalgo-Carcedo, C., Diss, G., and Lehner, B. (2022). Mapping the Energetic and Allosteric Landscapes of Protein Binding Domains. *Nature* 604, 175–183. doi:10.1038/s41586-022-04586-4

Ferreira, J., Gutiérrez, J. C. L., Carneiro, A., Araújo, A., Sousa, P. P., Braga, S., et al. (2021). CLOVES Syndrome Diagnosis and Treatment in an Adult Patient. *Ann. Vasc. Surg.* 75, 533.e5–e9. doi:10.1016/j.avsg.2021.03.044

Fetit, R., Price, D. J., Lawrie, S. M., and Johnstone, M. (2020). Understanding the Clinical Manifestations of 16p11.2 Deletion Syndrome: a Series of Developmental Case Reports in Children. *Psychiatr. Genet.* 30, 136–140. doi:10.1097/ypg.0000000000000259

Fink, D. A., Nelson, L. M., Pyeritz, R., Johnson, J., Sherman, S. L., Cohen, Y., et al. (2018). Fragile X Associated Primary Ovarian Insufficiency (FXPOI): Case Report and Literature Review. *Front. Genet.* 9, 529. doi:10.3389/fgene.2018.00529

Flannick, J., Beer, N. L., Bick, A. G., Agarwala, V., Molnes, J., Gupta, N., et al. (2013). Assessing the Phenotypic Effects in the General Population of Rare Variants in Genes for a Dominant Mendelian Form of Diabetes. *Nat. Genet.* 45, 1380–1385. doi:10.1038/ng.2794

Flower, M., Lomeikaite, V., Ciosi, M., Cumming, S., Morales, F., Lo, K., et al. (2019). MSH3 Modifies Somatic Instability and Disease Severity in Huntington's and Myotonic Dystrophy Type 1. *Brain* 142, 1876–1886. doi:10.1093/brain/awz115

Flydal, M. I., and Martinez, A. (2013). Phenylalanine Hydroxylase: Function, Structure, and Regulation. *IUBMB Life* 65, 341–349. doi:10.1002/iub.1150

Franke, M., Ibrahim, D. M., Andrey, G., Schwarzer, W., Heinrich, V., Schöpflin, R., et al. (2016). Formation of New Chromatin Domains Determines Pathogenicity of Genomic Duplications. *Nature* 538, 265–269. doi:10.1038/nature19800

Freund, M. K., Burch, K. S., Shi, H., Mancuso, N., Kichaev, G., Garske, K. M., et al. (2018). Phenotype-Specific Enrichment of Mendelian Disorder Genes Near GWAS Regions across 62 Complex Traits. *Am. J. Hum. Genet.* 103, 535–552. doi:10.1016/j.ajhg.2018.08.017

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., et al. (2017). Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants with Those of the General Population. *Am. J. Epidemiol.* 186, 1026–1034. doi:10.1093/aje/kwx246

Gallagher, S., Hughes, E., Wagner, S., Tshiaba, P., Rosenthal, E., Roa, B. B., et al. (2020). Association of a Polygenic Risk Score with Breast Cancer Among Women Carriers of High- and Moderate-Risk Breast Cancer Genes. *JAMA Netw. Open* 3, e208501. doi:10.1001/jamanetworkopen.2020.8501

Galupa, R., and Heard, E. (2017). Topologically Associating Domains in Chromosome Architecture and Gene Regulatory Landscapes during Development, Disease, and Evolution. *Cold Spring Harb. Symp. Quant. Biol.* 82, 267–278. doi:10.1101/sqb.2017.82.035030

Gerrits, M. C. F., Foncke, E. M. J., Koelman, J. H. T. M., and Tijssen, M. a. J. (2009). Pediatric Writer's Cramp in Myoclonus-Dystonia: Maternal Imprinting Hides Positive Family History. *Eur. J. Paediatr. Neurology* 13, 178–180. doi:10.1016/j.ejpn.2008.03.007

Girirajan, S., Rosenfeld, J. A., Cooper, G. M., Antonacci, F., Siswara, P., Itsara, A., et al. (2010). A Recurrent 16p12.1 Microdeletion Supports a Two-Hit Model for Severe Developmental Delay. *Nat. Genet.* 42, 203–209. doi:10.1038/ng.534

Glazier, A. A., Thompson, A., and Day, S. M. (2019). Allelic Imbalance and Haploinsufficiency in MYBPC3-Linked Hypertrophic Cardiomyopathy. *Pflugers Arch. - Eur. J. Physiol.* 471, 781–793. doi:10.1007/s00424-018-2226-9

Goodrich, J. K., Singer-Berk, M., Son, R., Sveden, A., Wood, J., England, E., et al. (2021). Determinants of Penetrance and Variable Expressivity in Monogenic Metabolic Conditions across 77,184 Exomes. *Nat. Commun.* 12, 3505. doi:10.1038/s41467-021-23556-4

Gordon, A. S., Zouk, H., Venner, E., Eng, C. M., Funke, B. H., Amendola, L. M., et al. (2020). Frequency of Genomic Secondary Findings Among 21,915 eMERGE Network Participants. *Genet. Med.* 22, 1470–1477. doi:10.1038/s41436-020-0810-9

Goula, A.-V., and Merienne, K. (2013). Abnormal Base Excision Repair at Trinucleotide Repeats Associated with Diseases: A Tissue-Selective Mechanism. *Genes.* 4, 375–387. doi:10.3390/genes4030375

Green, D. J., Sallah, S. R., Ellingford, J. M., Lovell, S. C., and Sergouniotis, P. I. (2020). Variability in Gene Expression Is Associated with Incomplete Penetrance in Inherited Eye Disorders. *Genes.* 11, 179. doi:10.3390/genes11020179

Gripp, K. W., and Rauen, K. A. (1993). "Costello Syndrome," in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, and A. Amemiya (Seattle (WA): University of Washington, Seattle).

Gross, M., Hanenberg, H., Lobitz, S., Friedl, R., Herterich, S., Dietrich, R., et al. (2002). Reverse Mosaicism in Fanconi Anemia: Natural Gene Therapy via Molecular Self-Correction. *Cytogenet. Genome Res.* 98, 126–135. doi:10.1159/000069805

Gruber, C., and Bogunovic, D. (2020). Incomplete Penetrance in Primary Immunodeficiency: a Skeleton in the Closet. *Hum. Genet.* 139, 745–757. doi:10.1007/s00439-020-02131-9

Gu, Y., Harley, I. T. W., Henderson, L. B., Aronow, B. J., Vietor, I., Huber, L. A., et al. (2009). Identification of IFRD1 as a Modifier Gene for Cystic Fibrosis Lung Disease. *Nature* 458, 1039–1042. doi:10.1038/nature07811

Gudmundsson, S., Singer-Berk, M., Watts, N. A., Phu, W., Goodrich, J. K., Solomonson, M., et al. (2021). *Genome Aggregation Database Consortium*. doi:10.1002/humu.24309Variant Interpretation Using Population Databases: Lessons from gnomAD*Hum. Mutat.*

Gui, B., Slone, J., and Huang, T. (2017). Perspective: Is Random Monoallelic Expression a Contributor to Phenotypic Variability of Autosomal Dominant Disorders? *Front. Genet.* 8, 191. doi:10.3389/fgene.2017.00191

Guillot, L., Beucher, J., Tabary, O., Le Rouzic, P., Clement, A., and Corvol, H. (2014). Lung Disease Modifier Genes in Cystic Fibrosis. *Int. J. Biochem. Cell. Biol.* 52, 83–93. doi:10.1016/j.biocel.2014.02.011

Haendel, M., Vasilevsky, N., Unni, D., Bologa, C., Harris, N., Rehm, H., et al. (2020). How Many Rare Diseases Are There? *Nat. Rev. Drug Discov.* 19, 77–78. doi:10.1038/d41573-019-00180-y

Haeri, M., and Knox, B. E. (2012). Endoplasmic Reticulum Stress and Unfolded Protein Response Pathways: Potential for Treating Age-Related Retinal Degeneration. *J. Ophthalmic Vis. Res.* 7, 45–59.

Hagerman, R. J., Berry-Kravis, E., Hazlett, H. C., Bailey, D. B., Moine, H., Kooy, R. F., et al. (2017). Fragile X Syndrome. *Nat. Rev. Dis. Prim.* 3, 17065. doi:10.1038/nrdp.2017.65

Hammer, M. F., Ishii, A., Johnstone, L., Tchourbanov, A., Lau, B., Sprissler, R., et al. (2017). Rare Variants of Small Effect Size in Neuronal Excitability Genes Influence Clinical Outcome in Japanese Cases of SCN1A Truncation-Positive Dravet Syndrome. *PLOS ONE* 12, e0180485. doi:10.1371/journal.pone.0180485

Hanany, M., and Sharon, D. (2019). Allele Frequency Analysis of Variants Reported to Cause Autosomal Dominant Inherited Retinal Diseases Question the Involvement of 19% of Genes and 10% of Reported Pathogenic Variants. *J. Med. Genet.* 56, 536–542. doi:10.1136/jmedgenet-2018-105971

Hanson, E., Bernier, R., Porche, K., Jackson, F. I., Goin-Kochel, R. P., Snyder, L. G., et al. (2015). The Cognitive and Behavioral Phenotype of the 16p11.2 Deletion in a Clinically Ascertained Population. *Biol. Psychiatry* 77, 785–793. doi:10.1016/j.biopsych.2014.04.021

Harper, A. R., Goel, A., Goel, A., Grace, C., Thomson, K. L., Petersen, S. E., et al. (2021). Common Genetic Variants and Modifiable Risk Factors Underpin Hypertrophic Cardiomyopathy Susceptibility and Expressivity. *Nat. Genet.* 53, 135–142. doi:10.1038/s41588-020-00764-0

Harrison, S. M., and Rehm, H. L. (2019). Is 'likely Pathogenic' Really 90% Likely? Reclassification Data in ClinVar. *Genome Med.* 11, 72. doi:10.1186/s13073-019-0688-9

Hart, M. R., Biesecker, B. B., Blout, C. L., Christensen, K. D., Amendola, L. M., Bergstrom, K. L., et al. (2019). Secondary Findings from Clinical Genomic Sequencing: Prevalence, Patient Perspectives, Family History Assessment, and Health-Care Costs from a Multisite Study. *Genet. Med.* 21, 1100–1110. doi:10.1038/s41436-018-0308-x

Hassanin, E., May, P., Aldisi, R., Krawitz, P., Maj, C., and Bobbili, D. R. (2021). Assessing the Role of Polygenic Background on the Penetrance of Monogenic Forms in Parkinson's Disease. *Medrxiv*. doi:10.1101/2021.06.06.21253270

Helmbacher, F., Schneider-Maunoury, S., Topilko, P., Tiret, L., and Charnay, P. (2000). Targeting of the EphA4 Tyrosine Kinase Receptor Affects Dorsal/ventral Pathfinding of Limb Motor Axons. *Dev. Camb. Engl.* 127, 3313–3324. doi:10.1242/dev.127.15.3313

Hervé, B., Roume, J., Cognard, S., Fauvert, D., Molina-Gomes, D., and Vialard, F. (2015). Low-level Mosaicism of a De Novo Derivative Chromosome 9 from a t(5;9)(q35.1;q34.3) Has a Major Phenotypic Impact. *Eur. J. Med. Genet.* 58, 346–350. doi:10.1016/j.ejmg.2015.04.005

Hesson, L. B., Packham, D., Kwok, C. T., Nunez, A. C., Ng, B., Schmidt, C., et al. (2015). Lynch Syndrome Associated with Two MLH1 Promoter Variants and Allelic Imbalance of MLH1 Expression. *Hum. Mutat.* 36, 622–630. doi:10.1002/humu.22785

Heusinkveld, L. E., Yim, E., Yang, A., Azani, A. B., Liu, Q., Gao, J.-L., et al. (2017). Pathogenesis, Diagnosis and Therapeutic Strategies in WHIM Syndrome Immunodeficiency. *Expert Opin. Orphan Drugs* 5, 813–825. doi:10.1080/21678707.2017.1375403

Hildebrand, M. S., Jackson, V. E., Scerri, T. S., Van Reyk, O., Coleman, M., Braden, R. O., et al. (2020). Severe Childhood Speech Disorder. *Neurology* 94, e2148–e2167. doi:10.1212/wnl.0000000000009441

Høie, M. H., Cagiada, M., Beck Frederiksen, A. H., Stein, A., and Lindorff-Larsen, K. (2022). Predicting and Interpreting Large-Scale Mutagenesis Data Using Analyses of Protein Stability and Conservation. *Cell. Rep.* 38, 110207. doi:10.1016/j.celrep.2021.110207

Holm, I. A., Agrawal, P. B., Agrawal, P. B., Ceyhan-Birsoy, O., Christensen, K. D., Fayer, S., et al. (2018). The BabySeq Project: Implementing Genomic Sequencing in Newborns. *BMC Pediatr.* 18, 225. doi:10.1186/s12887-018-1200-1

Holmans, P. A., Massey, T. H., and Jones, L. (2017). Genetic Modifiers of Mendelian Disease: Huntington's Disease and the Trinucleotide Repeat Disorders. *Hum. Mol. Genet.* 26, R83–R90. doi:10.1093/hmg/ddx261

Honda, A., Umegaki-Arao, N., Sasaki, T., Nakabayashi, K., Hata, K., Matsubara, Y., et al. (2017). Somatic HRAS p.G12S Mosaic Mutation Causes Unilaterally Distributed Epidermal Nevi, Woolly Hair and Palmoplantar Keratosis. *J. Dermatol.* 44, e109–e110. doi:10.1111/1346-8138.13801

Hopp, K., Cornec-Le Gall, E., Senum, S. R., Te Paske, I. B. A. W., Raj, S., Lavu, S., et al. (2020). Detection and Characterization of Mosaicism in Autosomal Dominant Polycystic Kidney Disease. *Kidney Int.* 97, 370–382. doi:10.1016/j.kint.2019.08.038

Hosseini, S. M., Kim, R., Udupa, S., Costain, G., Jobling, R., Liston, E., et al. (2018). Reappraisal of Reported Genes for Sudden Arrhythmic Death. *Circulation* 138, 1195–1205. doi:10.1161/circulationaha.118.035070

Hou, Y., Gratz, H. P., Ureña-Bailén, G., Gratz, P. G., Schilbach-Stückle, K., Renno, T., et al. (2021). Somatic Reversion of a Novel IL2RG Mutation Resulting in Atypical X-Linked Combined Immunodeficiency. *Genes.* 13, 35. doi:10.3390/genes13010035

Huang, L., and Wilkinson, M. F. (2012). Regulation of Nonsense-Mediated mRNA Decay. *WIREs RNA* 3, 807–828. doi:10.1002/wrna.1137

Hunter, P. (2022). Understanding Redundancy and Resilience. *EMBO Rep.* 23, e54742. doi:10.15252/embr.202254742

Huyghe, J. R., Bien, S. A., Harrison, T. A., Kang, H. M., Chen, S., Schmit, S. L., et al. (2019). Discovery of Common and Rare Genetic Risk Variants for Colorectal Cancer. *Nat. Genet.* 51, 76–87. doi:10.1038/s41588-018-0286-6

Ibrahim, D. M., Tayebi, N., Knaus, A., Stiege, A. C., Sahebzamani, A., Hecht, J., et al. (2016). A Homozygous HOXD13 Missense Mutation Causes a Severe Form of Synpolydactyly with Metacarpal to Carpal Transformation. *Am. J. Med. Genet.* 170, 615–621. doi:10.1002/ajmg.a.37464

Inoue, K., Khajavi, M., Ohyama, T., Hirabayashi, S.-i., Wilson, J., Reggin, J. D., et al. (2004). Molecular Mechanism for Distinct Neurological Phenotypes Conveyed by Allelic Truncating Mutations. *Nat. Genet.* 36, 361–369. doi:10.1038/ng1322

Ittisoponpisan, S., Alhuzimi, E., Sternberg, M. J. E., and David, A. (2017). Landscape of Pleiotropic Proteins Causing Human Disease: Structural and System Biology Insights. *Hum. Mutat.* 38, 289–296. doi:10.1002/humu.23155

Ittisoponpisan, S., Islam, S. A., Khanna, T., Alhuzimi, E., David, A., and Sternberg, M. J. E. (2019). Can Predicted Protein 3D Structures Provide Reliable Insights into whether Missense Variants Are Disease Associated?. *J. Mol. Biol.* 431 (11), 2197–2212. doi:10.1016/j.jmb.2019.04.009

Jackson, L., Weedon, M. N., Harrison, J., Wood, A. R., Ruth, K. S., Tyrrell, J., and Wright, C. (2022). Influence of family history on penetrance of hereditary cancers in a population setting. *Medrxiv.* 94, 415–425. doi:10.1101/2022.07.08.22277415

Jacquemont, S., Coe, B. P., Hersch, M., Duyzend, M. H., Krumm, N., Bergmann, S., et al. (2014). A Higher Mutational Burden in Females Supports a "Female Protective Model" in Neurodevelopmental Disorders. *Am. J. Hum. Genet.* 94, 415–425. doi:10.1016/j.ajhg.2014.02.001

Jansen, R.-P. (2001). mRNA Localization: Message on the Move. *Nat. Rev. Mol. Cell. Biol.* 2, 247–256. doi:10.1038/35067016

Jindal, R., Shirazi, N., and Rawat, K. (2019). Hereditary Segmental Neurofibromatosis: a Report of Three Cases in a Family. *BMJ Case Rep.* 12, e228826. doi:10.1136/bcr-2018-228826

Jing, H., Zhang, Q., Zhang, Y., Hill, B. J., Dove, C. G., Gelfand, E. W., et al. (2014). Somatic Reversion in Dedicator of Cytokinesis 8 Immunodeficiency Modulates Disease Phenotype. *J. Allergy Clin. Immunol.* 133, 1667–1675. doi:10.1016/j.jaci.2014.03.025

Johnston, J. J., Lewis, K. L., Ng, D., Singh, L. N., Wynter, J., Brewer, C., et al. (2015). Individualized Iterative Phenotyping for Genome-wide Analysis of Loss-Of-Function Mutations. *Am. J. Hum. Genet.* 96, 913–925. doi:10.1016/j.ajhg.2015.04.013

Johnston, J. J., Rubinstein, W. S., Facio, F. M., Ng, D., Singh, L. N., Teer, J. K., et al. (2012). Secondary Variants in Individuals Undergoing Exome Sequencing: Screening of 572 Individuals Identifies High-Penetrance Mutations in Cancer-Susceptibility Genes. *Am. J. Hum. Genet.* 91, 97–108. doi:10.1016/j.ajhg.2012.05.021

Jordan, D. M., Frangakis, S. G., Frangakis, S. G., Golzio, C., Cassa, C. A., Kurtzberg, J., et al. (2015). Identification of Cis-Suppression of Human Disease Mutations by Comparative Genomics. *Nature* 524, 225–229. doi:10.1038/nature14497

Jordan, W., Rieder, L. E., and Larschan, E. (2019). Diverse Genome Topologies Characterize Dosage Compensation across Species. *Trends Genet.* 35, 308–315. doi:10.1016/j.tig.2019.02.001

Kalia, S. S., Adelman, K., Bale, S. J., Chung, W. K., Eng, C., Evans, J. P., et al. (2017). Recommendations for Reporting of Secondary Findings in Clinical Exome and Genome Sequencing, 2016 Update (ACMG SF v2.0): a Policy Statement of the American College of Medical Genetics and Genomics. *Genet. Med.* 19, 249–255. doi:10.1038/gim.2016.190

Kammenga, J. E. (2017). The Background Puzzle: How Identical Mutations in the Same Gene Lead to Different Disease Symptoms. *FEBS J.* 284, 3362–3373. doi:10.1111/febs.14080

Kay, C., Collins, J. A., Miedzybrodzka, Z., Madore, S. J., Gordon, E. S., Gerry, N., et al. (2016). Huntington Disease Reduced Penetrance Alleles Occur at High Frequency in the General Population. *Neurology* 87, 282–288. doi:10.1212/wnl.0000000000002858

Kennedy, J., Goudie, D., Blair, E., Chandler, K., Joss, S., McKay, V., et al. (2019). KAT6A Syndrome: Genotype-Phenotype Correlation in 76 Patients with Pathogenic KAT6A Variants. *Genet. Med.* 21, 850–860. doi:10.1038/s41436-018-0259-2

Kerr, T. P., Sewry, C. A., Robb, S. A., and Roberts, R. G. (2001). Long Mutant Dystrophins and Variable Phenotypes: Evasion of Nonsense-Mediated Decay? *Hum. Genet.* 109, 402–407. doi:10.1007/s004390100598

Khajavi, M., Inoue, K., and Lupski, J. R. (2006). Nonsense-mediated mRNA Decay Modulates Clinical Outcome of Genetic Disease. *Eur. J. Hum. Genet.* 14, 1074–1081. doi:10.1038/sj.ejhg.5201649

Khanna, H., Davis, E. E., Murga-Zamalloa, C. A., Estrada-Cuzcano, A., Lopez, I., den Hollander, A. I., et al. (2009). A Common Allele in RPGRIP1L Is a Modifier of Retinal Degeneration in Ciliopathies. *Nat. Genet.* 41, 739–745. doi:10.1038/ng.366

Kharbanda, M., Kannike, K., Lampe, A., Berg, J., Timmusk, T., and Sepp, M. (2016). Partial Deletion of TCF4 in Three Generation Family with Non-syndromic Intellectual Disability, without Features of Pitt-Hopkins Syndrome. *Eur. J. Med. Genet.* 59, 310–314. doi:10.1016/j.ejmg.2016.04.003

Khera, A. V., Chaffin, M., Aragam, K. G., Haas, M. E., Roselli, C., Choi, S. H., Natarajan, P., Lander, E. S., Lubitz, S. A., Ellinor, P. T., and Kathiresan, S. (2018). Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* 50, 1219–1224. doi:10.1038/s41588-018-0183-z

Kim, E., Napierala, M., and Dent, S. Y. R. (2011). Hyperexpansion of GAA Repeats Affects Post-initiation Steps of FXN Transcription in Friedreich's Ataxia. *Nucleic Acids Res.* 39, 8366–8377. doi:10.1093/nar/gkr542

Kim, Y., and Connor, J. R. (2020). The Roles of Iron and HFE Genotype in Neurological Diseases. *Mol. Aspects Med.* 75, 100867. doi:10.1016/j.mam.2020.100867

Kingdom, R., Tuke, M., Wood, A., Beaumont, R. N., Frayling, T., Weedon, M. N., et al. (2022). Rare Genetic Variants in Dominant Developmental Disorder Loci Cause Milder Related Phenotypes in the General Population. *AJHG in Press.*

Kishore, S., De Franco, E., Cardenas-Diaz, F. L., Letourneau-Freiberg, L. R., Sanyoura, M., Osorio-Quintero, C., et al. (2020). A Non-coding Disease Modifier of Pancreatic Agenesis Identified by Genetic Correction in a Patient-Derived iPSC Line. *Cell. Stem Cell.* 27, 137–146. e6. doi:10.1016/j.stem.2020.05.001

Klaassen, K., Djordjevic, M., Skakic, A., Kecman, B., Drmanac, R., Pavlovic, S., et al. (2021). Untreated PKU Patients without Intellectual Disability: SHANK Gene Family as a Candidate Modifier. *Mol. Genet. Metabolism Rep.* 29, 100822. doi:10.1016/j.ymgmr.2021.100822

Klaassen, P., Duijff, S., Swanenburg de Veye, H., Beemer, F., Sinnema, G., Breetvelt, E., et al. (2016). Explaining the Variable Penetrance of CNVs: Parental Intelligence Modulates Expression of Intellectual Impairment Caused by the 22q11.2 Deletion. *Am. J. Med. Genet.* 171, 790–796. doi:10.1002/ajmg.b.32441

Kolder, I. C. R. M., Tanck, M. W. T., Postema, P. G., Barc, J., Sinner, M. F., Zumhagen, S., et al. (2015). Analysis for Genetic Modifiers of Disease Severity in Patients with Long-QT Syndrome Type 2. *Circ. Cardiovasc. Genet.* 8, 447–456. doi:10.1161/circgenetics.114.000785

Kraemer, K. H., and DiGiovanna, J. J. (1993). "Xeroderma Pigmentosum," in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, et al. (Seattle, WA: University of Washington, Seattle).

Kuchenbaecker, K. B., McGuffog, L., Barrowdale, D., Lee, A., Soucy, P., Dennis, J., et al. (2017). Evaluation of Polygenic Risk Scores for Breast and Ovarian Cancer Risk Prediction in BRCA1 and BRCA2 Mutation Carriers. *J. Natl. Cancer Inst.* 109. doi:10.1093/jnci/djw302

Kumar, K. R., Davis, R. L., Tchan, M. C., Wali, G. M., Mahant, N., Ng, K., et al. (2019). Whole Genome Sequencing for the Genetic Diagnosis of Heterogenous Dystonia Phenotypes. *Park. Relat. Disord.* 69, 111–118. doi:10.1016/j.parkreldis.2019.11.004

Lacaze, P., Sebra, R., Riaz, M., Tiller, J., Revote, J., Phung, J., et al. (2020). Medically Actionable Pathogenic Variants in a Population of 13,131 Healthy Elderly Individuals. *Genet. Med.* 22, 1883–1886. doi:10.1038/s41436-020-0881-7

Lachmann, R. H., Grant, I. R., Halsall, D., and Cox, T. M. (2004). Twin Pairs Showing Discordance of Phenotype in Adult Gaucher's Disease. *Qjm* 97, 199–204. doi:10.1093/qjmed/hch036

Lareau, L. F., and Brenner, S. E. (2015). Regulation of Splicing Factors by Alternative Splicing and NMD Is Conserved between Kingdoms yet Evolutionarily Flexible. *Mol. Biol. Evol.* 32, 1072–1079. doi:10.1093/molbev/msv002

Laskaratos, A., Breza, M., Karadima, G., and Koutsis, G. (2021). Wide Range of Reduced Penetrance Alleles in Spinal and Bulbar Muscular Atrophy: a Model-Based Approach. *J. Med. Genet.* 58, 385–391. doi:10.1136/jmedgenet-2020-106963

Lauritsen, K. F., Lildballe, D. L., Coucke, P. J., Monrad, R., Larsen, D. A., and Gregersen, P. A. (2017). A Mild Form of Stickler Syndrome Type II Caused by Mosaicism of COL11A1. *Eur. J. Med. Genet.* 60, 275–278. doi:10.1016/j.ejmg.2017.03.005

Lawson, D. J., Davies, N. M., Haworth, S., Ashraf, B., Howe, L., Crawford, A., et al. (2020). Is Population Structure in the Genetic Biobank Era Irrelevant, a Challenge, or an Opportunity? *Hum. Genet.* 139, 23–41. doi:10.1007/s00439-019-02014-8

Lee, A., Mavaddat, N., Wilcox, A. N., Cunningham, A. P., Carver, T., Hartley, S., et al. (2019). BOADICEA: a Comprehensive Breast Cancer Risk Prediction Model Incorporating Genetic and Nongenetic Risk Factors. *Genet. Med.* 21, 1708–1718. doi:10.1038/s41436-018-0406-9

Lee, D. S. M., Park, J., Kromer, A., Baras, A., Rader, D. J., Ritchie, M. D., et al. (2021). Disrupting Upstream Translation in mRNAs Is Associated with Human Disease. *Nat. Commun.* 12, 1515. doi:10.1038/s41467-021-21812-1

Lee, I., Lehner, B., Vavouri, T., Shin, J., Fraser, A. G., and Marcotte, E. M. (2010). Predicting Genetic Modifier Loci Using Functional Gene Networks. *Genome Res.* 20, 1143–1153. doi:10.1101/gr.102749.109

Lee, J., Meyerhardt, J. A., Giovannucci, E., and Jeon, J. Y. (2015). Association between Body Mass Index and Prognosis of Colorectal Cancer: A Meta-Analysis of Prospective Cohort Studies. *PLoS ONE* 10, e0120706. doi:10.1371/journal.pone.0120706

Lee, W., Zernant, J., Nagasaki, T., Molday, L. L., Su, P.-Y., Fishman, G. A., et al. (2021). Cis-acting Modifiers in the ABCA4 Locus Contribute to the Penetrance of the Major Disease-Causing Variant in Stargardt Disease. *Hum. Mol. Genet.* 30, 1293–1304. doi:10.1093/hmg/ddab122

Lek, M., Karczewski, K. J., Karczewski, K. J., Minikel, E. V., Samocha, K. E., Banks, E., et al. (2016). Analysis of Protein-Coding Genetic Variation in 60,706 Humans. *Nature* 536, 285–291. doi:10.1038/nature19057

Leon, E., Jamal, S. M., Zou, Y. S., and Milunsky, J. M. (2011). Partial Trisomy 8 Mosaicism Due to a Pseudoisodicentric Chromosome 8. *Am. J. Med. Genet.* 155, 1740–1744. doi:10.1002/ajmg.a.34073

Leopold, P., Amandine, B., Maykel, L., Michael, W. Y., Meredith, L., Bryan-Joseph, S. L., et al. (2021). Natural Variants Suppress Mutations in Hundreds of Essential Genes. *Mol. Syst. Biol.* 17, e10138. doi:10.15252/msb.202010138

Lewis, C. M., and Vassos, E. (2020). Polygenic Risk Scores: from Research Tools to Clinical Instruments. *Genome Med.* 12, 44. doi:10.1186/s13073-020-00742-5

Li, Q., Liang, P., Wang, S., Li, W., Wang, J., Yang, Y., et al. (2021). A Novel KCNQ4 Gene Variant (c.857A>G; p.Tyr286Cys) in an Extended Family with Non-syndromic D-eafness 2A. *Mol. Med. Rep.* 23, 420. doi:10.3892/mmr.2021.12059

Li, X.-H., and Babu, M. M. (2018). Human Diseases from Gain-Of-Function Mutations in Disordered Protein Regions. *Cell.* 175, 40–42. doi:10.1016/j.cell.2018.08.059

Li, Y., Wang, Y., Ming, Y., Chaolan, P., Jia, Z., Cheng, N., et al. (2021). A KRT6A Mutation p.Ile462Asn in a Chinese Family with Pachyonychia Congenita, and Identification of Maternal Mosaicism: a Case Report. *BMC Med. Genomics* 14, 259. doi:10.1186/s12920-021-01109-4

Lindeboom, R. G. H., Supek, F., and Lehner, B. (2016). The Rules and Impact of Nonsense-Mediated mRNA Decay in Human Cancers. *Nat. Genet.* 48, 1112–1118. doi:10.1038/ng.3664

Liu, X.-R., Xu, X.-X., Lin, S.-M., Fan, C.-Y., Ye, T.-T., Tang, B., et al. (2021). GRIN2A Variants Associated with Idiopathic Generalized Epilepsies. *Front. Mol. Neurosci.* 14, 720984. doi:10.3389/fnmol.2021.720984

Lu, L., Liu, X., Huang, W.-K., Giusti-Rodríguez, P., Cui, J., Zhang, S., et al. (2020). Robust Hi-C Maps of Enhancer-Promoter Interactions Reveal the Function of Non-coding Genome in Neural Development and Diseases. *Mol. Cell.* 79, 521–534. e15. doi:10.1016/j.molcel.2020.06.007

Lu, Y.-Y., and Krebber, H. (2021). Nuclear mRNA Quality Control and Cytoplasmic NMD Are Linked by the Guard Proteins Gbp2 and Hrb1. *Int. J. Mol. Sci.* 22, 11275. doi:10.3390/ijms222011275

Lupiáñez, D. G., Kraft, K., Heinrich, V., Krawitz, P., Brancati, F., Klopocki, E., et al. (2015). Disruptions of Topological Chromatin Domains Cause Pathogenic Rewiring of Gene-Enhancer Interactions. *Cell.* 161, 1012–1025. doi:10.1016/j.cell.2015.04.004

Magri, S., Nanetti, L., Gellera, C., Sarto, E., Rizzo, E., Mongelli, A., et al. (2022). Digenic Inheritance of STUB1 Variants and TBP Polyglutamine Expansions Explains the Incomplete Penetrance of SCA17 and SCA48. *Genet. Med.* 24, 29–40. doi:10.1016/j.gim.2021.08.003

Magrinelli, F., Balint, B., and Bhatia, K. P. (2021). Challenges in Clinicogenetic Correlations: One Gene - Many Phenotypes. *Mov. Disord. Clin. Pract.* 8, 299–310. doi:10.1002/mdc3.13165

Mahat, U., Ambani, N. M., Rotz, S. J., and Radhakrishnan, K. (2021). Heterozygous CTLA4 Splice Site Mutation c.458-1G > C Presenting with Immunodeficiency and Variable Degree of Immune Dysregulation in Three Generation Kindred of Caribbean Descent. *Pediatr. Hematol. Oncol.* 38, 658–662. doi:10.1080/08880018.2021.1906802

Manrai, A. K., Funke, B. H., Rehm, H. L., Olesen, M. S., Maron, B. A., Szolovits, P., et al. (2016). Genetic Misdiagnoses and the Potential for Health Disparities. *N. Engl. J. Med.* 375, 655–665. doi:10.1056/nejmsa1507092

Marian, A. J., and Braunwald, E. (2017). Hypertrophic Cardiomyopathy. *Circ. Res.* 121, 749–770. doi:10.1161/circresaha.117.311059

Maroilley, T., and Tarailo-Graovac, M. (2019). Uncovering Missing Heritability in Rare Diseases. *Genes.* 10, 275. doi:10.3390/genes10040275

Masnada, S., Hedrich, U. B. S., Gardella, E., Schubert, J., Kaiwar, C., Klee, E. W., et al. (2017). Clinical Spectrum and Genotype-Phenotype Associations of KCNA2-Related Encephalopathies. *Brain J. Neurol.* 140, 2337–2354. doi:10.1093/brain/awx184

Massey, T. H., and Jones, L. (2018). The Central Role of DNA Damage and Repair in CAG Repeat Diseases. *Dis. Model. Mech.* 11, dmm031930. doi:10.1242/dmm.031930

Mastromoro, G., Capalbo, A., Guido, C. A., Torres, B., Fabbretti, M., Traversa, A., et al. (2020). Small 7p22.3 Microdeletion: Case Report of Snx8 Haploinsufficiency and Neurological Findings. *Eur. J. Med. Genet.* 63, 103772. doi:10.1016/j.ejmg.2019.103772

Maussion, G., Cruceanu, C., Rosenfeld, J. A., Bell, S. C., Jollant, F., Szatkiewicz, J., et al. (2017). Implication of LRRC4C and DPP6 in Neurodevelopmental Disorders. *Am. J. Med. Genet.* 173, 395–406. doi:10.1002/ajmg.a.38021

McArthur, E., and Capra, J. A. (2021). Topologically Associating Domain Boundaries that Are Stable across Diverse Cell Types Are Evolutionarily Constrained and Enriched for Heritability. *Am. J. Hum. Genet.* 108, 269–283. doi:10.1016/j.ajhg.2021.01.001

McDermott, D. H., Gao, J.-L., Liu, Q., Siwicki, M., Martens, C., Jacobs, P., et al. (2015). Chromothriptic Cure of WHIM Syndrome. *Cell.* 160, 686–699. doi:10.1016/j.cell.2015.01.014

McDermott, J. H., Study, D. D. D., and Clayton-Smith, J. (2017). Sibling Recurrence of Total Anomalous Pulmonary Venous Drainage. *Eur. J. Med. Genet.* 60, 265–267. doi:10.1016/j.ejmg.2017.03.003

Mensa-Vilaró, A., Bravo García-Morato, M., de la Calle-Martin, O., Franco-Jarava, C., Martínez-Saavedra, M. T., González-Granado, L. I., et al. (2019). Unexpected Relevant Role of Gene Mosaicism in Patients with Primary Immunodeficiency Diseases. *J. Allergy Clin. Immunol.* 143, 359–368.

Michailidou, K., Lindström, S., Dennis, J., Beesley, J., Hui, S., Kar, S., et al. (2017). Association Analysis Identifies 65 New Breast Cancer Risk Loci. *Nature* 551, 92–94. doi:10.1038/nature24284

Mignone, F., Gissi, C., Liuni, S., and Pesole, G. (2002). Untranslated Regions of mRNAs. *Genome Biol.* 3, REVIEWS0004. doi:10.1186/gb-2002-3-3-reviews0004

Miller, E. E., Kobayashi, G. S., Musso, C. M., Allen, M., Ishiy, F. A. A., de Caires, L. C., et al. (2017). EIF4A3 Deficient Human iPSCs and Mouse Models Demonstrate Neural Crest Defects that Underlie Richieri-Costa-Pereira Syndrome. *Hum. Mol. Genet.* 26, 2177–2191. doi:10.1093/hmg/ddx078

Miller, J. N., and Pearce, D. A. (2014). Nonsense-mediated Decay in Genetic Disease: Friend or Foe? *Mutat. Research/Reviews Mutat. Res.* 762, 52–64. doi:10.1016/j.mrrev.2014.05.001

Minikel, E. V., Vallabh, S. M., Lek, M., Estrada, K., Samocha, K. E., Sathirapongsasuti, J. F., et al. (2016). Quantifying Penetrance in a Dominant Disease Gene Using Large Population Control Cohorts. *Sci. Transl. Med.* 8, 322ra9. doi:10.1126/scitranslmed.aad5169

Mirshahi, U. L., Colclough, K., Wright, C. F., Wood, A. R., Beaumont, R. N., Tyrrell, J., et al. (2021). The Penetrance of Age-Related Monogenic Disease Depends on Ascertainment Context. *MedRxiv* 2021, 21259641. doi:10.1101/2021.06.28.21259641

Miyazawa, H., and Wada, T. (2021). Reversion Mosaicism in Primary Immunodeficiency Diseases. *Front. Immunol.* 12, 783022. doi:10.3389/fimmu.2021.783022

Morales, F., Vásquez, M., Santamaría, C., Cuenca, P., Corrales, E., and Monckton, D. G. (2016). A Polymorphism in the MSH3 Mismatch Repair Gene Is Associated with the Levels of Somatic Instability of the Expanded CTG Repeat in the Blood DNA of Myotonic Dystrophy Type 1 Patients. *DNA Repair* 40, 57–66. doi:10.1016/j.dnarep.2016.01.001

Moreno-De-Luca, A., Evans, D. W., Boomer, K. B., Hanson, E., Bernier, R., Goin-Kochel, R. P., et al. (2015). The Role of Parental Cognitive, Behavioral, and Motor Profiles in Clinical Variability in Individuals with Chromosome 16p11.2 Deletions. *JAMA Psychiatry* 72, 119–126. doi:10.1001/jamapsychiatry.2014.2147

Moskwa, P., Buffa, F. M., Pan, Y., Panchakshari, R., Gottipati, P., Muschel, R. J., et al. (2011). miR-182-mediated Downregulation of BRCA1 Impacts DNA Repair and Sensitivity to PARP Inhibitors. *Mol. Cell.* 41, 210–220. doi:10.1016/j.molcel.2010.12.005

Muse, E. D., Chen, S.-F., and Torkamani, A. (2021). Monogenic and Polygenic Models of Coronary Artery Disease. *Curr. Cardiol. Rep.* 23, 107. doi:10.1007/s11886-021-01540-0

Musunuru, K., Strong, A., Frank-Kamenetsky, M., Lee, N. E., Ahfeldt, T., Sachs, K. V., et al. (2010). From Noncoding Variant to Phenotype via SORT1 at the 1p13 Cholesterol Locus. *Nature* 466, 714–719. doi:10.1038/nature09266

Nagy, E., and Maquat, L. E. (1998). A Rule for Termination-Codon Position within Intron-Containing Genes: when Nonsense Affects RNA Abundance. *Trends Biochem. Sci.* 23, 198–199. doi:10.1016/s0968-0004(98)01208-0

Nathan, N., Berdah, L., Delestrain, C., Sileo, C., and Clement, A. (20201983). Interstitial Lung Diseases in Children. *La Presse Médicale* 49, 103909. doi:10.1016/j.lpm.2019.06.007

Neeve, V. C. M., Samuels, D. C., Bindoff, L. A., van den Bosch, B., Van Goethem, G., Smeets, H., et al. (2012). What Is Influencing the Phenotype of the Common Homozygous Polymerase-γ Mutation p.Ala467Thr? *Brain J. Neurol.* 135, 3614–3626. doi:10.1093/brain/aws298

Newcomb, P. A., and Carbone, P. P. (1992). The Health Consequences of Smoking: Cancer. *Med. Clin. N. Am.* 76, 305–331. doi:10.1016/s0025-7125(16)30355-8

Ng, P. C., Levy, S., Huang, J., Stockwell, T. B., Walenz, B. P., Li, K., et al. (2008). Genetic Variation in an Individual Human Exome. *PLOS Genet.* 4, e1000160. doi:10.1371/journal.pgen.1000160

Nguengang Wakap, S., Lambert, D. M., Olry, A., Rodwell, C., Gueydan, C., Lanneau, V., et al. (2020). Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database. *Eur. J. Hum. Genet.* 28, 165–173. doi:10.1038/s41431-019-0508-0

Nguyen, L. S., Jolly, L., Shoubridge, C., Chan, W. K., Huang, L., Laumonnier, F., et al. (2012). Transcriptome Profiling of UPF3B/NMD-Deficient Lymphoblastoid Cells from Patients with Various Forms of Intellectual Disability. *Mol. Psychiatry* 17, 1103–1115. doi:10.1038/mp.2011.163

Nguyen, L. S., Kim, H.-G., Rosenfeld, J. A., Shen, Y., Gusella, J. F., Lacassie, Y., et al. (2013). Contribution of Copy Number Variants Involving Nonsense-Mediated mRNA Decay Pathway Genes to Neuro-Developmental Disorders. *Hum. Mol. Genet.* 22, 1816–1825. doi:10.1093/hmg/ddt035

Nguyen, L. S., Wilkinson, M. F., and Gecz, J. (2014). Nonsense-mediated mRNA Decay: Inter-individual Variability and Human Disease. *Neurosci. Biobehav. Rev.* 46, 175–186. doi:10.1016/j.neubiorev.2013.10.016

Nicoletti, E., Rao, G., Bueren, J. A., Río, P., Navarro, S., Surrallés, J., et al. (2020). Mosaicism in Fanconi Anemia: Concise Review and Evaluation of Published Cases with Focus on Clinical Course of Blood Count Normalization. *Ann. Hematol.* 99, 913–924. doi:10.1007/s00277-020-03954-2

Niday, Z., and Tzingounis, A. V. (2018). Potassium Channel Gain of Function in Epilepsy: An Unresolved Paradox. *Neuroscientist* 24, 368–380. doi:10.1177/1073858418763752

Niemi, M. E. K., Martin, H. C., Rice, D. L., Gallone, G., Gordon, S., Kelemen, M., et al. (2018). Common Genetic Variants Contribute to Risk of Rare Severe Neurodevelopmental Disorders. *Nature* 562, 268–271. doi:10.1038/s41586-018-0566-4

Oetjens, M. T., Kelly, M. A., Sturm, A. C., Martin, C. L., and Ledbetter, D. H. (2019). Quantifying the Polygenic Contribution to Variable Expressivity in Eleven Rare Genetic Disorders. *Nat. Commun.* 10, 4897. doi:10.1038/s41467-019-12869-0

Oliva, M., Muñoz-Aguirre, M., Kim-Hellmuth, S., Wucher, V., Gewirtz, A. D. H., Cotter, D. J., et al. (2020). The Impact of Sex on Gene Expression across Human Tissues. *Science* 369, eaba3066. doi:10.1126/science.aba3066

Olszewski, A. K., Radoeva, P. D., Fremont, W., Kates, W. R., and Antshel, K. M. (2014). Is Child Intelligence Associated with Parent and Sibling Intelligence in Individuals with Developmental Disorders? an Investigation in Youth with 22q11.2 Deletion (Velo-Cardio-Facial) Syndrome. *Res. Dev. Disabil.* 35, 3582–3590. doi:10.1016/j.ridd.2014.08.034

Omim (2022). OMIM Gene Map Statistics. Available at: https://www.omim.org/statistics/geneMap (Accessed 04 11, 2022).

Oprea, G. E., Kröber, S., McWhorter, M. L., Rossoll, W., Müller, S., Krawczak, M., et al. (2008). Plastin 3 Is a Protective Modifier of Autosomal Recessive Spinal Muscular Atrophy. *Science* 320, 524–527. doi:10.1126/science.1155085

Park, J. K., Martin, L. J., Zhang, X., Jegga, A. G., and Benson, D. W. (2012). Genetic Variants in SCN5A Promoter Are Associated with Arrhythmia Phenotype Severity in Patients with Heterozygous Loss-Of-Function Mutation. *Heart rhythm.* 9, 1090–1096. doi:10.1016/j.hrthm.2012.02.023

Pasmooij, A. M. G., Garcia, M., Escamez, M. J., Miranda Nijenhuis, A., Azon, A., Cuadrado-Corrales, N., et al. (2010). Revertant Mosaicism Due to a Second-Site Mutation in COL7A1 in a Patient with Recessive Dystrophic Epidermolysis Bullosa. *J. Investigative Dermatology* 130, 2407–2411. doi:10.1038/jid.2010.163

Paulson, H. (2018). Repeat Expansion Diseases. *Handb. Clin. Neurol.* 147, 105–123. doi:10.1016/b978-0-444-63233-3.00009-9

Payán-Gómez, C., Ramirez-Cheyne, J., and Saldarriaga, W. (2021). Variable Expressivity in Fragile X Syndrome: Towards the Identification of Molecular Characteristics that Modify the Phenotype. *Appl. Clin. Genet.* 14, 305–312.

Payne, J. L., and Wagner, A. (2015). Mechanisms of Mutational Robustness in Transcriptional Regulation. *Front. Genet.* 6, 322. doi:10.3389/fgene.2015.00322

Peltonen, L., Perola, M., Naukkarinen, J., and Palotie, A. (2006). Lessons from Studying Monogenic Disease for Common Disease. *Hum. Mol. Genet.* 15, R67–R74. doi:10.1093/hmg/ddl060

Pereira, S. V.-N., Ribeiro, J. D., Ribeiro, A. F., Bertuzzo, C. S., and Marson, F. A. L. (2019). Novel, Rare and Common Pathogenic Variants in the CFTR Gene Screened by High-Throughput Sequencing Technology and Predicted by In Silico Tools. *Sci. Rep.* 9, 6234. doi:10.1038/s41598-019-42404-6

Perez, B. A., Shorrock, H. K., Banez-Coronel, M., Zu, T., El Romano, L., Laboissonniere, L. A., et al. (2021). CCG●CGG Interruptions in High-Penetrance SCA8 Families Increase RAN Translation and Protein Toxicity. *EMBO Mol. Med.* 13, e14095. doi:10.15252/emmm.202114095

Petrovski, S., Gussow, A. B., Wang, Q., Halvorsen, M., Han, Y., Weir, W. H., et al. (2015). The Intolerance of Regulatory Sequence to Genetic Variation Predicts Gene Dosage Sensitivity. *PLOS Genet.* 11, e1005492. doi:10.1371/journal.pgen.1005492

Petrucelli, N., Daly, M. B., and Pal, T. (1993). BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, et al. (Seattle, WA: University of Washington, Seattle).

Pilling, L. C., Tamosauskaite, J., Jones, G., Wood, A. R., Jones, L., Kuo, C.-L., et al. (2019). Common Conditions Associated with Hereditary Haemochromatosis Genetic Variants: Cohort Study in UK Biobank. *BMJ* 364, k5222. doi:10.1136/bmj.k5222

Pinter, S. F., Colognori, D., Beliveau, B. J., Sadreyev, R. I., Payer, B., Yildirim, E., et al. (2015). Allelic Imbalance Is a Prevalent and Tissue-specific Feature of the Mouse Transcriptome. *Genetics* 200, 537–549. doi:10.1534/genetics.115.176263

Pipis, M., Cortese, A., Polke, J. M., Poh, R., Vandrovcova, J., Laura, M., et al. (2022). Charcot-Marie-Tooth Disease Type 2CC Due to NEFH Variants Causes a Progressive, Non-length-dependent, Motor-Predominant Phenotype. *J. Neurol. Neurosurg. Psychiatry* 93, 48–56. doi:10.1136/jnnp-2021-327186

Pizzo, L., Jensen, M., Polyak, A., Rosenfeld, J. A., Mannik, K., Krishnan, A., et al. (2019). Rare Variants in the Genetic Background Modulate Cognitive and Developmental Phenotypes in Individuals Carrying Disease-Associated Variants. *Genet. Med.* 21, 816–825. doi:10.1038/s41436-018-0266-3

Platzer, K., Yuan, H., Schütz, H., Winschel, A., Chen, W., Hu, C., et al. (2017). GRIN2Bencephalopathy: Novel Findings on Phenotype, Variant Clustering,

Functional Consequences and Treatment Aspects. *J. Med. Genet.* 54, 460–470. doi:10.1136/jmedgenet-2016-104509

Polyak, A., Rosenfeld, J. A., and Girirajan, S. (2015). An Assessment of Sex Bias in Neurodevelopmental Disorders. *Genome Med.* 7, 94. doi:10.1186/s13073-015-0216-5

Poot, M. (2015). Connecting the CNTNAP2 Networks with Neurodevelopmental Disorders. *Mol. Syndromol.* 6, 7–22. doi:10.1159/000371594

Posey, J. E., Harel, T., Liu, P., Rosenfeld, J. A., James, R. A., Coban Akdemir, Z. H., et al. (2017). Resolution of Disease Phenotypes Resulting from Multilocus Genomic Variation. *N. Engl. J. Med.* 376, 21–31. doi:10.1056/nejmoa1516767

Qiagen (2022). Human Gene Mutation Database (HGMD) Professional | QIAGEN. Available at: http://www.hgmd.cf.ac.uk/ac/index.php (Accessed 04 11, 2022).

Racanelli, A. C., Kikkers, S. A., Choi, A. M. K., and Cloonan, S. M. (2018). Autophagy and Inflammation in Chronic Respiratory Disease. *Autophagy* 14, 221–232. doi:10.1080/15548627.2017.1389823

Rahit, K. M. T. H., and Tarailo-Graovac, M. (2020). Genetic Modifiers and Rare Mendelian Disease. *Genes.* 11, 239. doi:10.3390/genes11030239

Ratto, A. B., Kenworthy, L., Yerys, B. E., Bascom, J., Wieckowski, A. T., White, S. W., et al. (2018). What about the Girls? Sex-Based Differences in Autistic Traits and Adaptive Skills. *J. Autism Dev. Disord.* 48, 1698–1711. doi:10.1007/s10803-017-3413-9

Raymond, D., Saunders-Pullman, R., and Ozelius, L. (1993). "SGCE Myoclonus-Dystonia," in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, et al. (Seattle (WA): University of Washington, Seattle).

Rieley, M. B., Stevenson, D. A., Viskochil, D. H., Tinkle, B. T., Martin, L. J., and Schorry, E. K. (2011). Variable Expression of Neurofibromatosis 1 in Monozygotic Twins. *Am. J. Med. Genet.* 155, 478–485. doi:10.1002/ajmg.a.33851

Rose, A. m., and Bhattacharya, S. s. (2016). Variant Haploinsufficiency and Phenotypic Non-penetrance inPRPF31-Associated Retinitis Pigmentosa. *Clin. Genet.* 90, 118–126. doi:10.1111/cge.12758

Rosenfeld, J. A., Coe, B. P., Eichler, E. E., Cuckle, H., and Shaffer, L. G. (2013). Estimates of Penetrance for Recurrent Pathogenic Copy-Number Variations. *Genet. Med.* 15, 478–481. doi:10.1038/gim.2012.164

Russell, G., Steer, C., and Golding, J. (2011). Social and Demographic Factors that Influence the Diagnosis of Autistic Spectrum Disorders. *Soc. Psychiatry Psychiatr. Epidemiol.* 46, 1283–1293. doi:10.1007/s00127-010-0294-z

Sacco, K. A., and Milner, J. D. (2019). Gene-environment Interactions in Primary Atopic Disorders. *Curr. Opin. Immunol.* 60, 148–155. doi:10.1016/j.coi.2019.06.002

Safi-Stibler, S., and Gabory, A. (2020). Epigenetics and the Developmental Origins of Health and Disease: Parental Environment Signalling to the Epigenome, Critical Time Windows and Sculpting the Adult Phenotype. *Seminars Cell. & Dev. Biol.* 97, 172–180. doi:10.1016/j.semcdb.2019.09.008

Sanna, S., van Zuydam, N. R., Mahajan, A., Kurilshikov, A., Vich Vila, A., Võsa, U., et al. (2019). Causal Relationships Among the Gut Microbiome, Short-Chain Fatty Acids and Metabolic Diseases. *Nat. Genet.* 51, 600–605. doi:10.1038/s41588-019-0350-x

Sarkar, H., Mitsios, A., Smart, M., Skinner, J., Welch, A. A., Kalatzis, V., et al. (2019). Nonsense-mediated mRNA Decay Efficiency Varies in Choroideremia Providing a Target to Boost Small Molecule Therapeutics. *Hum. Mol. Genet.* 28, 1865–1871. doi:10.1093/hmg/ddz028

Sarri, C. A., Roussaki-Schulze, A., Vasilopoulos, Y., Zafiriou, E., Patsatsi, A., Stamatis, C., et al. (2017). Netherton Syndrome: A Genotype-Phenotype Review. *Mol. Diagn. Ther.* 21, 137–152. doi:10.1007/s40291-016-0243-y

Sato, H., and Singer, R. H. (2021). Cellular Variability of Nonsense-Mediated mRNA Decay. *Nat. Commun.* 12, 7203. doi:10.1038/s41467-021-27423-0

Scacheri, C. A., and Scacheri, P. C. (2015). Mutations in the Noncoding Genome. *Curr. Opin. Pediatr.* 27, 659–664. doi:10.1097/mop.0000000000000283

Schacherer, J. (2016). Beyond the Simplicity of Mendelian Inheritance. *Comptes Rendus Biol.* 339, 284–288. doi:10.1016/j.crvi.2016.04.006

Schell, R., Hale, J. J., Mullis, M. N., Matsui, T., Foree, R., and Ehrenreich, I. M. (2022). Genetic Basis of a Spontaneous Mutation's Expressivity. *Genetics* 220, iyac013. doi:10.1093/genetics/iyac013

Schindler, T., Michel, S., and Wilson, A. W. M. (2015). Nutrition Management of Cystic Fibrosis in the 21st Century. *Nutr. Clin. Pract.* 30, 488–500. doi:10.1177/0884533615591604

Schmidt, L. S., and Linehan, W. M. (2018). FLCN : The Causative Gene for Birt-Hogg-Dubé Syndrome. *Gene* 640, 28–42. doi:10.1016/j.gene.2017.09.044

Scott, F. J., Baron-Cohen, S., Bolton, P., and Brayne, C. (2002). Brief Report Prevalence of Autism Spectrum Conditions in Children Aged 5-11 Years in Cambridgeshire, UK. *Autism* 6, 231–237. doi:10.1177/1362361302006003002

Senol-Cosar, O., Schmidt, R. J., Qian, E., Hoskinson, D., Mason-Suares, H., Funke, B., et al. (2019). Considerations for Clinical Curation, Classification, and Reporting of Low-Penetrance and Low Effect Size Variants Associated with Disease Risk. *Genet. Med.* 21, 2765–2773. doi:10.1038/s41436-019-0560-8

Servetti, M., Pisciotta, L., Tassano, E., Cerminara, M., Nobili, L., Boeri, S., et al. (2021). Neurodevelopmental Disorders in Patients with Complex Phenotypes and Potential Complex Genetic Basis Involving Non-coding Genes, and Double CNVs. *Front. Genet.* 12, 732002. doi:10.3389/fgene.2021.732002

Shawky, R. M. (2014). Reduced Penetrance in Human Inherited Disease. *Egypt. J. Med. Hum. Genet.* 15, 103–111. doi:10.1016/j.ejmhg.2014.01.003

Shieh, J. T. C. (2019). Genomic Sequencing Expansion and Incomplete Penetrance. *Pediatrics* 143, S22–S26. doi:10.1542/peds.2018-1099e

Silva, J., Fernandes, R., and Romão, L. (2019). Translational Regulation by Upstream Open Reading Frames and Human Diseases. *Adv. Exp. Med. Biol.* 1157, 99–116. doi:10.1007/978-3-030-19966-1_5

Sirp, A., Roots, K., Nurm, K., Tuvikene, J., Sepp, M., and Timmusk, T. (2021). Functional Consequences of TCF4 Missense Substitutions Associated with Pitt-Hopkins Syndrome, Mild Intellectual Disability, and Schizophrenia. *J. Biol. Chem.* 297, 101381. doi:10.1016/j.jbc.2021.101381

Sirugo, G., Williams, S. M., and Tishkoff, S. A. (2019). The Missing Diversity in Human Genetic Studies. *Cell.* 177, 26–31. doi:10.1016/j.cell.2019.02.048

Skakkebaek, A., Viuff, M., Nielsen, M. M., and Gravholt, C. H. (2020). Epigenetics and Genomics in Klinefelter Syndrome. *Am. J. Med. Genet. C Semin. Med. Genet.* 184, 216–225. doi:10.1002/ajmg.c.31802

Smith, F. J., Hansen, C. D., Hull, P. R., Kaspar, R. L., McLean, W. I., O'Toole, E., et al. (1993). "Pachyonychia Congenita," in *GeneReviews®*. Editors M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, et al. (Seattle (WA): University of Washington, Seattle).

Somaschini, M., Cavazza, A., Riva, S., Sassi, I., and Carrera, P. (2005). Genetic Basis in Chronic Interstitial Familial Pneumopathy. Familial Study of SFTPC. *Pediatr. Med. Chir.* 27, 103–107.

Speletas, M., Szilagyi, A., Psarros, F., Moldovan, D., Magerl, M., Kompoti, M., et al. (2015). Hereditary Angioedema: Molecular and Clinical Differences Among European Populations. *J. Allergy Clin. Immunol.* 135, 570–573. e10. doi:10.1016/j.jaci.2014.08.007

Stefansson, H., Meyer-Lindenberg, A., Steinberg, S., Magnusdottir, B., Morgen, K., Arnarsdottir, S., et al. (2014). CNVs Conferring Risk of Autism or Schizophrenia Affect Cognition in Controls. *Nature* 505, 361–366. doi:10.1038/nature12818

Stefl, S., Nishi, H., Petukh, M., Panchenko, A. R., and Alexov, E. (2013). Molecular Mechanisms of Disease-Causing Missense Mutations. *J. Mol. Biol.* 425, 3919–3936. doi:10.1016/j.jmb.2013.07.014

Steinberg, M. H., and Sebastiani, P. (2012). Genetic Modifiers of Sickle Cell Disease. *Am. J. Hematol.* 87, 795–803. doi:10.1002/ajh.23232

Stenson, P. D., Mort, M., Ball, E. V., Evans, K., Hayden, M., Heywood, S., et al. (2017). The Human Gene Mutation Database: Towards a Comprehensive Repository of Inherited Mutation Data for Medical Research, Genetic Diagnosis and Next-Generation Sequencing Studies. *Hum. Genet.* 136 (6), 665–677. doi:10.1007/s00439-017-1779-6

Stephanou, C., Tamana, S., Minaidou, A., Papasavva, P., Kleanthous, M., and Kountouris, P. (2019). Genetic Modifiers at the Crossroads of Personalised Medicine for Haemoglobinopathies. *J. Clin. Med.* 8, 1927. doi:10.3390/jcm8111927

Steri, M., Idda, M. L., Whalen, M. B., and Orrù, V. (2018). Genetic Variants in mRNA Untranslated Regions. *Wiley Interdiscip. Rev. RNA* 9, e1474. doi:10.1002/wrna.1474

Strehlow, V., Heyne, H. O., Vlaskamp, D. R. M., Marwick, K. F. M., Rudolf, G., de Bellescize, J., et al. (2019). GRIN2A-Related Disorders: Genotype and

Functional Consequence Predict Phenotype. *Brain.* 142 (1), 80–92. doi:10.1093/brain/awy304

Stoeklé, H.-C., Mamzer-Bruneel, M.-F., Vogt, G., and Hervé, C. (2016). 23andMe: a New Two-Sided Data-Banking Market Model. *BMC Med. Ethics* 17, 19.

Subaran, R. L., Conte, J. M., Stewart, W. C. L., and Greenberg, D. A. (2015). Pathogenic EFHC 1 Mutations Are Tolerated in Healthy Individuals Dependent on Reported Ancestry. *Epilepsia* 56, 188–194. doi:10.1111/epi.12864

Sulem, P., Helgason, H., Oddson, A., Stefansson, H., Gudjonsson, S. A., Zink, F., et al. (2015). Identification of a Large Set of Rare Complete Human Knockouts. *Nat. Genet.* 47, 448–452. doi:10.1038/ng.3243

Sun, C., Li, N., Yang, Z., Zhou, B., He, Y., Weng, D., et al. (2013). miR-9 Regulation of BRCA1 and Ovarian Cancer Sensitivity to Cisplatin and PARP Inhibition. *J. Natl. Cancer Inst.* 105, 1750–1758. doi:10.1093/jnci/djt302

Sun, J. H., Zhou, L., Emerson, D. J., Phyo, S. A., Titus, K. R., Gong, W., et al. (2018). Disease-Associated Short Tandem Repeats Co-localize with Chromatin Domain Boundaries. *Cell.* 175, 224–238. e15. doi:10.1016/j.cell.2018.08.005

Supek, F., Lehner, B., and Lindeboom, R. G. H. (2021). To NMD or Not to NMD: Nonsense-Mediated mRNA Decay in Cancer and Other Genetic Diseases. *Trends Genet.* 37, 657–668. doi:10.1016/j.tig.2020.11.002

Syrbe, S., Hedrich, U. B. S., Hedrich, U. B. S., Riesch, E., Djémié, T., Müller, S., et al. (2015). De Novo loss- or Gain-Of-Function Mutations in KCNA2 Cause Epileptic Encephalopathy. *Nat. Genet.* 47, 393–399. doi:10.1038/ng.3239

Taniguchi, Y., Takeda, N., Inuzuka, R., Matsubayashi, Y., Kato, S., Doi, T., et al. (2021). Impact of Pathogenic FBN1 Variant Types on the Development of Severe Scoliosis in Patients with Marfan Syndrome. *J. Med. Genet.*

Tarailo-Graovac, M., Zhu, J. Y. A., Matthews, A., van Karnebeek, C. D. M., and Wasserman, W. W. (2017). Assessment of the ExAC Data Set for the Presence of Individuals with Pathogenic Genotypes Implicated in Severe Mendelian Pediatric Disorders. *Genet. Med.* 19, 1300–1308. doi:10.1038/gim.2017.50

The Encode Project Consortium (2012). An Integrated Encyclopedia of DNA Elements in the Human Genome. *Nature* 489, 57–74.

Tolmacheva, E. N., Kashevarova, A. A., Nazarenko, L. P., Minaycheva, L. I., Skryabin, N. A., Lopatkina, M. E., et al. (2020). Delineation of Clinical Manifestations of the Inherited Xq24 Microdeletion Segregating with sXCI in Mothers: Two Novel Cases with Distinct Phenotypes Ranging from UBE2A Deficiency Syndrome to Recurrent Pregnancy Loss. *Cytogenet. Genome Res.* 160, 245–254. doi:10.1159/000508050

Tommasi, C., Pellegrino, B., Boggiani, D., Sikokis, A., Michiara, M., Uliana, V., et al. (2021). Biological Role and Clinical Implications of microRNAs in BRCA Mutation Carriers. *Front. Oncol.* 11, 700853. doi:10.3389/fonc.2021.700853

Torella, A., Zanobio, M., Zeuli, R., del Vecchio Blanco, F., Savarese, M., Giugliano, T., et al. (2020). The Position of Nonsense Mutations Can Predict the Phenotype Severity: A Survey on the DMD Gene. *PLOS ONE* 15, e0237803. doi:10.1371/journal.pone.0237803

Tørring, P. M., Kjeldsen, A. D., Ousager, L. B., and Brusgaard, K. (2017). ENG Mutational Mosaicism in a Family with Hereditary Hemorrhagic Telangiectasia. *Mol. Genet. Genomic Med.* 6, 121–125. doi:10.1002/mgg3.361

Tuke, M. A., Ruth, K. S., Wood, A. R., Beaumont, R. N., Tyrrell, J., Jones, S. E., et al. (2019). Mosaic Turner Syndrome Shows Reduced Penetrance in an Adult Population Study. *Genet. Med.* 21, 877–886. doi:10.1038/s41436-018-0271-6

Tukker, A. M., Royal, C. D., Bowman, A. B., and McAllister, K. A. (2021). The Impact of Environmental Factors on Monogenic Mendelian Diseases. *Toxicol. Sci.* 181, 3–12. doi:10.1093/toxsci/kfab022

Turner, H., and Jackson, L. (2020). Evidence for Penetrance in Patients without a Family History of Disease: a Systematic Review. *Eur. J. Hum. Genet.* 28, 539–550. doi:10.1038/s41431-019-0556-5

Um, J. W., and Ko, J. (2017). Neural Glycosylphosphatidylinositol-Anchored Proteins in Synaptic Specification. *Trends Cell. Biol.* 27, 931–945. doi:10.1016/j.tcb.2017.06.007

van der Kolk, D. M., de Bock, G. H., Leegte, B. K., Schaapveld, M., Mourits, M. J. E., de Vries, J., et al. (2010). Penetrance of Breast Cancer, Ovarian Cancer and Contralateral Breast Cancer in BRCA1 and BRCA2 Families: High Cancer Incidence at Older Age. *Breast Cancer Res. Treat.* 124, 643–651. doi:10.1007/s10549-010-0805-3

van der Lee, R., Correard, S., and Wasserman, W. W. (2020). Deregulated Regulators: Disease-Causing Cis Variants in Transcription Factor Genes. *Trends Genet.* 36, 523–539. doi:10.1016/j.tig.2020.04.006

van Karnebeek, C. D. M., and Stockler, S. (2012). Treatable Inborn Errors of Metabolism Causing Intellectual Disability: A Systematic Literature Review. *Mol. Genet. Metabolism* 105, 368–381. doi:10.1016/j.ymgme.2011.11.191

van Leeuwen, J., Pons, C., Boone, C., and Andrews, B. J. (2017). Mechanisms of Suppression: The Wiring of Genetic Resilience. *BioEssays* 39, 1700042. doi:10.1002/bies.201700042

van Moorsel, C. H. M., van der Vis, J. J., and Grutters, J. C. (2021). Genetic Disorders of the Surfactant System: Focus on Adult Disease. *Eur. Respir. Rev.* 30. doi:10.1183/16000617.0085-2020

van Rooij, J., Arp, P., Broer, L., Verlouw, J., van Rooij, F., Kraaij, R., et al. (2020). Reduced Penetrance of Pathogenic ACMG Variants in a Deeply Phenotyped Cohort Study and Evaluation of ClinVar Classification over Time. *Genet. Med.* doi:10.1038/s41436-020-0900-8

Vasilyev, S. A., Skryabin, N. A., Kashevarova, A. A., Tolmacheva, E. N., Savchenko, R. R., Vasilyeva, O. Y., et al. (2021). Differential DNA Methylation of the IMMP2L Gene in Families with Maternally Inherited 7q31.1 Microdeletions Is Associated with Intellectual Disability and Developmental Delay. *Cytogenet. Genome Res.* 161, 105–119. doi:10.1159/000514491

Velasco, G., and Francastel, C. (2019). Genetics Meets DNA Methylation in Rare Diseases. *Clin. Genet.* 95, 210–220. doi:10.1111/cge.13480

Viel, M., Hubert, D., Burgel, P.-R., Génin, E., Honoré, I., Martinez, B., et al. (2016). DCTN4 as a Modifier of chronicPseudomonas Aeruginosainfection in Cystic Fibrosis. *Clin. Respir. J.* 10, 777–783. doi:10.1111/crj.12288

Vu, V., Verster, A. J., Schertzberg, M., Chuluunbaatar, T., Spensley, M., Pajkic, D., et al. (2015). Natural Variation in Gene Expression Modulates the Severity of Mutant Phenotypes. *Cell.* 162, 391–402. doi:10.1016/j.cell.2015.06.037

Vuckovic, D., Bao, E. L., Akbari, P., Lareau, C. A., Mousas, A., Jiang, T., et al. (2020). *The Polygenic and Monogenic Basis of Blood Traits and Diseases (Genetic and Genomic Medicine).*

Wallace, D. R., Taalab, Y. M., Heinze, S., Tariba Lovaković, B., Pizent, A., Renieri, E., et al. (2020). Toxic-Metal-Induced Alteration in miRNA Expression Profile as a Proposed Mechanism for Disease Development. *Cells* 9, E901. doi:10.3390/cells9040901

Wallis, G. A., Starman, B. J., Zinn, A. B., and Byers, P. H. (1990). Variable Expression of Osteogenesis Imperfecta in a Nuclear Family Is Explained by Somatic Mosaicism for a Lethal Point Mutation in the Alpha 1(I) Gene (COL1A1) of Type I Collagen in a Parent. *Am. J. Hum. Genet.* 46, 1034–1040.

Walsh, R., Mazzarotto, F., Whiffin, N., Buchan, R., Midwinter, W., Wilk, A., et al. (2019). Quantitative Approaches to Variant Classification Increase the Yield and Precision of Genetic Testing in Mendelian Diseases: the Case of Hypertrophic Cardiomyopathy. *Genome Med.* 11, 5. doi:10.1186/s13073-019-0616-z

Walsh, R., Tadros, R., and Bezzina, C. R. (2020). When Genetic Burden Reaches Threshold. *Eur. Heart J.* 41, 3849–3855. doi:10.1093/eurheartj/ehaa269

Walsh, R., Thomson, K. L., Ware, J. S., Funke, B. H., Woodley, J., McGuire, K. J., et al. (2017). Reassessment of Mendelian Gene Pathogenicity Using 7,855 Cardiomyopathy Cases and 60,706 Reference Samples. *Genet. Med.* 19, 192–203. doi:10.1038/gim.2016.90

Weedon, M. N., Cebola, I., Cebola, I., Patch, A.-M., Flanagan, S. E., De Franco, E., et al. (2014). Recessive Mutations in a Distal PTF1A Enhancer Cause Isolated Pancreatic Agenesis. *Nat. Genet.* 46, 61–64. doi:10.1038/ng.2826

Wei, J., Rahman, S., Ayaub, E. A., Dickhout, J. G., and Ask, K. (2013). Protein Misfolding and Endoplasmic Reticulum Stress in Chronic Lung Disease. *Chest* 143, 1098–1105. doi:10.1378/chest.12-2133

Wei, W.-H., Hemani, G., and Haley, C. S. (2014). Detecting Epistasis in Human Complex Traits. *Nat. Rev. Genet.* 15, 722–733. doi:10.1038/nrg3747

Weinhold, B. (2006). Epigenetics: The Science of Change. *Environ. Health Perspect.* 114, A160–A167. doi:10.1289/ehp.114-a160

Whiffin, N., Karczewski, K. J., Karczewski, K. J., Zhang, X., Chothani, S., Smith, M. J., et al. (2020). Characterising the Loss-Of-Function Impact of 5' Untranslated Region Variants in 15,708 Individuals. *Nat. Commun.* 11, 2523. doi:10.1038/s41467-019-10717-9

White, M. C., Holman, D. M., Boehm, J. E., Peipins, L. A., Grossman, M., and Jane Henley, S. (2014). Age and Cancer Risk. *Am. J. Prev. Med.* 46, S7–S15. doi:10.1016/j.amepre.2013.10.029

Williamson, I., Kane, L., Devenney, P. S., Flyamer, I. M., Anderson, E., Kilanowski, F., et al. (2019). Developmentally Regulated Shh Expression Is Robust to TAD Perturbations. *Development* 146, dev179523. doi:10.1242/dev.179523

Wojcik, M. H., Zhang, T., Ceyhan-Birsoy, O., Genetti, C. A., Lebo, M. S., Yu, T. W., et al. (2021). Discordant Results between Conventional Newborn Screening and Genomic Sequencing in the BabySeq Project. *Genet. Med.* 23, 1372–1375. doi:10.1038/s41436-021-01146-5

Wonkam, A., Chimusa, E. R., Mnika, K., Pule, G. D., Ngo Bitoungui, V. J., Mulder, N., et al. (2020). Genetic Modifiers of Long-Term Survival in Sickle Cell Anemia. *Clin. Transl. Med.* 10, e152. doi:10.1002/ctm2.152

Wright, C. F., FitzPatrick, D. R., and Firth, H. V. (2018). Paediatric Genomics: Diagnosing Rare Disease in Children. *Nat. Rev. Genet.* 19, 253–268. doi:10.1038/nrg.2017.116

Wright, C. F., Prigmore, E., Rajan, D., Handsaker, J., McRae, J., Kaplanis, J., et al. (2019b). Clinically-relevant Postzygotic Mosaicism in Parents and Children with Developmental Disorders in Trio Exome Sequencing Data. *Nat. Commun.* 10, 2985. doi:10.1038/s41467-019-11059-2

Wright, C. F., Quaife, N. M., Ramos-Hernández, L., Danecek, P., Ferla, M. P., Samocha, K. E., et al. (2021). Non-coding Region Variants Upstream of MEF2C Cause Severe Developmental Disorder through Three Distinct Loss-Of-Function Mechanisms. *Am. J. Hum. Genet.* 108, 1083–1094. doi:10.1016/j.ajhg.2021.04.025

Wright, C. F., West, B., Tuke, M., Jones, S. E., Patel, K., Laver, T. W., et al. (2019a). Assessing the Pathogenicity, Penetrance, and Expressivity of Putative Disease-Causing Variants in a Population Setting. *Am. J. Hum. Genet.* 104, 275–286. doi:10.1016/j.ajhg.2018.12.015

Wu, S., Cho, E., Li, W.-Q., Weinstock, M. A., Han, J., and Qureshi, A. A. (2016). History of Severe Sunburn and Risk of Skin Cancer Among Women and Men in 2 Prospective Cohort Studies. *Am. J. Epidemiol.* 183, 824–833. doi:10.1093/aje/kwv282

Xue, Y., Chen, Y., Ayub, Q., Huang, N., Ball, E. V., Mort, M., et al. (2012). Deleterious- and Disease-Allele Prevalence in Healthy Individuals: Insights from Current Predictions, Mutation Databases, and Population-Scale Resequencing. *Am. J. Hum. Genet.* 91, 1022–1032. doi:10.1016/j.ajhg.2012.10.015

Yokoshi, M., Segawa, K., and Fukaya, T. (2020). Visualizing the Role of Boundary Elements in Enhancer-Promoter Communication. *Mol. Cell.* 78, 224–235. e5. doi:10.1016/j.molcel.2020.02.007

Young, S. K., Palam, L. R., Wu, C., Sachs, M. S., and Wek, R. C. (2016). Ribosome Elongation Stall Directs Gene-specific Translation in the Integrated Stress Response. *J. Biol. Chem.* 291, 6546–6558. doi:10.1074/jbc.m115.705640

Zernant, J., Lee, W., Nagasaki, T., Collison, F. T., Fishman, G. A., Bertelsen, M., et al. (2018). Extremely Hypomorphic and Severe Deep Intronic Variants in the ABCA4 Locus Result in Varying Stargardt Disease Phenotypes. *Cold Spring Harb. Mol. Case Stud.* 4, a002733. doi:10.1101/mcs.a002733

Zhang, L. X., Lemire, G., Gonzaga-Jauregui, C., Molidperee, S., Galaz-Montoya, C., Liu, D. S., et al. (2020). Further Delineation of the Clinical Spectrum of KAT6B Disorders and Allelic Series of Pathogenic Variants. *Genet. Med.* 22, 1338–1347. doi:10.1038/s41436-020-0811-8

Zhang, M., Lu, L., Wei, B., Zhang, Y., Li, X., Shi, Y., et al. (2020). Brachydactyly Type A3 Is Caused by a Novel 13 Bp HOXD13 Frameshift Deletion in a Chinese Family. *Am. J. Med. Genet.* 182, 2432–2436. doi:10.1002/ajmg.a.61788

Zhang, X., Walsh, R., Whiffin, N., Buchan, R., Midwinter, W., Wilk, A., et al. (2021). Disease-specific Variant Pathogenicity Prediction Significantly Improves Variant Interpretation in Inherited Cardiac Conditions. *Genet. Med.* 23, 69–79. doi:10.1038/s41436-020-00972-3

Zhou, J., and Troyanskaya, O. G. (2015). Predicting Effects of Noncoding Variants with Deep Learning-Based Sequence Model. *Nat. Methods* 12, 931–934. doi:10.1038/nmeth.3547

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Engagement marketing for social good: Application to the *All of Us* Research Program

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Engagement marketing, when applied to increasing the social good, involves making a deliberate effort to engage communities with an organization's brand that might not have otherwise happened organically. Organizations that typically focus on increasing the social good include non-profits, community organizations, public health departments, and federal, state, and local agencies. Engagement marketing builds relationships, gives a voice to, and fosters collaboration with community members to transform their insights into impactful experiences that motivate and empower them to act to increase the social good. These actions may include making an informed decision, changing a health or prosocial behavior, or joining an effort that promotes or increases social good. In this paper, we translate the commercial engagement marketing approach, typically used, and studied widely to increase profits, to one that uses engagement marketing to increase prosocial outcomes. We propose a new definition of engagement marketing applied to the social good, a multi-level conceptual framework that integrates individual, social, community and macro-level processes and outcomes, and illustrates an example applying this translated model to co-create digital engagement experiences using a human centered design approach for the *All of Us* Research Program. This model can also guide research and practice related to DNA-based population screening.

KEYWORDS

engagement marketing, social good, *All of Us* Research Program, human-centered design, co-creation

Introduction

Medicine and public health are at an inflection point in which advances in the collection, management and analysis of big data have the potential to lead to the development of more precise treatments and interventions. Precision medicine combines information about individual characteristics, including genetic, health behaviors and environmental exposures to deliver more tailored individual treatments (Ginsburg and Phillips, 2018). Precision public health integrates precision medicine with

population-based strategies to increase disease prevention and control (Khoury et al., 2016; Khoury and Galea, 2016). The promise of both fields is to provide the right treatment or intervention to the right individual or population at the right time; however, the promise of greater precision in both fields is yet to be fully realized. In combination, precision medicine, precision public health and DNA-based population screening hold promise to fuel novel, tailored individual and targeted population-level treatments and interventions, while addressing health care disparities (Murray et al., 2018). However, the success of these approaches depends on diverse communities across the United States actively participating (Ginsburg and Phillips, 2018).

The challenge is that many communities have been both historically under-represented in, and abused by, biomedical research in the name of science and medical care (Washington, 2006). Because of this history, many community members distrust biomedical research. Other barriers to engaging diverse community members include lack of awareness of, or comfort with research, and structural barriers such as finances, time, and transportation (Clark et al., 2019). To support DNA-based population screening and advance precision medicine and precision public health, communities historically underrepresented in biomedical research need to be engaged in a manner that fosters trust and inclusivity. To help achieve this goal we present a model of engagement marketing for social good as a framework for supporting community members' engagement in biomedical research. We acknowledge that attitudes, practices, and approaches on the part of those leading biomedical research needs to be addressed to support engagement. The model we propose provides an initial step for how researchers can frame problems and work with community members using an engagement-focused lens.

One research program that takes a different approach to enrolling participants in a longitudinal cohort is the *All of Us* Research Program (*All of Us* Research Program Investigators et al., 2019). *All of Us* aims to enroll 1,000,000 people that represent the diversity of the United States to drive innovations in biomedical research and precision medicine treatments. Central to the program's values-driven approach is acknowledging past abuses while working through trusted intermediaries to raise awareness and promote engagement. A key aspect of *All of Us* is engagement with communities that have been underrepresented in biomedical research to help build a relationship with the program that supports informed decisions about enrollment and retention (Richardson-Heron and Cantor, 2019).

Engagement entails active and intentional collaboration with stakeholders (e.g., patients, community members, advocates, health care providers (Chudyk et al., 2018)) to foster connection, interaction, and a long-term bidirectional relationship. The science supporting the benefit of engagement for enrollment and retention in large cohort studies is in its nascency. To help advance the field of engagement, we adapted a conceptual model of engagement marketing from the commercial marketing field and are applying it in our work as an *All of Us* Engagement and Retention Innovator Awardee. We begin by describing commercial engagement marketing, explain how engagement marketing can be translated for social good, describe the conceptual model, and illustrate how we are applying it in our co-creation process to design, develop, deliver, and evaluate digital experiences. These experiences co-created with diverse community members, and other *All of Us* stakeholders, such as health care providers, aim to engage and retain members of communities underrepresented in biomedical research. The engagement marketing for social good model has the potential to inform other efforts focused on DNA-based population screening.

Engagement marketing from a commercial marketing perspective

Commercial marketing defines consumer engagement as the strategic relationships fostered by an organization or brand, reciprocated by the consumer, and sustained through continuous interactions that supersede the traditional consumer-brand transactional relationship (Harmeling et al., 2016). Engagement marketing is an approach rooted in social exchange theory that leverages the dynamic consumer-organization relationship to advance marketing objectives. Engaged consumers are voluntary co-creators, facilitators, recruiters, and collaborators in developing and executing the organization's marketing functions (Hollebeek, 2011; Hollebeek, 2016). Engaged consumers are cognitively, emotionally, and behaviorally invested in the success of a brand or organization and their allegiance positions them as valued collaborators rather than mere participants in an economic transaction (Hollebeek, 2011). Engagement marketing values the contributions and active participation of consumers, shifts control from marketers to consumers, and results in consumers becoming engaged and educated intermediaries for a brand or campaign (Harmeling et al., 2016; Burrus et al., 2021).

Evidence indicates that engagement marketing leads to outcomes important to marketers in commercial sectors. Consumers who are engaged with the brands they purchase are more likely to spend more money per transaction, and companies that engage consumers experience an increase in net earnings (Kumar and Pansari, 2016; Alvarez-Milán et al., 2018). Furthermore, commercial engagement strategies can help sustain commerce in downward-spiraling economies (Kumar and Pansari, 2016), increase brand loyalty (Dwivedi, 2015), and endow organizations with valuable feedback on strategy to improve the brand (Dwivedi, 2015; Venkatesan, 2017). These findings suggest that translating and applying engagement marketing to the social good context may also

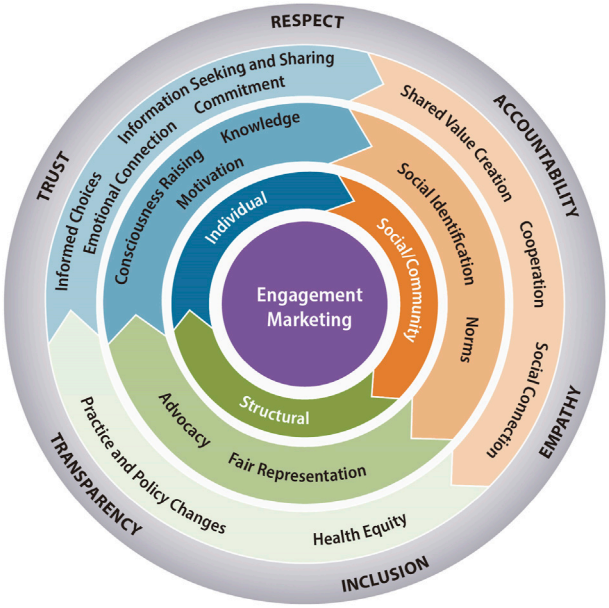


FIGURE 1
Engagement marketing for social good.

influence behaviors and motivate change for the benefit of individuals and communities in a variety of contexts, such as health and safety, the environment, and social activism (Burrus et al., 2021).

Engagement marketing from a social good perspective

Previously, we proposed engagement marketing principles can be adapted and applied to health contexts to motivate and empower people to enact prosocial behaviors (Burrus et al., 2021). Engagement marketing, when applied to increasing the social good, involves making a deliberate effort to engage communities with an organization and mission that might not otherwise happen organically (Harmeling et al., 2016). Organizations that typically focus on increasing the social good include non-profits, community organizations, public health departments, and federal, state, and local agencies. Engagement marketing builds relationships, gives a voice to, and fosters collaboration with stakeholders to transform their insights into impactful engagement experiences that motivate and empower them to act to increase the social good. These actions may include making an informed decision, changing a behavior, or joining an effort that promotes social good (Harmeling et al., 2016; Burrus et al., 2021). Engaging communities that have been underrepresented in biomedical research is central to building a diverse research cohort and ensuring that health disparities are not perpetuated by *All of Us*. We view engagement with diverse communities, and the desire to ensure health disparities are not perpetuated as a form of social good, that is, using engagement to enhance health and well-being on a population scale (Mor Barak, 2018).

Engagement marketing for social good: A conceptual model

Our proposed conceptual model is one that can be applied to many social problems. In the context of *All of Us*, an engagement marketing approach positions participant-volunteers, and other program stakeholders, as active collaborators who will work with us to design, develop, and evaluate digital experiences to support program engagement. This approach may foster trust and transparency that could reduce barriers to participation for members of communities historically underrepresented in biomedical research and the community organizations and health care providers who serve them. Over time, this collaborative approach may be instrumental in supporting ongoing, long-term, impactful engagement across the *All of Us* participant journey.

Figure 1 shows our engagement marketing conceptual model to promote the social good. First, we propose that engagement marketing for social good must account for multiple levels of influence, including individual, social/community and structural levels that could impact prosocial behavior and engagement as shown by the different colored sections of Figure 1. Second, we specify potential processes that support change and outcomes at each level, as shown by the colored rings that align with each level. Third, we propose that engagement marketing is driven by values that guide a different type of relationship between community members and researchers, as indicated by the gray ring. Researchers are responsible for upholding these values to foster a different type of relationship.

Individual-level processes. Individual-level processes are central to an engagement marketing approach because engagement marketing strategies may fortify a person's psychological, emotional, and behavioral connection with a social cause (Brodie et al., 2011). Ongoing interactions can increase knowledge and perceived value, and ultimate impact of social good programs. Educated community members become equipped to pass along their knowledge of programs and positive experiences interacting to others, thus expanding the reach and involvement in the program (Hollebeek, 2016). Furthermore, community members' knowledge and experience aid in the development, management, and dissemination of a cohesive program narrative. Sharing in the distribution of knowledge and information, community members become educated intermediaries who spread program information through their personal and social networks (Harmeling et al., 2016).

Engagement marketing strategies may also prove beneficial for motivating individuals to participate or contribute their own resources to a social cause. Cognitive engagement is a psychological state in which the individual is motivated to advance their relationship with an organization with the expectation that the experience will have greater benefits than costs. (Alvarez-Milán et al., 2018). Positive, memorable, and beneficial experiences may motivate and empower individuals to contribute resources otherwise unattainable to organizers—specifically, network assets, persuasion capital, knowledge, and creative ideas—which may amplify and support program engagement over time.

Engagement with social programs can also raise consciousness about the socio-structural barriers and other sources of oppression contributing to injustices and inequities barring many from better health (Freire, 2000). From an engagement marketing for social good perspective, as individuals become aware of opportunities to reduce inequities through activities perceived as within their realm of control and influence, they may be more likely to participate in developing solutions.

Individual-level outcomes. Engagement marketing strategies can cultivate, reinforce, or strengthen a relationship with a social cause. An individual's perception of having an emotional connection to a program is foundational to their engagement (Kumar and Pansari, 2016). Engagement marketing strategies can help establish and sustain emotional ties to a social cause through reciprocal commitments and ongoing and meaningful social exchanges (Alvarez-Milán et al., 2018).

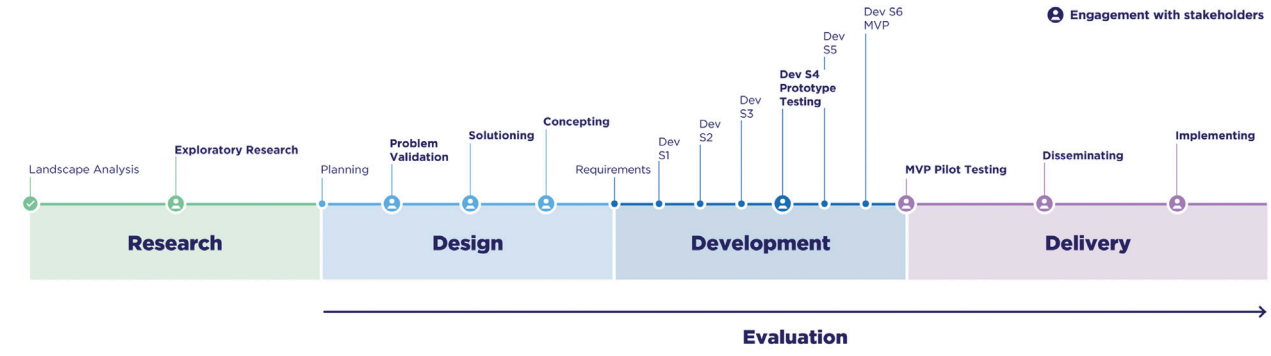
As community members learn about a cause, become emotionally connected, and motivated they may be more likely to seek out and share information about a social cause. A key outcome predicted in our application of engagement marketing to the social good, information seeking and sharing may be related to involvement in genomics research (Dijkstra et al., 2012). At the individual level, engaging with a social cause may support informed decisions related to taking action to support the effort (Forsythe et al., 2019).

Social and community level processes. Social and community level processes are central to an engagement marketing approach, because the approach relies on social exchanges (Hollebeek, 2016). A social exchange approach is consistent with *All of Us* which seeks to develop a longer-term relationship with participants and program stakeholders by exchanging value and promoting collaboration between participants and researchers (Richardson-Heron and Cantor, 2019). Social and community contexts that an individual identifies with can play an important role in shaping openness to engagement with research (American Psychological Association, 2021). Many studies indicate racial or ethnic groups may share levels of awareness, perceptions, or norms surrounding genetic testing and research, perhaps owing to the historic exploitation of African Americans in the Tuskegee syphilis study (e.g., Fairchild & Bayer (1999)) or Native Americans being pressured to demonstrate their heritage through blood and DNA (e.g., Tallbear (2013)). There are also regional differences in awareness and attitudes surrounding genetic testing, sometimes over and above racial or ethnic identification (Jonassaint et al., 2010). Group-level identities and norms provide possible avenues for communicating about the benefits of research involvement which underscores the importance of involving diverse community members in the development of experiences that support engagement with *All of Us*.

Social and community level outcomes. From an engagement marketing for social good perspective, potential outcomes related to social and community level processes include creating greater social connection, cooperation, and shared value creation. Because engagement marketing relies on building a relationship with community members and listening to their ideas and concerns, social connections are created by their active participation and co-creation of solutions (Harmeling et al., 2016). This process may also foster shared values and strengthen the capacity of community members to participate in research and achieve collective impact (Porter and Kramer, 2011). Cooperative behavior is a potential outcome of engagement marketing at this level because involving diverse stakeholders in the process of designing solutions that promote engagement is a way of promoting fairer processes and outcomes (Tyler and Blader, 2000).

Structural level processes. An engagement marketing perspective is fundamentally a structural change in the way marketing is typically conducted, because it shifts the communication and control between marketers and priority audiences from unidirectional to bidirectional, and a more relationship-based perspective (Harmeling et al., 2016). From an engagement marketing for social good viewpoint, fair representation of diverse voices ensures that the dialogue and decision making is joint, and inclusive of various viewpoints in developing solutions. This is important because fair representation has the potential to make the outcomes of the process more relevant and useful for community members (Israel et al., 1998; Macaulay, 2017), and potentially actionable by the systems that serve them. As community members, and other stakeholders, become more engaged with a social cause, they may be more likely to use their social capital to advocate for the cause (Putland et al., 2013).

Structural level outcomes. To date, there has been no empirical examination of how fair representation and advocacy could lead to structural level changes in practice and policy that support an engagement marketing for social good approach. However, there are influential research institutions in place that are investing in building infrastructures that support practice and policy changes that require engagement, representation, and inclusion of diverse patient, community, and system stakeholders. For example, the Patient Centered Outcomes Research Institute (PCORI) has built a research infrastructure in which the voices of patients, community



Note: Dev=Development; S1-S6=Sprint sessions; MVP=Minimum viable product.

FIGURE 2
Inclusive approach to engaging stakeholders in the design, development, and delivery of experiences to involve community members and stakeholders with *All of Us*.

members, and other health care system stakeholders are central to the research process (Frank et al., 2015). The value of this engaged research approach is currently under study through PCORI's Science of Engagement Initiative.

Values-based approach. A values-based approach is important for all levels of engagement marketing for social good. As shown in the outer ring in Figure 1, we believe transparency, inclusion, empathy, accountability, respect, and trust are key values when engaging with stakeholders, especially community members that have been historically marginalized from the research process. By enacting these values as part of engaging stakeholders, our model addresses important ethical issues raised by scholars who study genomic translation. For example, our model addresses responsive justice defined as "starting with the real-world needs of socially situated groups that experience systematic disadvantage" (Burke et al., 2011, p. 12). In addition, the model encompasses the three component parts of responsive justice: fairness (distributive justice), understanding the views of those who have been under-represented and faced discrimination (recognition) and honoring the obligation as researchers with power to identify injustice and make sure fairness and recognition are achieved (responsibility) (Burke et al., 2011).

An inclusive process to involve stakeholders for developing digital experiences for *All of Us*

The application of engagement marketing for social good is illustrated through our use of human centered design (HCD) to design digital experiences to engage community members and other stakeholders with *All of Us*. HCD can provide an ethical and effective approach to design products and services for underserved populations by understanding their needs, desires, and experiences (IDEO, 2015; Bartlett et al., 2021). HCD aims to understand the core needs of everyone experiencing or impacted by a problem, and to design with those communities to create solutions rooted in people's actual needs (IDEO, 2015). Similarly, co-creation can be defined as, "collaborative knowledge generation by academics working alongside other stakeholders" (Greenhalgh et al., 2016). Evidence is lacking regarding the application of an amalgam of popular approaches and processes to product design that considers stakeholders, in this case, the end users as a co-creator throughout the product life cycle. Greenhalgh et al.'s review (2016) found unifying principles of successful co-creation include a systems perspective, framing research as a creative endeavor focused on improving human experience, and attention to governance and processes, which is consistent with our engagement marketing model.

To address this gap in applied knowledge, we drew from these unifying principles, industry best practices, and lived experiences to create a systematic process intended to rapidly co-create with a variety of diverse stakeholders to understand and overcome their unique challenges to engaging with *All of Us*. In product design it can be challenging to implement these approaches in a holistic manner; it is not uncommon for stakeholder input to be limited to a single stage in a larger process that limits collaboration and input at critical time points (e.g., concept testing, user testing, and implementation). Our co-creation process is comprised of a design sprint and a development sprint that engages stakeholders at multiple touch points and through a variety of formats (e.g., collaborative workshops, polls, surveys, unmoderated interviews) and techniques that welcome stakeholders as co-creators in designing and developing digital engagement experiences. As shown in Figure 2, we propose to involve

stakeholders across the continuum of design, development, and delivery activities that will produce engagement experiences for *All of Us*.

Conclusion

Beyondmandatednewborn screening, there are no large-scale national programs that implement DNA-based population screening in the United States. *All of Us* is not a screening program but provides one potential model for understanding large-scale collection of genomic information, and how diverse communities across the United States may become involved in DNA-based population screening efforts. As models for DNA-based population screening evolve, greater involvement and trust between historically marginalized community members and researchers will be required. Researchers need to use new models to support greater involvement and engagement in research with communities to make DNA-based population screening successful. We translated an evidence-based engagement marketing approach used in commercial marketing to one that promotes the social good and is being applied to our work as part of the *All of Us* Research Program. This conceptual approach will be continually evaluated using a developmental evaluation approach (Patton, 2010), to understand the extent to which it is successful in promoting engagement, inclusion, collaboration, and trust, which will enable us to refine the process, based on input from the stakeholders who are collaborating with us—furthering value creation. Fostering these outcomes will be essential to advance research and practice for any DNA-based population screening program.

Author contributions

ML and JU developed the conceptual approach described. All authors contributed to the manuscript, and approve the submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

All of Us Research Program Investigators, Denny, J. C., Rutter, J. L., Goldstein, D. B., Philippakis, A., Smoller, J. W., et al. (2019). The "*All of Us*" research program. *N. Engl. J. Med.* 381 (7), 668–676. doi:10.1056/NEJMsr1809937

Alvarez-Milán, A., Felix, R., Rauschnabel, P. A., and Hinsch, C. (2018). Strategic customer engagement marketing: A decision making framework. *J. Bus. Res.* 92, 61–70. doi:10.1016/j.jbusres.2018.07.017

American Psychological Association (2021). Social identity. APA dictionary of psychology [online]. Available at: https://dictionary.apa.org/social-identity (Accessed December 27, 2021).

Bartlett, R., Boyle, J. A., Simons Smith, J., Khan, N., Robinson, T., Ramaswamy, R., et al. (2021). Evaluating human-centred design for public health: A case study on developing a healthcare app with refugee communities. *Res. Involv. Engagem.* 7 (1), 32. doi:10.1186/s40900-021-00273-2

Brodie, R. J., Hollebeek, L. D., Jurić, B., and Ilić, A. (2011). Customer engagement. *J. Serv. Res.* 14 (3), 252–271. doi:10.1177/1094670511411703

Burke, W., Edwards, K., Goering, S., Holland, S., and Trinidad, S. B. (2011). *Achieving justice in genomic translation: Rethinking the pathway of benefit*. New York: Oxford University Press.

Burrus, O., Uhrig, J. D., and Lewis, M. A. (2021). "Using engagement marketing for social good," in *The Palgrave encyclopedia of social marketing*. Editors C. Fourali and J. French (Cham: Palgrave Macmillan).

Chudyk, A. M., Waldman, C., Horrill, T., Demczuk, L., Shimmin, C., Stoddard, R., et al. (2018). Models and frameworks of patient engagement in health services research: A scoping review protocol. *Res. Involv. Engagem.* 4, 28. doi:10.1186/s40900-018-0111-5

Clark, L. T., Watkins, L., Pina, I. L., Elmer, M., Akinboboye, O., Gorham, M., et al. (2019). Increasing diversity in clinical trials: Overcoming critical barriers. *Curr. Probl. Cardiol.* 44 (5), 148–172. doi:10.1016/j.cpcardiol.2018.11.002

Dijkstra, A. M., Gutteling, J. M., Swart, J. A., Wieringa, N. F., van Derwindt, H. J., Seydel, E. R., et al. (2012). Public participation in genomics research in the

Netherlands: Validating a measurement scale. *Public Underst. Sci.* 21 (4), 465–477. doi:10.1177/0963662510381036

Dwivedi, A. (2015). A higher-order model of consumer brand engagement and its impact on loyalty intentions. *J. Retail. Consumer Serv.* 24, 100–109. doi:10.1016/j.jretconser.2015.02.007

Fairchild, A. L., and Bayer, R. (1999). Uses and abuses of tuskegee. *Science* 284 (5416), 919–921. doi:10.1126/science.284.5416.919

Forsythe, L. P., Carman, K. L., Szydlowski, V., Fayish, L., Davidson, L., Hickam, D. H., et al. (2019). Patient engagement in research: Early findings from the patient-centered outcomes research institute. *Health Aff. (Millwood)* 38 (3), 359–367. doi:10.1377/hlthaff.2018.05067

Frank, L., Forsythe, L., Ellis, L., Schrandt, S., Sheridan, S., Gerson, J., et al. (2015). Conceptual and practical foundations of patient engagement in research at the patient-centered outcomes research institute. *Qual. Life Res.* 24 (5), 1033–1041. doi:10.1007/s11136-014-0893-3

Freire, P. (2000). *Pedagogy of the oppressed*. New York: Continuum.

Ginsburg, G. S., and Phillips, K. A. (2018). Precision medicine: From science to value. *Health Aff. (Millwood)* 37 (5), 694–701. doi:10.1377/hlthaff.2017.1624

Greenhalgh, T., Jackson, C., Shaw, S., and Janamian, T. (2016). Achieving research impact through co-creation in community-based health services: Literature review and case study. *Milbank Q.* 94 (2), 392–429. doi:10.1111/1468-0009.12197

Harmeling, C. M., Moffett, J. W., Arnold, M. J., and Carlson, B. D. (2016). Toward a theory of customer engagement marketing. *J. Acad. Mark. Sci.* 45 (3), 312–335. doi:10.1007/s11747-016-0509-2

Hollebeek, L. D. (2016). "Exploring customer engagement: A multi-stakeholder perspective," in *Customer engagement: Contemporary issues and challenges*. Editors R. J. Brodie, L. D. Hollebeek, and J. Conduit (New York, NY: Routledge).

Hollebeek, L. (2011). Exploring customer brand engagement: Definition and themes. *J. Strategic Mark.* 19 (7), 555–573. doi:10.1080/0965254x.2011.599493

IDEO (2015). *The field guide to human-centered design*. Available at: https://www.designkit.org/resources/1.

Israel, B. A., Schulz, A. J., Parker, E. A., and Becker, A. B. (1998). Review of community-based research: Assessing partnership approaches to improve public health. *Annu. Rev. Public Health* 19, 173–202. doi:10.1146/annurev.publhealth.19.1.173

Jonassaint, C. R., Santos, E. R., Glover, C. M., Payne, P. W., Fasaye, G. A., Oji-Njideka, N., et al. (2010). Regional differences in awareness and attitudes regarding genetic testing for disease risk and ancestry. *Hum. Genet.* 128 (3), 249–260. doi:10.1007/s00439-010-0845-0

Khoury, M. J., and Galea, S. (2016). Will precision medicine improve population health? *JAMA* 316 (13), 1357–1358. doi:10.1001/jama.2016.12260

Khoury, M. J., Iademarco, M. F., and Riley, W. T. (2016). Precision public health for the era of precision medicine. *Am. J. Prev. Med.* 50 (3), 398–401. doi:10.1016/j.amepre.2015.08.031

Kumar, V., and Pansari, A. (2016). Competitive advantage through engagement. *J. Mark. Res.* 53 (4), 497–514. doi:10.1509/jmr.15.0044

Macaulay, A. C. (2017). Participatory research: What is the history? Has the purpose changed? *Fam. Pract.* 34 (3), 256–258. doi:10.1093/fampra/cmw117

Mor Barak, M. E. (2018). The practice and science of social good: Emerging paths to positive social impact. *Res. Soc. Work Pract.* 30 (2), 139–150. doi:10.1177/1049731517745600

Murray, M. F., Evans, J. P., Angrist, M., Uhlmann, W. R., Lochner Doyle, D., Fullerton, S. M., et al. (2018). A proposed approach for implementing genomics-based screening programs for healthy adults. *NAM Perspect.* doi:10.31478/201812a

Patton, M. (2010). *Developmental evaluation applying complexity concepts to enhance innovation and use*. New York, NY: Guilford Press.

Porter, M. E., and Kramer, M. R. (2011). *Creating shared value*. Harvard Business Review. [Online].

Putland, C., Baum, F., Ziersch, A., Arthurson, K., and Pomagalska, D. (2013). Enabling pathways to health equity: Developing a framework for implementing social capital in practice. *BMC Public Health* 13, 517. doi:10.1186/1471-2458-13-517

Richardson-Heron, D., and Cantor, K. (2019). Envisioning future research and clinical practice with a bioethics lens: A word for the next generation of researchers (*All of Us* research program, activism, and policy implications). *J. Health Care Poor Underserved* 30 (4S), 36–42. doi:10.1353/hpu.2019.0113

TallBear, K. (2013). *Native American DNA: Tribal belonging and the false promise of genetic science*. Minneapolis, MN: University of Minnesota Press.

Tyler, T., and Blader, S. (2000). *Cooperation in groups: Procedural justice, social identity, and behavioral engagement*. Philadelphia, USA: Taylor & Francis Group.

Venkatesan, R. (2017). Executing on a customer engagement strategy. *J. Acad. Mark. Sci.* 45 (3), 289–293. doi:10.1007/s11747-016-0513-6

Washington, H. A. (2006). *Medical apartheid: The dark history of medical experimentation on black Americans from colonial times to the present*. New York, NY: Random House.

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Environmental scan of family chart linking for genetic cascade screening in a U.S. integrated health system

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Background: An alternative to population-based genetic testing, automated cascade genetic testing facilitated by sharing of family health history, has been conceptualized as a more efficient and cost-effective approach to identify hereditary genetic conditions. However, existing software and applications programming interfaces (API) for the practical implementation of this approach in health care settings have not been described.

Methods: We reviewed API available for facilitating cascade genetic testing in electronic health records (EHRs). We emphasize any information regarding informed consent as provided for each tool. Using semi-structured key informant interviews, we investigated uptake of and barriers to integrating automated family cascade genetic testing into the EHR.

Results: We summarized the functionalities of six tools related to utilizing family health history to facilitate cascade genetic testing. No tools were explicitly capable of facilitating family cascade genetic testing, but few enterprise EHRs supported family health history linkage. We conducted five key informant interviews with four main considerations that emerged including: 1) incentives for interoperability, 2) HIPAA and regulations, 3) mobile-app and alternatives to EHR deployment, 4) fundamental changes to conceptualizing EHRs.

Discussion: Despite the capabilities of existing technology, limited bioinformatic support has been developed to automate processes needed for family cascade genetic testing and the main barriers for implementation are nontechnical, including an understanding of regulations, consent, and workflow. As the trade-off between cost and efficiency for population-based and family cascade genetic testing shifts, the additional tools necessary for their implementation should be considered.

KEYWORDS

genomic medicine, cascade genetic testing, electronic health record, family health history communication, genetics, technology

Introduction

Cascade genetic screening is the practice of identifying at-risk relatives of individuals with known pathogenic genetic variants (Henrikson et al., 2020). Compared to population-based genetic testing, cascade genetic testing has been a historically more efficient and economical approach. In the United States, a person with actionable genetic test results is responsible for contacting their at-risk family members and communicating risk (Newson and Humphries, 2005). However, cascade testing communication is low and up to a third of at-risk relatives who may have actionable genetic findings go un-notified (Newson and Humphries, 2005; Griffin et al., 2020; Unger et al., 2020). This is thought to be in large part due to dependence on patients to share the information with family members (Henrikson et al., 2019). Preliminary data suggests that patients who receive genetic testing are open to having their health system directly contact relatives who receive care in the same system to notify them of their potential risk (Mai et al., 2011; Henrikson et al., 2019).

Chart linkage is a functionality that enables connecting part or all of the electronic health records (EHRs) of different individuals. Family chart linkage is a potential strategy for facilitating information sharing needed for cascade testing (Hampel, 2016; Ohno-Machado et al., 2018; Caswell-Jin et al., 2019). If the presence of one person's confirmed pathogenic variant could be noted in the EHR of their biologic relatives, care teams could use this information to recommend and order cascade genetic testing, potentially improving rates of both risk notification and cascade genetic testing. However, chart linkage and its implementation represent a substantial change from current practice and requires consideration of the clinical, technical, ethical, regulatory, and organizational implications, as well as patient and family preferences (Novak et al., 2013).

The Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009 provided the catalyst for developing an incentive program for updating EHR systems to improve quality of care while maintaining compliance use the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. The HITECH Act led to marked increases in structured and standardized documentation of family health history in EHRs, providing the potential for sharing family history information between family members using APIs.

We conducted an environmental scan of the current state of family chart linking bioinformatic tools and application programming interface (API), their limitations, and suggest an ethical framework for considering their clinical implementation. Along with identifying these tools, we sought to understand how policy- and decision-makers consider deciding whether to implement such a tool in clinical settings in the U.S.

Methods

This study was reviewed and approved by the Institutional Review Board at the Kaiser Permanente Washington Health Research Institute.

Guiding framework

We developed a conceptual framework to guide our environmental scan of tools for family chart linking between relatives in an EHR system (Figure 1) (Henrikson et al., 2021). In this representational model, the family health history or genetic information of Relative A as recorded in an EHR is processed through a tool before being modified and shared or transferred to the EHR of a consenting Relative B. The tool or API may be internal to the health care system EHRs or an external process that communicates through both relatives' medical records (e.g., through a smartphone app that allows for bi-directional sharing of information between patients and their EHR). Output from the API is processed based on the preferences of Relative B and then used to inform clinical decision-making. Under this framework we assessed possible tools that might be used to achieve the process of sharing family health history between relatives in an EHR as envisioned in this model.

We were further guided in the development of the interview questions by the socio-technical model (Sittig and Singh, 2010), an 8-dimensional conceptual model of designed to identify sociotechnical challenges for health information technology, with the following domains: 1) *Hardware and software*, 2) *Clinical content*, 3) *Human computer interface*, 4) *People*, 5) *Workflow and communication*, 6) *Internal organization features (e.g., policies, procedures, and culture)*, 7) *External rules and regulations*, 8) *Measurement and monitoring*.

Electronic health record tools

We conducted an environmental scan to identify the current tools available for family chart linking and to understand the factors affecting clinical implementation (Choo, 2005). We used the Office of the National Coordinator for Health Information Technology (ONC Health IT) to identify certified Health IT products available from 2015 and later with active certification status and which met the certification criteria "170.315(A) (12): Family Health History". We ended our tool search using ONC Health IT in February 2021. We focused our review on products developed for primary care practices, excluding those for specialized practices or intended exclusively for purposes related to prescriptions. For products with multiple versions listed we reviewed the latest version as of 5 February 2021. Additional tools were identified during key informant interviews and/or team reviews through the date of the last key informant interview, which was 14 March 2021.

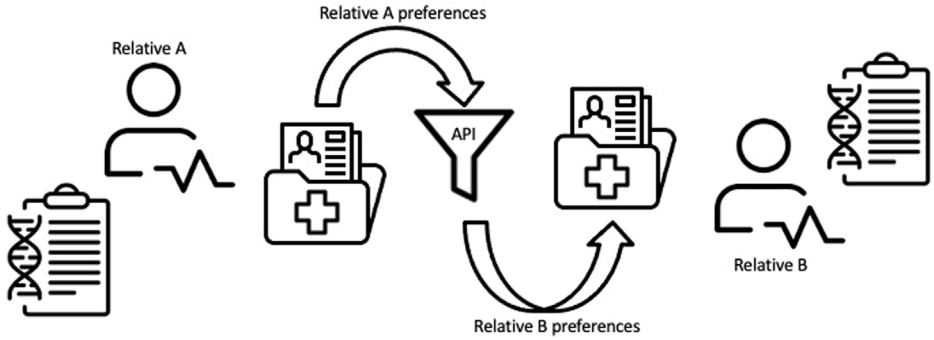

FIGURE 1
Conceptual framework for linking family health information between relatives within an EHR system.

TABLE 1 Key concepts for reviewing electronic health record functional requirements for cascading genetic testing using family health history.

Concept	Description
Structure	Family history can be stored as structured or free-text data in the EHR system. While recent work in HL7 allows for standardized recording, ubiquitous adoption has been slow and unstructured documentation has been used in previous work applying natural language processing (Wang et al., 2017)
Interoperability	An increasingly valued component of EHR is the ability to share information between systems and healthcare providers. Interoperability allows for cooperative access and exchange between systems, with the goal to optimize communication. Linking between apps and EHR has been further facilitated by federal funding and the 21st Century Cures Act through lobbying efforts from SMART on FHIR, an open, free and standards-based API (Mandl and Kohane, 2009)
Decision support process	The primary utility of family health history in healthcare settings is to provide support for provider and patient in the shared decision-making process. Collection of family health history is the first step in reaching the potential health impact
Updates to interpretation	The dynamic nature of genetics requires reinterpretation and up-to-date information to identify clinically actionable findings. Most EHR systems are not designed to perform such tasks, as most family health history is considered static unless otherwise specified by patients
Consent	Describes the process for obtaining consent as recommended by the tool developer

We abstracted product names, functions and capabilities, interoperability, data structure and standards, recommended consents from system providers, and comparisons across systems into tables. We used concepts as described in Table 1 to characterize the minimal functional requirements for EHR suitability (Marsolo and Spooner, 2013), as well as the recommended consent process for each tool. Developers were contacted for additional commentary on the recommended consent process for the tools included in our analysis. We summarized notable features from these domains for each of the identified tools.

Key informant interviews

We identified potential key informants based on our objective of representing the perspectives of decision-makers managing healthcare system data and EHRs at public or private organizations and those who had and had not implemented family chart linking. We conducted key informant interviews to identify the considerations guiding decision-making and possible barriers to implementing family chart linking functionality in clinical systems. We used sequential non-independent review, receiving input from the study team after each source of data before proceeding to the next. Using an inductive approach, we developed frameworks for analyzing sources of information (Braun and Clarke, 2006).

The initial list of key informants included clinicians, industry or product developers, and researchers with expertise in family health history or genetic screening. We applied snowball sampling at the end of each interview to identify other relevant stakeholders. Key informants were invited by email to participate in an informational interview of 1–1.5 h durations and conducted using a video conferencing app (e.g., Zoom, Microsoft Teams). Financial incentives were not offered to key informants. The final key informant interview was conducted on 14 March 2021.

TABLE 2 Summary of tools and API with functionalities relevant to family chart linking and family health history sharing as of February 2021.

Product/Tool	Developer	Consent
Allow Clinicians to Copy Family History from a Patient's Sibling	EpicCare®	Should consider same consent as Let Clinicians View or Edit Links to Family Members' Chart (below). A system-wide setting can allow for an upper age limit for copying from a patient's sibling
Let Clinicians View or Edit Links to Family Members' Charts	EpicCare®	Expected that consenting policies will vary by organization. Each consenting policy could involve the following A new document type a relative digitally signs before their chart can be linked to other family members' pedigrees. Clinicians would need to check for the form in the system before establishing the link A record of verbal consent from a relative
MyLegacy	Cerner	Patient enters data independently in a web-based questionnaire is SMART on FHIR compatible
myFHR	CareEvolution	myFHR allows you to share access to your health data with family and friends. Those that you have given access to will be able to use their myFHR app to view your health data such as lab results, current medications, and procedures and services. You can also request access to their health data
MeTree	Genomedical Connection	Patient initiated data collection and integration with medical records that support the SMART-FHIR standard
AncestryHealth kit	Ancestry (discontinued)	Consent is obtained at the time of purchase

We developed a semi-structured interview guide for use during the interviews (Supplementary material). We referred to the domains of the socio-technical model as a guide for inclusion of questions for key informants. The interview guide was designed to meet the two following objectives: 1) to understand current use of family chart linking tools within the stakeholder's system, and their choice of API (if currently using a tool) or their choice to forego using any API (if not currently using any tool); and 2) to understand the considerations or concerns for exemplary API for family chart linking from a systems perspective.

A single team member (CH) conducted interviews between February and March 2021. Interviews were recorded but not transcribed. Summarized notes were reviewed with participants at the end of each interview to verify points. The interviewer took extensive field notes during the interviews and wrote episode profiles of each interview. We used framework analysis, a rapid analysis technique where a priori codes are assigned based on the conceptual framework (Braun and Clarke, 2006). We iteratively summarized recurring considerations as they emerged, as related to dimensions of the socio-technical model. Findings were segmented into "users" and "non-users" of family chart linking API for a deductive approach of facilitators and barriers to implementing a tool in a clinical setting.

Results

Electronic health record tools

We identified six tools from five developers with functionalities related to family chart linking (Table 2). Search of the ONC Health IT database resulted in 181 unique products from 161 developers, (Supplementary Table S1). Reasons for exclusion included a focus on ambulatory services, pharmacy and prescriptions, optometry, and oncology or other specializations related to tertiary care. We explored online and publicly accessible resources for 45 products for mention of collecting either family health history or genetic information. We contacted 15 of those product developers with some online material regarding family health history for additional information and details related to tools available for family chart linking. We heard from one developer and accessed the remaining products based on available resources.

Four of the included API were developed by EHR providers: EpicCare®, Cerner, and CareEvolution. One was a web-based program with Fast Healthcare Interoperability Resources (FHIR) standardizations to support EHR integration. The AncestryHealth kit was a shareable health report for clinicians and intended to be shared across family members based on direct-to-consumer (DTC) genetic test results, but the product has since been discontinued.

EpicCare® provides two tools for relatives in the same EHR system. The first allows clinicians to copy structured family health history from one patient's EHR to another's. Transferring of this information is a one-time event and charts are not updated automatically between individuals. This functionality was created for scenarios in which newborn siblings are added to a health care system to eliminate the need to re-enter identical information. However, there is no upper age limit for which this tool can be applied. The second is the function to link individuals within an EHR system so that clinicians can view the charts of both family members. The links for this option are not bi-directional, meaning that the clinicians of Relative A could

TABLE 3 Key informant interview considerations for family chart linking and facilitating cascade genetic testing in electronic health record systems.

Sociotechnical Model Component	Considerations for Family Chart Linking
Hardware and software	• Interoperability between systems is possible and essential for widespread implementation
	• Paradigm shift toward shared information across the charts of family members
Clinical content	• Standardized data formats for clinical information required (e.g., genetic test results)
Human computer interface	• Third party apps where patients control flow of their information are possible alternatives to sharing within an EHR system
People	• Patient preferences for sharing genetic information with family members not well understood
Workflow and communication	• Paradigm shift away from physicians as gatekeepers of patient data
	• Large changes to workflow may be barriers to physicians already busy with competing demands
Internal organization features (e.g., policies, procedures, and culture)	• Competing demands for systems with high IT resource needs
	• Perceived evolution away from family-based genetic testing to universal screening
External rules and regulations	• HIPAA compliance
	• Procedures for patient and relative to consent to chart linking unclear
Measurement and monitoring	• Alternatives may be more favorable than chart linkage tools (e.g., maintain status quo; patient-controlled third party apps; universal genetic testing rather than family linkage with cascade testing)

view the charts of Relative B but not necessarily vice versa (Table 2).

A separate approach, as exhibited by MyLegacy and myFHR, is a web-based program administered by a patient's EHR system. The patients record family health history themselves and the data is collected in a standardized format (i.e., SMART on FHIR) to be viewed by the clinicians. This process allows a patient to share access to their information with others without giving direct access to their EHR. This option emphasizes external content for personalized decision-support. Similar to MyLegacy and myFHR, MeTree is a web-based app with an API to EHR systems.

Across all included tools, we found a lack of explicit guidance on the recommended consent process for sharing of family health history between relatives. EpicCare® recommends healthcare organizations determine and implement consent policy and process necessary for sharing family history between relatives and recognizes that consenting policies may vary by organization.

Key stakeholder interviews

We conducted five stakeholder interviews. Key informants (with abbreviated identifiers in parathesis) included a clinical geneticist from a not-for-profit medical group (CG), a population genetics researcher (R), a privacy management advisor for an integrated health care delivery system (P), a health services researcher (HS) and clinician with the U.S. Department of Veterans Affairs (VA), and a project manager for a private health IT developer (PM). The main considerations that emerged from summary of key informant interviews are described in Table 3.

Interoperability and standardization between systems was viewed as a critical technical requirement for family chart linkage

For an API that is external to a health care system EHR, emphasis on interoperability through standardized codes, "specifically HL7 (SMART on FHIR), would allow for better utility of family health history" (PM) Free-text or open comment fields have been historical means to collect history of family diseases, without a set standard of how the information should be collected or structured (PM). Another key informant was more concerned about the standardization of specific genetic test results, rather than the collection of family health history (CG). The key informant had concerns with how evolving interpretation of genetic test results could be standardized, as photocopies of paper results are still common in many EHR systems.

Clarity about HIPAA-related constraints was the primary barrier to implementation of family chart linkage programs

Nearly all participants mentioned HIPAA as the regulating factor when sharing family health history between patients, noting that it "governs when patient authorization is necessary" (P). However, one key informant felt that HIPAA was often over-interpreted and used as justification for lagging technology despite a lack of specific guidance in most circumstances (R).

Third-party and app-based solutions where patients manage data and sharing might have broader reach than linking individuals within the same EHR system

Some informants felt that there was little incentive for EHR systems to consider sharing of family health history between

relatives since adult relatives do not commonly use the same EHR system (HS). One participant felt that we will need automated and patient-initiated solutions that are external to clinical EHR systems and that there would be more advancement in mobile apps with standardizing to SMART on FHIR (R). That key informant also suggested that HIPAA and consent might be easier to navigate in patient-initiated solutions rather than in a health care provider-initiated solution (R).

Paradigm shift in structure and directionality of EHR systems could be a solution for sharing family health information across relatives

One participant felt that a paradigm shift of the directionality of medical charts would need to shift from patient-provider to patient-patient in order to facilitate record linkages. They felt that clinicians are generally viewed as the gatekeepers of patient charts, even family health history, with the discretion to consult and share with other physicians as needed. Changing to a structure in which EHR data can be shared between patients would require a re-thinking of how health IT is structured (PM). Another paradigm shift would be thinking of family health history as a collective family chart rather than owned by a single individual. Patient records are thought of as individually owned, so a collective family record may change that mentality (HS). For this solution, the key informant envisioned a separate medical chart with family history information to which relative can link and share, rather than linking between family member charts directly and therefore restricting access to individual-level information. The key informant felt that a shared family record could also eliminate the concern for privacy regarding information not relevant to family members, as family-level data would be shared but individual-level data could still be restricted.

We noted additional comments that were mentioned by only a single key informant. For systems in which the health information technology is already lagging, automation of family health history and cascade genetic testing is low priority (HS). For primary care providers, for whom there is already a strain on resources and time, universal genetic testing presents a more simplified approach to identifying carriers of actionable genetic mutations (CG). We also note that these limitations to implementing family chart linkage and automated cascade genetic testing came from users of EHR systems, as opposed to non-patient-facing key informants. The consent process should be customizable to reflect the variation in comfort of patients to share their information with family members (P). A broad consent would be inadequate, particularly because future discoveries may change how to think about what we want to keep private (P). Some stakeholders felt that most EHR systems have to prioritize clinical support tools and interpretable genetic test results, and the ability to address the improvements required for cascade genetic testing will be obsolete once genetic testing becomes affordable for a universal testing approach (CG).

Discussion

We conducted an environmental scan and key informant interviews to describe the current state of EHR-based or EHR-connected platforms for family chart linkage. Across evaluation of six chart-linkage tools and key informant interviews, we found that the technical capacity to build and implement family chart linkage exists. These technical aspects related to several domains in the socio-technical model, and most specifically show that the first domain, hardware and software, is not a main challenge facing the implementation of this functionality. However, several non-technical barriers may limit their adoption, including lack of clarity around HIPAA compliance issues; lack of guidance about optimal consent procedures for patient and relative consent to participate in chart linking; competing organizational demands; large changes to workflow required for implementation; and conceptual shifts in the current prevailing thought about the role of the physician and the structure and purpose of EHRs themselves. In the socio-technical model, these issues around the external rules and regulations appear to be a prominent challenge in the context of link family records. Additionally, in organizational settings facing competing demands for time and resources, alternative functionalities may exist that might appear more attractive, such as app-based health information sharing platforms where information flow is controlled by patients, not health care systems. The idea that family-based cascade genetic testing may soon be replaced by universal genetic screening was also noted.

Some record-linking functionality is currently available, but there are few tools for this specific purpose within the current EHR structure. Of the tools we identified, two were available through EpicCare®. EpicCare® maintains over 30% of the EHR market share, particularly for large-scale health care systems in which generational family members are more like to be included and functions could be applied. Similarly, Cerner provides some functionality and represents a substantial market share of EHR systems, including the VA, where it is rare to have family members within the same health care system for which sharing of family health history would apply.

Interviews with key informants suggested that overcoming the limitation of sharing family health history between relatives of different EHR systems may best be solved through interoperability and third-party tools. Meaningful Use (MU), a result of the HITECH Act, outlines such incentives through the Center for Medicare and Medicaid System (CMS) and has been pivotal in creating incentives for electronic health record systems to improve their technology and functionality (Blumenthal and Tavenner, 2010). As of 2017, collection of family health history has been included as an optional component of MU, incentivizing health care systems to implement tools that allow for aggregating and reporting on family health history (Aziz et al., 2017). Stage 2 objectives of MU included the ability to record patient family health history in a structured data format

and by 2013 over 85% of EHR systems had adopted this function (ONC, O. of the N. C. for H. I., 2014). A product of this emphasis on standardization has been wider adoption of Health Level Seven (HL7) International which has developed Fast Healthcare Interoperability Resources (FHIR), standards for API to allow the exchanging of EHRs. Building off of FHIR, SMART on FHIR was developed to transform EHRs into mobile-app based platforms. Standardization of family health history has been developed using HL7 FHIR but is still up for public comment of the current draft.

The future landscape of technology suggested to several of our key informants that third-party apps could be the most likely solution to sharing family health history between relatives for cascade genetic testing. A similar approach to using third-party tools for the interpretation of genetic DTC may be necessary to fill the current gap in needs (Nelson, Bowen and Fullerton, 2019), as well as for communicating genetic test results to at-risk family members (Haas et al., 2021). These mobile-based app approaches could provide additional tools for external content and shared clinical decision making. However, it is important to note that these types of patient-controlled solutions effectively put the onus of relative notification on patients. This is the current state of risk notification between relatives, where health systems have no direct role in risk notification, and has noted problems, including incomplete risk disclosure and patient burden (Henrikson et al., 2021). It is still unknown whether app-based notification would solve the known issues related to incomplete disclosure, which include; problematic family relationships, concerns about accuracy of patient-led disclosure, patient burden, and concern about distressing relatives. In that context, the use of third-party apps for risk sharing has to date shown limited promise (Haas et al., 2021).

Tools for collecting family health history have lagged compared to the advance in technology, with most still relying on paper-based forms and limited integration with EHR systems (Cleophat et al., 2018). The most widely used tools by genetic counselors, My Family Health Portrait (MFHP; freely available at www.familyhistory.hhs.gov) and Family Healthware (http://www.cdc.gov/genomics/about/family.htm), are not integrated into EHR systems (Feero, Bigley and Brinner, 2008). Qualitative work by Widmer et al. among genetic counselors found limited adoption of these tools because of their lack of integration into EHR systems (Widmer et al., 2013), seeking tools that were consistent (i.e., standardized), reduce repetitive questions, and improve clarity of clinical implications.

Non-intuitive or additional work arounds would likely put added burdens on clinicians. Primary care providers (PCP) continue to view their role to include the collection of family health history (Carroll et al., 2019). However, PCPs have often reported a lack of resources and tools for collecting and interpreting these details despite an expansion of genetic technology (Mikat-Stevens, Larson and Tarini, 2015; Carroll et al., 2019). As suggested by our interview with a clinical geneticist, the added burden of navigating cascade screening may point to universal genetic testing as a more feasible solution. While stakeholders interviewed in our study implied acceptability of universal genetic testing from their own perspective, future work should investigate patient perspectives with regards to implementing such an approach.

Several solutions to sharing family health history between relatives in an EHR system were suggested by key informants. However, these required major shifts in conceptualizing the purpose and directionality of patient records. Additionally, EHR systems are also structured within policies and regulations that would likely put constraints on changing this structure. Key informants felt that the limiting factor is the interpretation of regulations rather than the technological aspects, since the capacity to perform these tasks exists. However, one key informant felt that there was a tendency to be overly cautious with how regulations (e.g., HIPAA) are interpreted.

We acknowledge some limitations to this exploratory study. Our sample of key informants was small, and it is possible we missed some perspectives and settings, such as in oncology tertiary care. Due to the proprietary nature of the included tools, it is possible that there is guidance or information not publicly available to our team. Importantly, we were unable to interview patients and families given the limited scope of this project. Future research could explore patient and family thoughts on chart linking in more detail.

Limited progress has been made in terms of EHR functionality and interoperability. However, SMART on FHIR for smart devices may be filling the gap in needs for sharing of relevant information between family member but is limited the gatekeepers of patient EHR. More recent emphasis has been placed on improving clinical decision support and interpretation, benefits of which would not be confined to either a cascade screening or universal genetic testing approach (Carroll et al., 2019). Limited bioinformatic support has been developed to automate family cascade genetic testing. Though the technology to support family chart linkage is available, to date multiple substantial non-technical barriers exist to its implementation. The potential clinical benefits of these types of tools in facilitating cascade genetic testing and alleviating patient burden associated with patient-led risk disclosure could be explored in future research and contribute to the weighing of potential barriers.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Kaiser Permanente Washington Health Research Institute.

Author contributions

CH, JR, SF, and NH were responsible for conceptualization. CH and NH contributed to methodology, investigation, and formal analysis. CH was responsible for data curation, interviewing, and writing the original draft and revisions of the manuscript. NH provided supervision and funding acquisition. AS was responsible for project administration. JR, SF, and NH contributed to manuscript review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.886650/full#supplementary-material

References

Aziz, A., Pflieger, L., O'Connell, N., Schiffman, J., and Welch, B. M. (2017). Compatibility of family history cancer guidelines with meaningful use standards. *JCO Clin. Cancer Inf.* 1, CCI.17.00076. doi:10.1200/CCI.17.00076

Blumenthal, D., and Tavenner, M. (2010). The "meaningful use" regulation for electronic health records. *N. Engl. J. Med.* 363 (6), 501–504. doi:10.1056/NEJMp1006114

Braun, V., and Clarke, V. (2006). Using thematic analysis in psychology. *Qual. Res. Psychol.* 3 (2), 77–101. doi:10.1191/1478088706qp063oa

Carroll, J. C., Allanson, J., Morrison, S., Miller, F. A., Wilson, B. J., Permaul, J. A., et al. (2019). Informing integration of genomic medicine into primary care: An assessment of current practice, attitudes, and desired resources. *Front. Genet.* 10, 1189. doi:10.3389/fgene.2019.01189

Caswell-Jin, J. L., Zimmer, A. D., Stedden, W., Kingham, K. E., Zhou, A. Y., and Kurian, A. W. (2019). Cascade genetic testing of relatives for hereditary cancer risk: Results of an online initiative. *J. Natl. Cancer Inst.* 111 (1), 95–98. doi:10.1093/jnci/djy147

Choo, C. W. (2005). The art of scanning the environment. *Bul. Am. Soc. Info. Sci. Tech.* 25 (3), 21–24. doi:10.1002/bult.117

Cleophat, J. E., Nabi, H., Pelletier, S., Bouchard, K., and DorvalM. (2018). What characterizes cancer family history collection tools? A critical literature review. *Curr. Oncol.* 25 (4), e335–e350. doi:10.3747/co.25.4042

Feero, W. G., Bigley, M. B., and Brinner, K. M. (2008). New standards and enhanced utility for family health history information in the electronic health record: An update from the American health information community's family health history multi-stakeholder workgroup. *J. Am. Med. Inf. Assoc.* 15 (6), 723–728. doi:10.1197/jamia.M2793

Griffin, N. E., Buchanan, T. R., Smith, S. H., Leon, A. A., Meyer, M. F., Liu, J., et al. (2020). Low rates of cascade genetic testing among families with hereditary gynecologic cancer: An opportunity to improve cancer prevention. *Gynecol. Oncol.* 156 (1), 140–146. doi:10.1016/j.ygyno.2019.11.005

Haas, C. B., Scrol, A., Jujjavarapu, C., Jarvik, G. P., and Henrikson, N. B. (2021). Usefulness of mobile apps for communication of genetic test results to at-risk family members in a U.S. Integrated health system: A qualitative approach from user-testing. *Health Policy Technol.* 10 (2), 100511. doi:10.1016/j.hlpt.2021.100511

Hampel, H. (2016). Genetic counseling and cascade genetic testing in Lynch syndrome. *Fam. Cancer* 15 (3), 423–427. doi:10.1007/s10689-016-9893-5

Henrikson, N. B., Blasi, P., Figueroa Gray, M., Tiffany, B. T., Scrol, A., Ralston, J. D., et al. (2021). Patient and family preferences on health system-led direct contact for cascade screening. *J. Pers. Med.* 11 (6), 538. doi:10.3390/jpm11060538

Henrikson, N. B., Blasi, P. R., Fullerton, S. M., Grafton, J., Leppig, K. A., Jarvik, G. P., et al. (2019). It would be so much easier": Health system-led genetic risk notification-feasibility and acceptability of cascade screening in an integrated system. *J. Community Genet.* 10 (4), 461–470. doi:10.1007/s12687-019-00412-z

Henrikson, N. B., Wagner, J. K., Hampel, H., DeVore, C., Shridhar, N., Williams, J. L., et al. (2020). What guidance does HIPAA offer to providers considering familial risk notification and cascade genetic testing? *J. Law Biosci.* 7 (1), lsaa071. doi:10.1093/jlb/lsaa071

Mai, P. L., Garceau, A. O., Graubard, B. I., Dunn, M., McNeel, T. S., Gonsalves, L., et al. (2011). Confirmation of family cancer history reported in a population-based survey. *J. Natl. Cancer Inst.* 103 (10), 788–797. doi:10.1093/jnci/djr114

Mandl, K. D., and Kohane, I. S. (2009). No small change for the health information economy. *N. Engl. J. Med.* 360 (13), 1278–1281. doi:10.1056/NEJMp0900411

Marsolo, K., and Spooner, S. A. (2013). Clinical genomics in the world of the electronic health record. *Genet. Med.* 15 (10), 786–791. doi:10.1038/gim.2013.88

Mikat-Stevens, N. A., Larson, I. A., and Tarini, B. A. (2015). Primary-care providers' perceived barriers to integration of genetics services: A systematic review of the literature. *Genet. Med.* 17 (3), 169–176. doi:10.1038/gim.2014.101

Nelson, S. C., Bowen, D. J., and Fullerton, S. M. (2019). Third-party genetic interpretation tools: A mixed-methods study of consumer motivation and behavior. *Am. J. Hum. Genet.* 105 (1), 122–131. doi:10.1016/j.ajhg.2019.05.014

Newson, A. J., and Humphries, S. E. (2005). Cascade testing in familial hypercholesterolaemia: How should family members be contacted? *Eur. J. Hum. Genet.* 13 (4), 401–408. doi:10.1038/sj.ejhg.5201360

Novak, L. L., Holden, R. J., Anders, S. H., Hong, J. Y., and Karsh, B. T. (2013). Using a sociotechnical framework to understand adaptations in health IT implementation. *Int. J. Med. Inf.* 82 (12), e331–44. doi:10.1016/j.ijmedinf.2013.01.009

Ohno-Machado, L., Kim, J., Gabriel, R. A., Kuo, G. M., and Hogarth, M. A. (2018). Genomics and electronic health record systems. *Hum. Mol. Genet.* 27 (R1), R48–R55. doi:10.1093/hmg/ddy104

ONC, O. of the N. C. for H. I. (2014). Hospital adoption of meaningful use stage 2 functionalities: U.S. Hospital adoption of computerized capabilities to meet meaningful use stage 2 objectives, health IT quick-stat #23. Available at: https://dashboard.healthit.gov/quickstats/pages/FIG-Hospital-Adoption-Meaningful-Use-Stage-Two-2013.php.

Sittig, D. F., and Singh, H. (2010). A new sociotechnical model for studying health information technology in complex adaptive healthcare systems. *Qual. Saf. Health Care* 19 Suppl 3, i68–74. doi:10.1136/qshc.2010.042085

Unger, S.Division of Genetic Medicine; Centre Hospitalier Universitaire Vaudois (2020). *Dissemination of genetic information in Swiss families with lynch syndrome: A qualitative exploratory study*. Lausanne, Switzerland: Clinical Oncology and Research, 1–5. doi:10.31487/j.COR.2020.01.01

Wang, Y., Wang, L., Rastegar-Mojar, M., Liu, S., Shen, F., and Liu, H. (2017). Systematic analysis of free-text family history in electronic health record. *AMIA Jt. Summits Transl. Sci. Proc.* 2017, 104–113.

Widmer, C., Deshazo, J. P., Bodurtha, J., Quillin, J., and Creswick, H. (2013). Genetic counselors' current use of personal health records-based family histories in genetic clinics and considerations for their future adoption. *J. Genet. Couns.* 22 (3), 384–392. doi:10.1007/s10897-012-9557-z

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Population-based screening of newborns: Findings from the newborn screening expansion study (part two)

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Rapid advances in genomic technologies to screen, diagnose, and treat newborns will significantly increase the number of conditions in newborn screening (NBS). We previously identified four factors that delay and/or complicate NBS expansion: 1) variability in screening panels persists; 2) the short duration of pilots limits information about interventions and health outcomes; 3) recent recommended uniform screening panel (RUSP) additions are expanding the definition of NBS; and 4) the RUSP nomination and evidence review process has capacity constraints. In this paper, we developed a use case for each factor and suggested how model(s) could be used to evaluate changes and improvements. The literature on models was reviewed from a range of disciplines including system sciences, management, artificial intelligence, and machine learning. The results from our analysis highlighted that there is at least one model which could be applied to each of the four factors that has delayed and/or complicate NBS expansion. In conclusion, our paper supports the use of modeling to address the four challenges in the expansion of NBS.

KEYWORDS

newborn screening, genomics, pilot studies, metabolic disease, immunodeficiencies, ducheme muscular dystrophy, public health, population based screening

Introduction

In the United States, every year, at least 12,905 babies are identified with genetic disease by population-based newborn screening (NBS) (Sontag et al., 2020). The goal of NBS is to enable the early diagnosis and treatment of disease in newborns to improve health outcomes, at both an individual and population level. While screening is directed at newborns, the health benefits of a positive screen can be multiplied through the testing of parents, siblings, and other at-risk relatives (known as cascade testing), and this increases the population impact of NBS screening (Caggana et al., 2013). NBS is a complex but well-established system involving diverse stakeholders, including researchers, state public health departments, pediatricians and family physicians, subspecialists and geneticists, industry, parents and advocates, and federal agencies. These entities contribute to the key components of NBS: 1) Prenatal Education, 2) Laboratory and Hospital-based Screening, 3) Diagnosis, and 4) Medical Management/Surveillance (www.aphl.org).

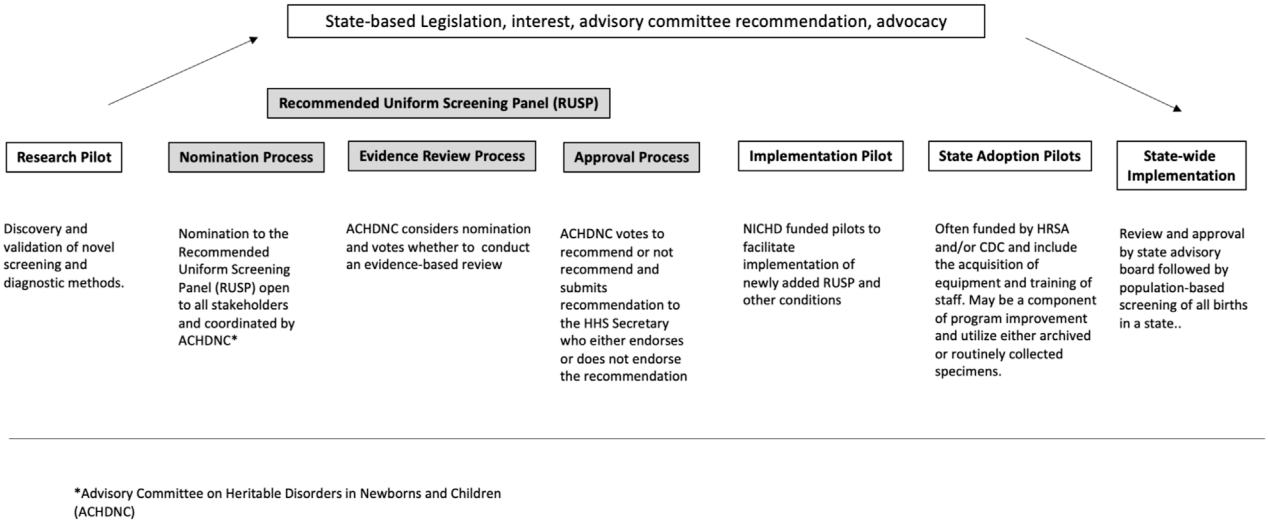

FIGURE 1
Pathway of candidate conditions (adapted from Brower et al., 2022).

NBS began in the 1960s with screening for a single disorder. It has expanded over time and now encompasses a recommended uniform screening panel (RUSP) of 35 core and 25 secondary conditions[1] that the Secretary of the Department of Health and Human Services (HHS) recommends for states to screen as part of their state NBS programs and up to an additional 20 non-RUSP conditions screened in at least one state (https://www.hrsa.gov/advisory-committees/heritable-disorders/index.html; www.newsteps.org; and www.nbstrn.org)[2]. On the Newborn Screening Translational Research Network (NBSTRN) website (www.nbstrn.org), information regarding the composition of state NBS panels, including the RUSP and non-RUSP conditions can be found on the NBS-Virtual Repository of States, Subjects & Samples (NBS-VR) data tool, which provides national and state-level views of these policies and procedures, and the NBS Conditions Resource (NBS-CR), which provides a centralized resource[3] of facts and statistics for each condition. The expansion of NBS increases the number of screened conditions and is usually triggered by the approval of novel therapies and interventions, or the discovery of new screening or diagnostic technologies (McCandless and Wright 2020). With rapid advancements in genomic technologies to screen, diagnose, and treat newborns, there are conceivably hundreds to thousands of conditions that could be detected; however, not all would be considered as candidates for NBS and for NBS pilots (Berg et al., 2017; Milko et al., 2019). Historically, the evolution of a condition from being a candidate for NBS to implementation of nationwide screening involves a series of steps and pilots conducted by researchers and state NBS programs that are supported by advocacy groups, industry, and/or federal agencies (such as National Institutes of Health (NIH), Center for Disease and Control Prevention (CDC), and Health Resources and Services Administration (HRSA)).

To review the expansion of NBS and the role of NBS pilots in this expansion, NBSTRN conducted the NBS Expansion Study which included a meeting of experts and a series of analyses summarized in our companion paper "*Population-based Screening of Newborns: Findings from the NBS Expansion Study* (Part One)" (Brower et al., 2022). NBSTRN is a resource for investigators engaged in NBS-related research led by the American College of Medical Genetics and Genomics (ACMG) and is funded by a contract from the *Eunice Kennedy Shriver* National Institute of Child Health and Development (NICHD). Brower et al. describes the current approach to expansion that uses research and implementation pilots of short duration and limited sizes in a small number of states, followed by condition-by-condition review by a federal advisory committee, and state by state adoption (Figure 1, adapted from Brower et al., 2022). Brower and others found that the current system of NBS expansion is not able to keep pace with the pipeline of NBS screening and pilot candidate conditions and described in detail four factors that delay and/or complicate NBS expansion (Table 1). In this paper, we describe how decision modelling can be used to address these four factors in a cost-effective and efficient way. This purpose of the paper is a call to action for additional resources to support research in developing, hypothesis testing, and applying of the use of models in NBS pilot studies.

TABLE 1 Four challenges in newborn screening pilot*.

Factor 1. Variability in screening panels persists.
Factor 2. The short duration of pilots limits information about interventions and health outcomes.
Factor 3. Recent RUSP additions are expanding the definition of NBS.
Factor 4. The RUSP nomination and evidence review process has capacity constraints.

*These four challenges are discussed further in Brower et al (2022)

Suggestions on the use of models to facilitate the expansion strategies in newborn screening

The fundamental purpose of decision modeling in public health is to compare different policy options or strategies by calculating and comparing the expected value of the outcomes that result from the possible choices. Models have been used to simulate clinical trials, hypothetical scenarios, and projection of cost-effectiveness analysis (Prosser et al., 2013). In the context of NBS expansion, decision analysis that uses models can provide a quantitative analysis of all the relevant inputs (e.g., resources, screening parameters, incidence, cost of treatments) according to their probabilities (e.g., disease prevalence, likelihood of disease onset) and their relative importance at the different stages of NBS expansion from research pilots to nationwide implementation (Figure 1). Research studies are mechanisms to discover novel technologies to screen, diagnose, treat, and manage NBS conditions, and clinical trials are conducted to establish the safety and efficacy of treatments. Both efforts inform NBS pilot studies that most often assess the analytical and clinical validity of screening and, in some cases, diagnostic methods. Taken together, research studies, clinical trials, and NBS pilots by their design generate only a small fraction of the knowledge needed to inform the broad clinical implementation and public health practice changes are needed to realize NBS expansion. Decision modelling could be used to address these limitations and augment the information derived from research, clinical trials, and NBS pilots, ultimately improving the current approach to NBS expansion (Caggana et al., 2013; Gantt et al., 2016). This type of modeling may be helpful for the several scenarios encountered in NBS expansion and rare diseases including: different population sizes, the often very low disease incidences of rare diseases that are candidates for NBS and NBS pilots, variable costs of and access to treatments and interventions, and differences in analytical approaches based on individual state practices, including screening algorithms and thresholds for determining screen positives, access to expertise, and resources for follow-up and treatment.

How do you select the models to use?

To identify model(s) that could address the four factors in NBS expansion, we reviewed the literature to find models that have been used to address similar problems. In addition to our literature review, we noted that models have been and are being used in NBS. Examples include the decision analytic modeling that is currently conducted during the evidence-based review of conditions considered by the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC). Over 100 articles were reviewed and we identified models that were applicable to support the development, implementation, and expansion of NBS for rare diseases (Boshuizen et al., 2001; Carroll and Downs, 2006; Castilla-Rodríguez et al., 2017; Chan et al., 2011; Ding et al., 2016; Gantt et al., 2016; Hamers and Rumeau-Pichon, 2012; Kemper and Downs, 2000; Khneisser et al., 2015; Pandor et al., 2004; Peterson et al., 2013; Thiboonboon et al., 2015; Tran et al., 2007; van den Akker-van Marle et al., 2006). In our inclusion criteria, we reviewed models that were used and could be used for the following purposes: 1) research studies including efforts to discover and validate new technologies and treatments, 2) research pilots, 3) implementation pilots, and 4) state adoption pilots in newborn screening. Because the NBS system includes public health and clinical care, we also searched for models used to address similar system level challenges encountered in healthcare. These models may be particularly helpful in NBS expansion if they prove useful and future efforts are given the opportunity and support to further explore their value. To expand the application of other models to NBS expansion and pilot studies, we also included literature from the fields of system sciences, business, economics, and healthcare. From this review, we summarized the commonly used decision analytic models that may be appropriate for NBS decision-making (Table 2). It is important to note that this list is not exhaustive; rather, this list should act as an open invitation for all NBS stakeholders to explore and apply models to address NBS expansion challenges (Table 3).

What are models?

Models can be used to simulate a reasonable representation of real-life scenarios. In NBS expansion, decision modeling can be used to study the *"context"* and *"complexity"* of a condition that is a candidate for a NBS pilot or for the RUSP. Models can inform how screening for a condition may transpire during state-wide implementation and/or adoption. By *context*, we can define the study population, the natural history of the disease, and the treatments, interventions, and management approaches that are to be studied. Context can also help decision-makers determine the portion of the problem to be included in the analysis. For example, in the case of conducting a cost-effectiveness analysis for lysosomal

TABLE 2 Types of analysis derived from modelling.

Type of analysis	Description	References
Economic evaluation	A process of systematic identification, measurement and valuation of the inputs and outcomes of two alternative activities, and the subsequent comparative analysis of these	Grosse et al. (2016); Prosser et al. (2013); Wright et al. (2015)
Programmatic cost analysis	A process to compare the program costs to program outcomes which can include all the resources required to implement an intervention, including personnel, space and utilities, travel, materials, and supplies	Bessey et al. (2018)
Cost-effectiveness analysis	A process that examines both the costs and health outcomes of one or more interventions and compares an intervention to another intervention (or the status quo) by estimating how much it costs to gain a unit of a health outcome, such as a life year gained, or a death prevented	Castilla-Rodríguez et al. (2017); Chan et al. (2011); Kemper and Downs, (2000)
Cost of illness analysis	A method of measuring medical and other costs resulting from a specific disease or condition	Tran et al. (2007)
Cost-benefit analysis	A systematic approach where the program costs and benefits are converted into dollars to estimate the strengths and weaknesses of alternatives used to determine options which provide the best approach to achieving benefits while preserving savings	Ding et al. (2016); Khneisser et al. (2015); Lord et al. (1999)
Cost-utility analysis	A special type of cost-effectiveness analysis which includes health outcomes in the analysis (such as quality adjusted life year (QALYs))	Carroll and Downs, (2006)
Budget Impact analysis (also called 'business case analysis)	A type of economic assessment that estimates the financial consequences of adopting a new intervention and evaluates whether the high-value intervention is affordable. A process that provides the best-value analysis that considers not only cost but also other quantifiable and non-quantifiable factors supporting an investment decision	Garattini and van de Vooren, (2011)
Return of Investment	A way to calculate the financial gains (or losses), while taking into account all the resources invested and all the amounts gained through increased revenue, reduced costs, or both	Bertram et al. (2018); Stenberg et al. (2016)
Social Return of investment	A pragmatic form of cost-benefit analysis that measures the social value generated by an intervention by considering its broader impact on all stakeholders within the locality of the intervention and incorporating social value where it is appropriate	Banke-Thomas et al. (2015)

TABLE 3 Selected models proposed to address NBS expansion*.

Type of Model	Description	References
Decision analytic model	A framework for compiling clinical and economic evidence in a systematic fashion, determining your product's value, and communicating that value to decision makers.	Grosse et al. (2016); Prosser et al. (2013), Prosser et al. (2018) www.treeage.com
Markov Model	A mathematical model using the probabilities of different health states and the rates of transitions among them to recognize patterns, make predictions and to apply the statistics of sequential data.	Chan et al. (2011) www.treeage.com
Discrete Event Simulation Model	A method of simulating the behavior and performance of a real-life process, facility, or system.	Salleh et al. (2017) www.mathworks.com
Microsimulation model	A method of using individual-based state-transition models to reflect individual clinical pathways, incorporate the impact of history on future events, and capture the variation in patients' characteristics at baseline.	Verkleij et al. (2021) www.treeage.com
Agent-based model	A computational model for simulating the actions and interactions of autonomous agents in order to understand the behavior of a system and what governs its outcomes.	Tracy et al. (2018) www.anylogic.com
System dynamic models	A computer-aided approach for strategy and policy design, which can portray processes of accumulation and feedback and that may be tested systematically to find effective policies for overcoming policy resistance.	Yu et al. (2019) https://systemdynamics.org
System thinking models	A way of approaching problems that asks how various elements within a system, (which could be an ecosystem, an organization, or something more dispersed such as a supply chain) can influence one another.	Carey et al. (2015) www.vensim.com

*Table 3 highlights the different models that can be used to conduct the different analyses indicated in Table 2. The availability of models is not limited to the list depicted here.

storage disorders (LSDs), we may ask ourselves, "Do we consider the consequence (cost and benefit) of the detection of possible comorbidities (i.e., deafness, blindness, pulmonary, and cardiac problems) in our decision making?" By *complexity*, we can define the appropriate scope and parameters of the NBS system component(s) to include in the analysis. The complexity of the analysis will depend on the study's purpose, the availability of data, and the time allotted for the study's design and examination. The *time horizon* of the model describes the study's length of time, which can be informed by the length of a typical research pilot. The model can also include the time frame of the natural history of the disease and the disease process and compare newborns identified through NBS versus clinical presentation of symptoms. The findings from modeling could be a part of nomination information submitted to the ACHDNC.

The ACHDNC reviews the nominations to the RUSP and the evidence review process defines the net benefit of early identification through NBS and quantifies the opportunity for early treatment as compared to identification through symptomatology and clinical presentation and presumably later treatment. For example, a decision analysis model for NBS screening for spinal muscular atrophy (SMA) can be used to examine the time horizon of six-months with early treatment after NBS identification, compared to later treatment in the absence of NBS SMA screening. As another example: if the goal is to understand to the long-term benefits of treatment administrated at six-month over the next 5 years, a Markov model can be used to understand the long-term benefits of early treatment by modeling a 5-years time horizon comparing health outcomes resulting from interventions that occurred at different disease progression stages. Models can be applied prospectively throughout the pilot study as well as retrospectively after the pilot is completed.

Potential use cases and models in newborn screening

While there are many models to select from, additional research is needed to determine which models work best, to develop additional models if needed, and then to apply the model(s) to address NBS expansion challenges. In this paper, we highlight how one "could" use models to facilitate NBS expansion in the United States. For each factor listed in Table 1, we describe 1) the *"use case,"* which highlights how the identified factor has delayed NBS expansion, 2) the "potential solution(s)" in addressing the challenges, and 3) a "*model*" that could be developed and applied to solve or address the challenges. The model(s) suggested below is an example for discussion; thus, we believe additional research is needed to support the development of models to further the discovery of solutions in addressing the challenges.

Factor 1. Variability in screening panels persists

a. Use Case: State NBS screening panels shows that the number of conditions screened ranges from a low of 32 core conditions to a high of 71 core, secondary, and non-RUSP conditions combined, which indicates the persistence of variability in the composition of NBS screening panels by state. A total of 81 different conditions are screened across the United States Addition of conditions to screening panels is done by individual states, and each develops its own screening and follow-up algorithm. ACHDNC has established a nomination and evidence review process that established the RUSP. However, state laws can mandate screening for conditions not included on the RUSP. These state-specific legislative mandates and differences in practices lead to implementation differences across the United States and limit opportunities to systematically apply best practices, assess quality, and aggregate data. The lack of systematic data collection and interoperability between states makes it challenging to obtain and maintain data regarding barriers and facilitators of screening for new conditions within NBS.
b. Potential Solutions(s): To help decrease the variability in screening panels, states could adopt a real-time tracking and assessment of state practices that is assessable on a shared platform (such as on NBSTRN).
c. Models: With modeling, the researchers can use real-time data (the number of cases identified) and assumptions (the different treatment options—conventional treatment vs experimental treatment) to simulate different scenarios (to screen with test 1 vs test 2) to test different hypotheses (to screen 50,000 vs 100,000 babies per year in the pilot study). For example: It took 10 years for every state to implement screening for severe combined immunodeficiency (SCID). During the 10 years, a baby born with SCID in a state that was not offering SCID screening may not had been identified early enough to benefit from treatment before the onset of opportunistic infections. In some cases, SCID babies identified through the presentation of clinical symptoms did not survive and/or had a more challenging course of treatment and poorer outcomes. Data collected at the state level could be used to document the variation in practices and be used to inform models to explore the impact of screening vs not screening as well as the impact of different screening approaches. This has the potential to provide guidance to policymakers and decision-makers to support implementation in their own state based on the state-specific contextual factors included in the model. A decision analytic model could be used to document the increase in number of individuals who achieve the best health outcomes when all states adhere to a uniform screening panel. The decision analytic model could be used to define cost-effectiveness (comparing screening vs no-

screening), cost-utility (examining the quality adjusted of life) with screening, or cost-of-illness analysis (to account for the additional inpatient hospitalization and other health expenditures related to care of the patient identified with a late diagnosis of a genetic condition). The model uses different cost ranges for the NBS screening components (point of care or laboratory equipment, reagents, expertise, quality assurance (QA) etc.). To project the budget to offer screening for a specific new condition or to use a new screening instrument for a current RUSP condition, a business case analysis template could be developed for different states with varied population sizes to account for operationalization factors (such as hospital versus laboratory screening, the salary of NBS team members), effort, contractual issues, upgrading, and maintenance support for implementing screening. Creating a system of models (or templates) used for projecting cost and benefits can help facilitate the adoption and implementation of new conditions.

Factor 2. The short duration of pilots limits information about interventions and health outcomes

a. Use Case: There are no standardized protocols used to conduct NBS research, implementation, and/or adoption pilots. NBS research pilots often end when a single newborn with the targeted condition has been identified, and the diagnosis confirmed. In contrast, implementation pilots may screen for a pre-determined duration or until ~80,000 newborns have been screened. Research and implementation pilots usually provide sufficient data to determine the analytical and clinical validation of at least one state-specific screening test and algorithm. For a state to expand its panel to include a new condition, an adoption pilot that replicates the analytical and clinical validation studies of the research and/or implementation pilots is required, and the results are not typically published. The amount of funding that is available to support NBS pilots as well as their short timeframe does not support the longitudinal data collection that is necessary to assess the benefit of early identification through screening, including information about the type, duration, and availability of treatments and the health outcomes of treated individuals. However, models can be used to simulate the natural history and clinical course of a patient identified through NBS beyond the pilot study duration.

DMD pilot study as a case study

NBS for Duchenne Muscular Dystrophy (DMD) is a useful case study for several reasons: 1) DMD is relatively common with ~1 in 5,000 males diagnosed with DMD, 2) X-linked inheritance leading to carrier identification in mother's and other family members, 3) an FDA-cleared kit for NBS is available, 4) two advocacy groups operate longitudinal patient registries that provide health outcome data, 5) the presentation of clinical symptoms and average diagnosis of over 4 years of age often results in a second, younger child in the family having DMD which helps sets up an informative comparison in early versus later treatment, and 6) new treatment and management approaches provide "before and after" scenarios that are useful for comparisons.

b. Possible Solution(s): Research is needed to understand the health services and medical management of positively screened individual beyond the NBS pilot study duration. The findings can help create an infrastructure of long-term follow-up that includes care coordination and data collection to inform clinicians, state programs, and families with the goal of improving the care and needs of the affected individuals.
c. Models: While the medical and health data for the affected individuals may be limited, using models such as decision analytic models, Markov models, and/or system dynamics models can simulate different health pathways and the impact of different interventions in hypothetical settings. These models can test a range of variables that may be sensitive to the NBS expansion process and nationwide adoption including: 1) population size, 2) duration of the pilot, 3) incidence rate, and 4) workforce capacity at the state based NBS program (www.vensim.com). Decision analytical models use parameters such as an incidence rate, specificity, and sensitivity of the screening test, as well as the positive predictive value to project the effectiveness of screening. Thus, it is possible to use models as needed to identify a specific number of cases with a genetic condition that could be expected in a given population size. For DMD, an incidence of 1 in 5,000 means that one could expect to identify a newborn with DMD in the first 5,000 newborns screened. The use of patient registries to compare outcomes of the affected members in families with more than one child is a useful surrogate for long-term follow-up outcome studies. In fact, once a family history of DMD is documented and/or a mother is identified as a carrier of DMD, prenatal identification of DMD could mimic NBS identified DMD and help add data to determine whether early identification, management, and treatment improves outcomes. In addition, policy makers want to assess the impact of adding a screening test. To understand the impact of making a change to the system, a system dynamic model that studies the impact of "feedback loops" into the system could be used. Feedback loops are used to capture the interactions between the parts of the system and how they lead to a certain overall pattern of trend over time and are described as a *positive feedback loop* or *negative feedback loop*. For example, a screening test with a higher sensitivity may result in an increase in positive cases which is an example of *positive feedback*, while screening test with a lower specificity may result in an increase in false positives which is an example of *negative feedback*. The increase in false

positives may then lead to an increase in parental anxiety due to unnecessary follow-up testing and increase health care costs (another example of *positive feedback*). System dynamic models can help identify areas in the system where changes to policy (i.e., improving specificity rate to reduce false positives) will have the highest return on investment. ACHDNC uses NBS pilot data to determine whether to recommend addition of a condition to the RUSP. NBS pilots of short duration may provide sufficient data if there is surrogate data for outcomes such as patient registries, families with multiple affected individuals and/or prenatal identification.

Factor 3. Recent additions to the recommended uniform screening panel (RUSP) expand the definition of newborn screening

a. Use Case: Several hallmarks of NBS are evolving based on recent additions to the RUSP, including age of disease onset and the need for neonatal treatment. In addition, past efforts have shown that once a condition is screened on a population basis a spectrum of clinical disease, beyond the target condition, is often discovered (Puck, 2019). While there are some diseases with a strong correlation between genotype and age of onset (e.g. multiple endocrine neoplasia, type IIB), the current RUSP is organized into core and secondary conditions with variable onsets and/or defined late-onset forms that will manifest far beyond the newborn period, if at all. The fine line between individuals who will be late onset versus non-penetrant complicates diagnosis as well as decision-making regarding when and whether to treat.

Case example infantile vs. late-onset Pompe disease

Pompe disease has both infantile (IOPD) and late-onset (LOPD) forms. Newborns with IOPD have muscle problems that begin in early infancy and these problems can worsen quickly and cause death within the first year. Most newborns who have a positive NBS screen have LOPD, thus symptoms may not appear until later childhood throughout adulthood. This means that a condition identified through NBS may not be actionable until adulthood, if at all (https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/pompe-27-june-2018.pdf).

b. Possible Solution(s): To capture a diverse of perspectives on the addition of condition on the RUSP, an ongoing real-time survey collecting information regarding facilitators and barriers of NBS expansion could be created. Also, these insights can be extrapolated from stakeholders on a NBSTRN Forum which is a secured site for a member directed-discussion board. A best practices checklist for diagnosis, intervention, and management can be generated from this community of diverse stakeholders. For example, from these discussion board insights or real-time survey, a *short-term* follow-up data can be used in models to project *long-term* health outcomes.

c. Models: A Markov model can be created to simulate health states beyond the newborn period and project different health outcomes scenarios. In the case of IOPD vs LOPD, Markov models describing affected individuals identified by NBS for IOPD can be compared to LOPD, and used to understand the impact of different diagnostic, treatment, and management approaches beyond the NBS pilot study.

Factor 4. The RUSP nomination and evidence review process has capacity constraints

a. Use Case: ACHDNC mostly reviews one condition at a time and in some special cases, two conditions. State NBS program readiness for expanded screening is not standardized because many factors impact the implementation process. Different entities fund different aspects of the various pilot studies, and there is a lack of coordination and alignment of pilot goals (refer to companion Paper One) (Brower et al., 2022). There is a lack of information about the development and measurement of economic outcomes from both the National and State Program perspectives. This is exemplified by the scenario where one State program covers all cost of care for a condition if managed through State metabolic program, whereas another State program plays no role in the care coordination. One challenge is the lack of direct assessment of the impact of NBS expansion on health care providers including primary care, specialty physicians, genetic counselors, and other allied professionals. In addition, aspects related to funding varies across states and may change on a monthly or annual basis. Because the goal of NBS is to improve health outcomes through early diagnosis and treatment, an assessment of the benefit of NBS requires longitudinal health information. Although longitudinal data collection may be possible, there is no national registry or system to collect this information, and the complexity of some NBS conditions makes the determination of the clinical relevance more challenging such as specific disease issues related to milder expression, novel forms of disorder identified through screening, later onset, non-penetrance, carriers, and X-linked. Data sources are also diverse and not always easily accessible (such as school data). The majority of NBS conditions require lifelong treatment and management, therefore health outcomes may take years or decades to accumulate, and NBS pilots are not designed to meet this need.

b. Possible Solution(s): NBS expansion most often occurs one condition at a time and is triggered either by the nomination, evidence review and recommendation on a national level by the ACHDNC or by the adoption of new state laws. A solution could be an overarching system that collects data over time of

NBS conditions in pilot studies or simulated pilot studies which could provide an evidence base, identifies, and archives the parameters that support the implementation of multiple candidate conditions simultaneously. For example, if a set of conditions have similar expected incidence rates and the screening tests have acceptable specificity and sensitivity rates, then the use of a model can shorten the duration of a pilot studies which are focused on the analytical and clinical validation of the screening tests to a few months (instead of 18 months). The model can also be used to simulate and extend the duration of pilot studies as needed. This data system could also include longitudinal health records that could be made available to parents and caregivers to improve communication with the healthcare team and lessen care disparities. With input from multiple stakeholders from different state, this could facilitate a "regional state" approach for adoption, and even screening, instead of the current approach (state by state); with input about multiple conditions, we could facilitate the adoption of more than one condition. Real-time models can be created to simulate input from parents and physicians on the different late-onset disorders using a unified database providing similar data and data fields such as the NBSTRN Longitudinal Pediatric Data Resource (LPDR). We can also explore a collaborative model with industry for new experimental diagnostic and treatment technologies for new conditions, clinical care for new interventions, treatments and management approaches, and state based NBS programs to identify new cases and coordinate timely referral and care.

c. Models: These types of simulation models have been used to project health outcomes. For example, estimates of the number of lives in a large population saved from infections due to vaccination and documentation of the subsequent reduction in disease incidence, uses preliminary data obtained from smaller populations. Further research is needed to determine which models can be used to best predict the impact of using different approaches for adoption (regional versus individual state; more than one condition versus one condition). It is also important to note that the ability to model the proposed scenarios would be predicated on the sharing of data via a repository or some other such infrastructure in a concerted effort to facilitate such an effort. NBSTRN created the data tool, LPDR to support an infrastructure for data sharing for secondary use of the original data set. The data extrapolated from these data set would an example of secondary use for modelling.

Discussion

As the number and type of conditions that would benefit from early identification and intervention through NBS continues to increase, models can be employed to rethink and reimagine the process that traditionally governs NBS expansion and the approach to pilot studies from research to state and nationwide adoption can be improved. NBSTRN has created an array of data tools (LPDR, NBS-CR, NBS-VR, and ELSI Advantage) to facilitate secondary use of original data sets because the ability to capture clinical information early in the clinical course of a disease can help advance our understanding of disease etiology, contribute to new knowledge for new treatments and therapy development, and identify areas for improvement in disease management throughout the lifespan for affected families (https://nbstrn.org/tools). The use of modelling can help further address the challenges described in *Population-based Screening of Newborns: Findings from the NBS Expansion Study (Part One)* (Brower et al., 2022).

Advantages of using models

The advantages of using models include: 1) reducing expense in comparison with conducting a large-scale pilot study; 2) estimating the public health and clinical outcomes from models is timesaving compared to the time horizon of a typical pilot study (i.e., at least 1–2 years); 3) simulating different real-world scenarios (i.e., different cut-off levels); and 4) informing the design of a pilot study and identifying those outcomes most critical to measure in the pilot. Models depend heavily on data inputs, and the quality of the data will impact the robustness and validity of the model outcomes. Several options can be considered to inform the data inputs including real-world data from prior implementations, robust data-informed assumptions, and the use of expert opinions for reasonable estimates when data are not available, coupled with sensitivity analyses described below.

One of the concerns for using models is the uncertainty or variation in the model assumptions, which can significantly impact the outcome. To address uncertainty, sensitivity analysis is a powerful tool that explores the variability of the model under different sets of assumptions, including different incidences, different population sizes, and different cut-off levels based on specificity and sensitivity screening parameters. Decision modeling and sensitivity analysis can accompany small-scale pilot studies to determine the which inputs are most "*sensitive*" to variation and assess how this may impact conclusions, decision-making, and screening policies. For example, a policymaker may be deciding whether to allocate funding to support implementation of a state-wide screening program for a new condition, and while the true incidence of the condition is unknown, the reported range is between 1 in 25,000 and 1 in 500,000. A model coupled with a sensitivity analysis studying model outputs based on incidence rates between 1 in 25,000 and 1 in 500,000 could determine the incidence threshold at which the program would be deemed cost-effective (a threshold analysis). The

probability that the incidence falls at or above the threshold can be determined by the model.

Future directions using models for NBS expansion

To help guide NBS expansion and create a roadmap for improvement, NBSTRN is like the "hub" of the wheel, where diverse stakeholders such as clinicians, researchers, state NBS programs, families, and advocacy organizations are among the "spokes", driving implementation and innovation. To realize the promise of models for NBS expansion, new stakeholders from system sciences, health economics, supply chain management, data engineering, and communication must be additional spokes of the wheel. Artificial intelligence and machine learning have also been used on existing screening data to improve the prediction of true and false positive results (Peng et al., 2020), and this is an additional area of interest as we work to identify new strategies. The development of interdisciplinary efforts and systems approaches to implementation could help advance NBS research and improve NBS expansion.

An ideal scenario is for researchers conducting NBS pilot studies to partner with system scientists to develop models that simulate and project the consequences of expanding NBS by exploring different model parameters. NBSTRN is a designed to facilitate these types of innovative efforts in newborn screening-related research to discover new screening technologies, treatments, and interventions. As a key component of the *Eunice Kennedy Shriver* NICHD Hunter Kelly NBS Research Program, NBSTRN can continue organizing network meetings to bring together the different disciplines to create models to evaluate the different NBS scenarios. ACMG has developed and coordinated the NBSTRN since its beginning in 2008, and the alignment between NBSTRN objectives and ACMG's mission enhances the NBSTRN ability to advocate for improvements in NBS. For example, instead of carrying out an 18-months pilot study traditionally, State Department of Public Health can collaborate with system scientists to use data in real-time to project the likelihood of identifying a case and if case is identified, what is the likelihood of obtaining treatment early to yield a 'better' health outcome (improved quality of life for the baby with the condition and family). In conjunction with tools and specialized training provided by the NBSTRN, models can be used to evaluate the impact of barriers (i.e., lack of infrastructure) and facilitators (i.e., sufficient funding) in NBS pilot studies. To support the use of models in a pilot study, additional funding is needed to support modeling research and implementation to hypothesize whether models could be used, and if used, under what conditions, parameters, and assumptions. With appropriate funding to support online training and in-person workshops on the fundamentals, application, and implementation of models, this new innovative new approach can be broadly used for conducting pilot studies as well as for policymaking. Thus, to address these needs and foster collaboration for new solutions using modeling, active and growing membership of diverse expertise in and support of the NBSTRN network is critical for developing new approaches to advance and sustain NBS research.

Author contributions

KC, AB and WM contributed to the conception and design of the work and drafted the work critically for important intellectual content.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Banke-Thomas, A. O., Madaj, B., Charles, A., and van den Broek, N. (2015). Social return on investment (SROI) methodology to account for value for money of public health interventions: A systematic review. *BMC Public Health* 15, 582. doi:10.1186/s12889-015-1935-7

Berg, J. S., Agrawal, P. B., Bailey, D. B., Jr, Beggs, A. H., Brenner, S. E., Brower, A. M., et al. (2017). Newborn sequencing in genomic medicine and public health. *Pediatrics* 139 (2), e20162252. doi:10.1542/peds.2016-2252

Bertram, M. Y., Sweeny, K., Lauer, J. A., Chisholm, D., Sheehan, P., Rasmussen, B., et al. (2018). Investing in non-communicable diseases: An estimation of the return on investment for prevention and treatment services. *Lancet (London, Engl.* 391 (10134), 2071–2078. doi:10.1016/S0140-6736(18)30665-2

Bessey, A., Chilcott, J. B., Leaviss, J., and Sutton, A. (2018). Economic impact of screening for X-linked Adrenoleukodystrophy within a newborn blood spot screening programme. *Orphanet J. Rare Dis.* 13 (1), 179. doi:10.1186/s13023-018-0921-4

Boshuizen, H. C., van der Lem, G. J., Kauffman-de Boer, M. A., van Zanten, G. A., Oudesluys-Murphy, A. M., and Verkerk, P. H. (2001). Costs of different strategies for neonatal hearing screening: A modelling approach. *Arch. Dis. Child. Fetal Neonatal Ed.* 85 (3), F177–F181. doi:10.1136/fn.85.3.f177

Brower, A., Chan, K., Williams, M., Berry, S., Currier, R., Rinaldo, P., et al. (2022). Population-based screening of newborns: Findings from the NBS expansion study (Part One). *Front. Genet* 13, 867337. doi:10.3389/fgene.2022.867337

Caggana, M., Jones, E. A., Shahied, S. I., Tanksley, S., Hermerath, C. A., and Lubin, I. M. (2013). Newborn screening: From Guthrie to whole genome sequencing. *Public Health Rep.* 128 (2), 14–19. doi:10.1177/00333549131280S204

Carey, G., Malbon, E., Carey, N., Joyce, A., Crammond, B., and Carey, A. (2015). Systems science and systems thinking for public health: A systematic review of the field. *BMJ Open* 5 (12), e009002. doi:10.1136/bmjopen-2015-009002

Carroll, A. E., and Downs, S. M. (2006). Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics* 117 (2), S287–S295. doi:10.1542/peds.2005-2633H

Castilla-Rodríguez, I., Vallejo-Torres, L., Couce, M. L., Valcárcel-Nazco, C., Mar, J., and Serrano-Aguilar, P. (2017). Cost-effectiveness methods and newborn screening assessment. *Adv. Exp. Med. Biol.* 1031, 267–281. doi:10.1007/978-3-319-67144-4_16

Chan, K., Davis, J., Pai, S.-Y., Bonilla, F. A., Puck, J. M., and Apkon, M. (2011). A Markov model to analyze cost-effectiveness of screening for severe combined immunodeficiency (SCID). *Mol. Genet. Metab.* 104 (3), 383–389. doi:10.1016/j.ymgme.2011.07.007

Ding, Y., Thompson, J. D., Kobrynski, L., Ojodu, J., Zarbalian, G., and Grosse, S. D. (2016). Cost-effectiveness/cost-benefit analysis of newborn screening for severe combined immune deficiency in Washington state. *J. Pediatr.* 172, 127–135. doi:10.1016/j.jpeds.2016.01.029

Gantt, S., Dionne, F., Kozak, F. K., Goshen, O., Goldfarb, D. M., Park, A. H., et al. (2016). Cost-effectiveness of universal and targeted newborn screening for congenital cytomegalovirus infection. *JAMA Pediatr.* 170 (12), 1173–1180. doi:10.1001/jamapediatrics.2016.2016

Garattini, L., and van de Vooren, K. (2011). Budget impact analysis in economic evaluation: A proposal for a clearer definition. *Eur. J. Health Econ.* 12 (6), 499–502. doi:10.1007/s10198-011-0348-5

Grosse, S. D., Thompson, J. D., Ding, Y., and Glass, M. (2016). The use of economic evaluation to inform newborn screening policy decisions: The Washington state experience. *Milbank Q.* 94 (2), 366–391. doi:10.1111/1468-0009.12196

Hamers, F. F., and Rumeau-Pichon, C. (2012). Cost-effectiveness analysis of universal newborn screening for medium chain acyl-CoA dehydrogenase deficiency in France. *BMC Pediatr.* 12, 60. doi:10.1186/1471-2431-12-60

Kemper, A. R., and Downs, S. M. (2000). A cost-effectiveness analysis of newborn hearing screening strategies. *Arch. Pediatr. Adolesc. Med.* 154 (5), 484–488. doi:10.1001/archpedi.154.5.484

Khneisser, I., Adib, S., Assaad, S., Megarbane, A., and Karam, P. (2015). Cost-benefit analysis: Newborn screening for inborn errors of metabolism in Lebanon. *J. Med. Screen.* 22 (4), 182–186. doi:10.1177/0969141315590675

Lord, J., Thomason, M. J., Littlejohns, P., Chalmers, R. A., Bain, M. D., Addison, G. M., et al. (1999). Secondary analysis of economic data: A review of cost-benefit studies of neonatal screening for phenylketonuria. *J. Epidemiol. Community Health* 53 (3), 179–186. doi:10.1136/jech.53.3.179

McCandless, S. E., and Wright, E. J. (2020). Mandatory newborn screening in the United States: History, current status, and existential challenges. *Birth Defects Res.* 112 (4), 350–366. doi:10.1002/bdr2.1653

Milko, L. V., O'Daniel, J. M., DeCristo, D. M., Crowley, S. B., Foreman, A., Wallace, K. E., et al. (2019). An age-based framework for evaluating genome-scale sequencing results in newborn screening. *J. Pediatr.* 209, 68–76. doi:10.1016/j.jpeds.2018.12.027

Pandor, A., Eastham, J., Beverley, C., Chilcott, J., and Paisley, S. (2004). Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: A systematic review. *Health Technol. Assess.* 8 (12), 1–121. doi:10.3310/hta8120

Peng, G., Tang, Y., Cowan, T. M., Enns, G. M., Zhao, H., and Scharfe, C. (2020). Reducing false-positive results in newborn screening using machine learning. *Int. J. Neonatal Screen.* 6 (1), 16. doi:10.3390/ijns6010016

Peterson, C., Grosse, S. D., Oster, M. E., Olney, R. S., and Cassell, C. H. (2013). Cost-effectiveness of routine screening for critical congenital heart disease in US newborns. *Pediatrics* 132 (3), e595–603. doi:10.1542/peds.2013-0332

Prosser, L. A., Grosse, S. D., Kemper, A. R., Tarini, B. A., and Perrin, J. M. (2013). Decision analysis, economic evaluation, and newborn screening: Challenges and opportunities. *Genet. Med.* 14 (8), 703–712. doi:10.1038/gim.2012.24

Prosser, L. A., Lam, K. K., Grosse, S. D., Casale, M., and Kemper, A. R. (2018). Using decision analysis to support newborn screening policy decisions: A case study for Pompe disease. *MDM Policy Pract.* 3 (1), 238146831876381. doi:10.1177/2381468318763814

Puck, J. M. (2019). Newborn screening for severe combined immunodeficiency and T-cell lymphopenia. *Immunol. Rev.* 287 (1), 241–252. doi:10.1111/imr.12729

Salleh, S., Thokala, P., Brennan, A., Hughes, R., and Dixon, S. (2017). Discrete event simulation-based resource modelling in health technology assessment. *PharmacoEconomics* 35 (10), 989–1006. doi:10.1007/s40273-017-0533-1

Sontag, M. K., Yusuf, C., Grosse, S. D., Edelman, S., Miller, J. I., McKasson, S., et al. (2020). Infants with congenital disorders identified through newborn screening — United States, 2015–2017. *MMWR. Morb. Mortal. Wkly. Rep.* 69, 1265–1268. doi:10.15585/mmwr.mm6936a6

Stenberg, K., Sweeny, K., Axelson, H., Temmerman, M., and Sheehan, P. (2016). "Returns on investment in the continuum of care for reproductive, maternal, newborn, and child health," in *Reproductive, maternal, newborn, and child health: Disease Control priorities*. Editors R. E. Black, R. Laxminarayan, M. Temmerman, and N. Walker. Third Edition (Washington (DC): The International Bank for Reconstruction and Development/The World Bank), 2. doi:10.1596/978-1-4648-0348-2_ch16

Thiboonboon, K., Leelahavarong, P., Wattanasirichaigoon, D., Vatanavicharn, N., Wasant, P., Shotelersuk, V., et al. (2015). An economic evaluation of neonatal screening for inborn errors of metabolism using tandem mass spectrometry in Thailand. *PloS One* 10 (8), e0134782. doi:10.1371/journal.pone.0134782

Tracy, M., Cerdá, M., and Keyes, K. M. (2018). Agent-based modeling in public health: Current applications and future directions. *Annu. Rev. Public Health* 39, 77–94. doi:10.1146/annurev-publhealth-040617-014317

Tran, K., Banerjee, S., Li, H., Noorani, H. Z., Mensinkai, S., and Dooley, K. (2007). Clinical efficacy and cost-effectiveness of newborn screening for medium chain acyl-CoA dehydrogenase deficiency using tandem mass spectrometry. *Clin. Biochem.* 40 (3–4), 235–241. doi:10.1016/j.clinbiochem.2006.10.022

van den Akker-van Marle, M. E., Dankert, H. M., Verkerk, P. H., and Dankert-Roelse, J. E. (2006). Cost-effectiveness of 4 neonatal screening strategies for cystic fibrosis. *Pediatrics* 118 (3), 896–905. doi:10.1542/peds.2005-2782

Verkleij, M. L., Heijnsdijk, E. A. M., Bussé, A. M. L., Carr, G., Goedegebure, A., Mackey, A. R., et al. (2021). Cost-effectiveness of neonatal hearing screening programs: A micro-simulation modeling analysis. *Ear Hear.* 42 (4), 909–916. doi:10.1097/AUD.0000000000000981

Wright, S. J., Jones, C., Payne, K., Dharni, N., and Ulph, F. (2015). The role of information provision in economic evaluations of newborn bloodspot screening: A systematic review. *Appl. Health Econ. Health Policy* 13 (6), 615–626. doi:10.1007/s40258-015-0177-2

Yu, Z., Deng, M., Peng, C., Song, X., Chen, Y., Zhang, X., et al. (2019). A system dynamics modelling simulation based on a cohort of Hepatitis B epidemic research in east China community. *Epidemiol. Infect.* 147, e86. doi:10.1017/S0950268819000220

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Population genomic screening: Ethical considerations to guide age at implementation

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Currently, most genetic testing involves next generation sequencing or panel testing, indicating future population-based screening will involve simultaneous testing for multiple disease risks (called here "panel testing"). Genomic screening typically focuses on single or groups of related disorders, with little utilization of panel testing. Furthermore, the optimal age for test ordering is rarely addressed in terms of whether it should coincide with the age of majority (18 years old) or after the age of majority (26 years old). We conducted an ethical analysis utilizing a hypothetical "narrow" panel test comprised of the CDC Tier 1 Genomic Applications: Familial Hypercholesterolemia (FH), increases individuals' cardiovascular risk due to elevated low-density lipoprotein (LDL) cholesterol levels; Hereditary Breast and Ovarian Cancer (HBOC), increases lifetime risk of developing cancer; and Lynch Syndrome (LS), increases lifetime risk of developing colorectal cancer. We conducted a utilitarian analysis, on the assumption that health systems seek to maximize utility for patients. Screening at the "age of majority" is preferred for FH due to lowering FH patients' cholesterol levels *via* statins providing high lifetime benefits and low risks. Screening "after the age of majority" is preferred for HBOC and LS due to availability of effective surveillance, the recommendation for screening activities to begin at age 26, and prophylactic interventions connected to surveillance. We also utilized a supplemental principlist-based approach that identified relevant concerns and trade-offs. Consideration of clinical, non-clinical, and family planning implications suggests narrow panel testing would be best deployed after 26 (rather than at 18) years of age.

KEYWORDS

bundled genomic screening, population screening, principlist ethics, utilitarian ethics, implementation

Introduction

Population-level genomic screening for future disease risk is one of the ultimate goals of precision medicine. (Green et al., 2015). As most genetic testing involves next generation sequencing or panel testing, it is likely that future screening will involve simultaneous testing for multiple disease risks (called here "panel testing"). (Green et al., 2013; Marshall et al., 2020). However, most decision-making about the implementation of

genomic screening has focused on considerations relevant to independent conditions, with no analysis of the implications of panel testing or their relationship to the age at which such screening, ideally, would be offered.

The need for such a decision-making framework is clear. Pediatric and newborn population genomic screening have been discussed at length but there is currently only limited guidance related to genomic screening of healthy adults. (Burke et al., 2013; Committee on Bioethics Committee on Genetics ACMG Genomics SocialEthical and Legal Issues Committee, 2013; Ross et al., 2013; Clayton et al., 2014; Murray et al., 2018). Various recommendations for adult genomic screening address timing of screening, associated risk management strategies, and follow-on surveillance activities for a variety of conditions including cancers and cardiovascular disease. Age of screening takes on special significance in the context of panel testing due to interactions between the age of onset for conditions included within the panel test and the degree to which treatment or intervention is tied to the age of the patient. While it might seem straightforward to plan for offering panel testing to patients as they reach the "age of majority" (18 years old in the United States, when individuals are granted full legal and decision-making capacity; also, the age at which most can consent to medical care), various trade-offs may make implementation later in adulthood preferable. (Legal Information Institute). For example, health systems may prefer to initiate screening after 26 years of age, the age at which the U.S Department of Health & Human Services require patients to cycle off their parent's health insurance and establish coverage on their own behalf (called here "after the age of majority").

In anticipation of the need for systematic values-based analysis that can inform health system leaders' decisions about the appropriate age at which to offer panel testing, we conducted an ethical analysis assuming a hypothetical "narrow" panel test comprised of just the Center for Disease Control and Prevention (CDC) Tier 1 Genomic Applications: Familial Hypercholesterolemia (FH), Hereditary Breast and Ovarian Cancer (HBOC), and Lynch Syndrome (LS). CDC Tier 1 Genomic Applications are conditions that have significant potential for positive impact on public health based on available evidence-based guidelines and recommendations. (Centers for Disease Control and Prevention, 2014). Specifically, we describe key classes of test implications (clinical, non-clinical, and family planning related) for this case and demonstrate how utilitarian and principlist frameworks might help guide decision-making about the offer of this, and potentially any, panel testing. Our analysis assumes "population" refers to a demographically representative sample of the United States. We also assumed that patients will be offered panel testing in a primary care wellness exam and have access to these services through either insurance coverage or public health initiatives. There will likely be additional Tier 1 conditions added over time and characteristics of panel testing highlighted in this analysis are intended to guide considerations of future, broader panel testing. The characteristics of this analysis are highlighted in Table 1.

Narrow panel test conditions

Familial Hypercholesterolemia

FH is a common monogenic condition, with a prevalence of ~1/250, that increases individuals' cardiovascular risk primarily due to elevated low-density lipoprotein (LDL) cholesterol levels and independent risk associated with FH variants. (Goldberg et al., 2011; Sjouke et al., 2015; Benn et al., 2016). Individuals with untreated FH may have a 20 times higher life risk of coronary heart disease compared to the general population. (NIH). Individuals with FH also have an increased risk of experiencing a cardiovascular event earlier in life compared to individuals without FH. (Kuchenbaecker et al., 2017). In the CASCADE-FH registry in the United States the median age at FH diagnosis was 47 (IQR 31-59), the median age of initiation for LDL-lowering therapy was 39 (IQR 25-50), and median age of onset for coronary heart disease was 51 (IQR 42-61). (Cleveland Clinic, 2022).

Hereditary breast and ovarian cancer

HBOC genetic variants confer increased lifetime risk of developing cancer. (Manickam et al., 2018). For example, BRCA1 and BRCA2 carriers experience ~40 percent cumulative risk of breast cancer and ~10 percent cumulative risk of ovarian cancer by the time they are 50. (Manickam et al., 2018). The prevalence of pathogenic HBOC variant carriers is ~1/200. (Domchek et al., 2010; Dewey et al., 2016). Identification of HBOC variants allows for more intensive precancer screening practices such as magnetic resonance imaging (MRI) and for individuals to engage in chemoprevention, prophylactic risk-reducing mastectomy (RRM), and/or risk-reducing salpingo-oophorectomy (RRSO) to lower cancer risk and cancer mortality. (Hampel et al., 2008; US Preventive Services Task Force, 2019).

Lynch syndrome

LS is the most common inherited cause of colorectal cancer (CRC), involved in ~4% of incident cases. (Bonadona et al., 2011; Moreira et al., 2012; Ahnen et al., 2014). Individuals with LS develop cancer at younger ages compared to the general population, with an average age of CRC diagnosis between roughly 30 to 50 depending on the associated gene mutation.

TABLE 1 Characteristics of panel test for analysis.

Condition	Presentation	Age of onset	Screening recommendation	Treatment options
Familial Hypercholesterolemia	Prevalence of ~1/250, that increases individuals' cardiovascular risk primarily due to elevated low-density lipoprotein (LDL) cholesterol levels (Goldberg et al., 2011; Sjouke et al., 2015; Benn et al., 2016)	Median age of onset for coronary heart disease: 51 (IQR 42-61) (Cleveland Clinic, 2022)	Surveillance through cholesterol screening (Simon Broome Register Group, 1991; Newman et al., 2019)	Preventative intervention may provide meaningful benefit *via* lipid lowering therapy and related clinical actions (Simon Broome Register Group, 1991; Newman et al., 2019)
Hereditary Breast and Ovarian Cancer	Prevalence of ~1/200, increased lifetime risk of developing cancer (Manickam et al., 2018)	BRCA carriers have 4% cumulative risk of breast and ovarian cancer by age 30[92]	Increased surveillance for affected individuals such as mammography or MRI (National Cancer Institute, 2021)	Prophylactic surgery such as mastectomy and/or oophorectomy is recommended after 30 years old
Lynch Syndrome	Prevalence of ~1/300, develop colorectal and other cancers at younger ages compared to the general population (Kastrinos et al., 2008; Jasperson et al., 2010; ten Broeke et al., 2015; Oliveri et al., 2018)	Average age of CRC diagnosis between ages 30 to 50 depending on the associated gene mutation (Oliveri et al., 2018)	Individuals with LS are recommended to engage in intensive colonoscopy surveillance including annual or biennial colonoscopy surveillance beginning at 25 years old (; Degoma et al., 2016; Daly et al., 2020)	Polyps identified by screening can be resected and prophylactic surgery may be necessary such as a colectomy (Cleveland Clinic, 2022; Katz et al., 2017)

(Kastrinos et al., 2008; Jasperson et al., 2010; ten Broeke et al., 2015; Oliveri et al., 2018). LS is also associated with increased risk for endometrial, ovarian, and prostate cancers. (Møller et al., 2017; Dominguez-Valentin et al., 2020;). Current guidelines recommend decennial colonoscopy surveillance for CRC beginning at 50 years old for the general population and individuals with LS are recommended to engage in intensive colonoscopy surveillance including annual or biennial colonoscopy surveillance beginning at age 25 years. ; Degoma et al., 2016; Daly et al., 2020).

Types of test implications considered

A targeted literature review, patient interviews, and reports of expert roundtable discussions were utilized to identify implications related to panel testing for the purpose of the proposed ethical analysis. (Research on Genomics et al., 2018)· (Chowdhury et al., 2013)· (Khoury, 2013) This targeted review identified implications such as disease prevention, treatment, care management, patient experiences, psychosocial effects, reproductive decision-making, and other considerations. Once these implications were identified, they were characterized for implementation in the proposed ethical analysis. To simplify the ethical analysis, these implications were organized into three main categories: (1) clinical, (2) non-clinical, and (3) family planning related

Clinical implications include the extent to which a given screening test provides effective disease prevention, appropriate treatment, and/or care management. (Khoury, 2013; Research on Genomics et al., 2018). Prevention of disease includes prophylactic interventions or other recommended treatments. (NIH,; US Preventive Services Task Force, 2019; Hampel et al., 2008;). Appropriate treatment and care management considered time sensitivity related to care, recommendations and/or evidence of an optimal age for an intervention or care pathway, and whether care management involves screening, surveillance, or clinical activities. (Bowen et al., 2012; Khoury, 2013; Research on Genomics et al., 2018).

Non-clinical implications include impacts associated with, or related to, a given screening test, including patient experiences and/or psychosocial effects. (Burke et al., 2011; Research on Genomics et al., 2018). These behavioral impacts may be difficult to quantify but require consideration because they can affect clinical utilization, surveillance adherence, and/or clinical outcomes. Family planning implications include actions or considerations related to reproductive decision-making, such as the use of carrier and/or prenatal genetic screening, cascade testing in family members, or the adjustment to treatment to enable conception. (George et al., 2015).· (Lokich et al., 2014)

Age at which to offer "narrow" panel testing: Ethical considerations

The three categories of implications were used in a two-phased ethical analysis focused on the appropriate age at which to offer a hypothetical "narrow" panel test comprised of just the CDC Tier 1 Genomic Applications (for FH, HBOC, and LS) to adult patients. First, a utilitarian framework was employed, on the assumption that health systems may similarly seek to maximize utility for patients. Next, we supplemented the analysis with a principlist-based approach that identified additional relevant concerns and trade-offs. In both analyses we consider the offer of panel testing at either the "Age of

Majority" (i.e., 18 years old) or "After the Age of Majority" (i.e. 26 years or older).

Utilitarian analysis

Utilitarianism claims that an act is morally right if and only if it maximizes the good or utility for the largest number of people. (Driver, 2014; Marseille and Kahn, 2019). Utilitarianism is not focused on to whom the benefits are distributed when utilizing a population genomic screen.

Health economics and outcomes research such as a cost-utility analysis can assist with providing insight into what actions maximize benefits for a population. (Beheshti et al., 2018). For this utilitarian analysis, we focused on the clinical implications of screening along with the clinical benefits and risks related to surveillance, preventative therapeutics, or interventions, and/or the need for surgical prophylaxis. Clinical benefits and risks were contextualized within the age of onset for disease.

FH is a condition with an "early" age of onset insofar as the adverse effects of increased cholesterol levels begin prior to the experience of a cardiovascular event such as MI or stroke. (Ademi et al., 2019). FH diagnosis does not have an associated prophylactic surgery that affects the risk level of affected individuals but does have therapeutic options. (Simon Broome Register Group, 1991; Newman et al., 2019). Surveillance and preventative intervention may provide meaningful benefit through cholesterol screening, lipid lowering therapy, and related clinical actions. Research has shown that children undergoing population genetic screening is likely cost-effective and has benefit in a non-US setting. (Sturm et al., 2018; Ademi et al., 2020). Preliminary results from Spencer et al. indicate that population genomic screening is more cost-effective for younger patients (20-year-old compared to 35-year-olds). (National Cancer Institute, 2021). While there are potential side effects of lipid lowering therapy such as diabetes mellitus, and muscle pain or weakness, the overall safety profile of lipids suggests that they are relatively well tolerated by most patients. (Spencer et al.). As lowering patients' cholesterol levels *via* statin use has high lifetime benefits and relatively low iatrogenic risks, screening at the "Age of Majority" is preferred when this condition alone is considered.

HBOC, in contrast, is generally characterized as having a later age of onset due to a 4% cumulative risk of experiencing breast cancer up to age 30. (Manickam et al., 2018). As a result, most individuals with *BRCA* mutations experience a breast cancer diagnosis after the age of 30 and prophylactic surgery is recommended afterwards due to its invasive and irreversible nature. (National Cancer Institute, 2021). HBOC recommendations also include increased surveillance for affected individuals such as mammography or MRI. While genetic testing for HBOC is recommended for women who have a family history or who have experienced triple-negative breast cancer before age 60, (Nelson et al., 2019) *Guzauskas et al.* found that population genomic screening for HBOC was likely cost-effective for 30-year-old women. (Guglielmo et al., 2018; Guzauskas et al., 2020). Due to the availability of effective surveillance, the majority of cancer diagnoses occurring after age 30, and the recommendation of prophylaxis after age 30, screening "After the Age of Majority" is preferred when this condition alone is considered.

The typical age of onset of LS is also variable; nevertheless those who screen positive for LS are recommended to pursue colonoscopy annually or biannually beginning at the age of 25 or 25 years before the youngest familial CRC diagnosis, as well as to consider annual endometrial sampling or transvaginal ultrasound (TVUS) where relevant, and/or esophagogastroduodenoscopy (EGD) beginning at age 30. (Beauchamp and Childress, 2001; Vasen et al., 2013; Giardiello et al., 2014a; National Comprehensive Cancer Network, 2021). Polyps identified by screening can be resected to significantly lower the likelihood that a patient will experience a late-stage cancer diagnosis or unknown cases of cancer. (Cleveland Clinic, 2022; Katz et al., 2017). In some cases additional prophylactic surgery may be necessary, such as a colectomy, or an oophorectomy for patients affected by endometrial or ovarian cancers (recommended after childbearing has been completed). Given the availability of effective surveillance, the recommendation for screening activities to begin at age 25, and prophylactic interventions connected to surveillance, screening "After the Age of Majority" is preferred when this condition alone is considered.

In summary and when considered independently, a utilitarian analysis of–primarily clinical–implications suggests that it is more appropriate to offer screening for both HBOC and LS "After the Age of Majority" whereas screening for FH may be preferred at the "Age of Majority" as shown in Table 2. As a panel test, however, and under a "majority rules" understanding, on balance it would be better to offer a combined test "After the Age of Majority". This recommendation, which could delay lipid lowering interventions for those with FH, nevertheless carries fewer risks than initiating expensive and (for LS, invasive) surveillance modalities well in advance of the expected age of disease onset.

There are, as noted above, additional implications not easily integrated into these considerations. Building on the utilitarian analysis, the same case was evaluated using the ethical framework of principlism, with an additional focus on non-clinical and family planning implications.

Principlist analysis

Principlism applies the ethical principles of respect for autonomy, justice, beneficence, and non-maleficence to consider the morality of an action. (Beauchamp and Childress,

TABLE 2 Utilitarian analysis.

Condition	Utilitarian recommendation	Rationale
FH	"Age of Majority"	- Availability of effective surveillance - Majority of cancer diagnoses occurring after age 30 - Recommendation of prophylaxis after age 30
HBOC	"After Age of Majority"	- Availability of effective surveillance - The majority of cancer diagnoses occurring after age 30 - Recommendation of prophylaxis after age 30
LS	"After Age of Majority"	- Availability of effective surveillance - Recommendation for screening activities to begin at age 25 - Prophylactic interventions connected to surveillance
Narrow Panel Test	"After Age of Majority"	- Analysis recommends 2 of the 3 conditions at "After Age of Majority"

TABLE 3 Principlist analysis.

	Respect for autonomy	Beneficence	Non-maleficence	Justice
FH	(+)	(-)	(+)	(+)
HBOC	(-)	(+)	(-)	(-)
LS	(-)	(+)	(-)	(+)

(+): Indicates discordance from Utilitarian Recommendation.
(-): Indicates no discordance from utilitarian recommendation.

2001; Pal and Vadaparampil, 2012). Respect for autonomy is an individual's ability to make decisions for themselves with adequate information about the consequences of their choices and without coercion. Beneficence refers to acting to benefit others which may involve preventing harms or actively promoting some sort of specific benefit(s). Non-maleficence refers to not intentionally causing harm or avoiding actions that are expected to harm individuals. Justice refers to considerations related to the fair distribution of the benefits and harms or costs of an action. While joint consideration of these principles can often point to a consistent course of action, in practice different principles may lead to different evaluations of the morality of an action. Table 3 highlights which principles present discordance with the utilitarian recommendation.

Respect for autonomy is relevant to considerations surrounding family planning. Individuals may want to take steps to limit the likelihood of passing a risk variant to offspring *via* preimplantation genetic diagnosis or related activities. Having risk information at the "Age of Majority" may provide additional time for reproductive planning, allow affected individuals to stop or delay therapeutic interventions, such as statin therapy for FH, when intending to conceive a child, or to delay prophylactic interventions such as a mastectomy for HBOC. (Wert, 2005; McGowan et al., 2019). Implementing a narrow panel test "After the Age of Majority" therefore interferes with patients' autonomy by limiting their ability to make such decisions in a timely fashion.

Waiting until "After the Age of Majority", may raise issues with family members' autonomy by not respecting their right not to know their own genetic status. (Koçan and Gürsoy, 2016). Similarly, not all individuals may benefit from implementation "After the Age of Majority," i.e., the utilitarian recommendation, raising broader beneficence concerns. Individuals may be exposed costs or harms of unnecessary screening, especially since many patients will not receive a positive result, in contrast with providing benefits to the population at large. Providing opt-out options for patients who do not feel they will benefit may address this concern, in conjunction with educational resources regarding the purpose and potential benefits of such a program. Of course, autonomy may also be infringed by an earlier age of implementation, where strongly encouraged clinical actions, such as mastectomy in females, have noted to negative impacts on self-image, body image, identity, or other factors. (Kenen et al., 2007; Petrucelli et al., 2016).

Non-maleficence and beneficence may appear in discordance with one another. With an opt-out option for the narrow panel test, individuals may wish to opt-in to screening for a particular condition or disease prior to the recommended time. However, individual conditions within a panel test may challenge the timing of a screen in relation to doing no harm. An opt-in option, or adequate information and counseling for individuals who would elect to begin screening earlier than proposed, may help individuals and other stakeholders limit patient harm while allowing pragmatic implementation.

There is potential for undue harm from utilizing a narrow panel test at too young an age. The possibility of exposing individuals to information that leads to unnecessary prophylaxis such as a mastectomy, oophorectomy, or colectomy could cause undue harm. (Howard et al., 2010; Rendle et al., 2015). Risk reducing prophylaxis presents the potential for psychosocial harm. (Hamilton et al., 2017; Shugar, 2017). Non-maleficence may exist within a panel test as a result of these potential harms and is important to identify explicit trades-offs to limit harms. Clear training and provider familiarity with the clinical care pathways can assist with minimizing the risk of these harms. (Bensend et al., 2014). Provision of educational programs and access to genetic counseling can assist with balancing benefits against risks such as anxiety or psychosocial impacts. (Khera et al., 2016).

Justice considerations center on the degree to which specific subsets of (potentially already marginalized or underserved) patients may be unfairly impacted by the age of implementation chosen to maximize utility for the overall population. For example, with implementation at the "Age of Majority", females may experience increased impact related to their family planning and non-clinical dimensions due prophylactic surgery such as mastectomy and/or oophorectomy. (MD Anderson Cancer Center, 2010; Collier, 2012; Centers for Disease Control and Prevention, 2020). Additionally, people who are pregnant or trying to conceive are not able to stay on statin therapy, increasing their cardiovascular risk. Earlier screening may give additional time to mitigate these potential harms and increase potential benefits through different family planning activities including when to attempt conception, how many children to have, and therapeutic interventions and conception(s) timing.

As with the application of the Utilitarian framework, competing considerations are in play when the principles are applied to implications associated with screening. Whereas a Utilitarian consideration suggests that implementation "After the Age of Majority" may, overall, be most appropriate, Principlism allows for broader consideration of implications. This additional consideration is important because the non-clinical or family planning implications, while more difficult to quantify, can be highly impactful as noted above. Principlist considerations do not change the over-arching conclusion that offering panel testing may be more appropriate at later life stages, but it *does* suggest important trade-offs with potential implications for responsible implementation. For example, offering population-based genomic screening on an opt-in basis, while desirable to respect patients' autonomy, may expose patients to harms related to delayed diagnosis or put providers at risk of failing in their duty to do no harm. Similarly, implementing panel testing fairly may require restrictions related to individuals' autonomy. While fairest to offer the screen to everyone at the same age, this may restrict the autonomy of those who wish to participate in screening earlier in adulthood.

It is important to realize that while this analysis assumed a population representative of the US population, this may not be the case for many health systems. Differences in disease prevalence by population background, or the presence of additional conditions, may need to be considered in relationship to the benefits expected from engaging in aggregate screening activities. As a result, it will be important to also consider appropriate demographic data when utilizing a principlist approach including non-clinical and family planning implications.

Conclusion

For the hypothetical 'narrow' panel test considered here, our two-phase ethical analysis suggests that the most appropriate age of implementation may be "After the Age of Majority" (i.e., at 26 years of age or later). This conclusion is supported by the availability of cancer surveillance activities, recommendations for screening activities to begin at age 25, and prophylaxis to be considered after age 30 for HBOC and LS. While this timing is less optimal for FH screening, when considered as part of a panel test, our assessment is that the risks of delayed screening for FH are outweighed by other benefits. As we have demonstrated, a pragmatic approach can begin from a Utilitarian ethical framework based in a consideration of clinical implications, in a manner consistent with the need for health systems to weigh impacts on clinical outcomes relative to budgetary constraints, fiduciary responsibilities, and complex regulatory landscapes. Invoking Principlism in a secondary analysis considering non-clinical and family planning implications can then supplement the Utilitarian approach by identifying additional trade-offs.

Future research

Future work in this space will assist with providing context for evaluations surrounding larger panel tests, which may include many more conditions than the current CDC Tier 1 genomic applications. These future analyses may encompass a broader set of potential implications including those associated with disease prevalence, modes of inheritance, and condition characteristics such as age of onset, severity, and other components. Explicit evaluation of non-clinical and family planning dimensions through discrete choice experiments or other qualitative and quantitative methods would add more insight into areas of ethical discordance. This work may allow for more accurate assessment of individuals' preferences providing more appropriate and thorough considerations of the age at which panel testing should be implemented.

Author contributions

The authors, SS and SF, confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Ademi, Z., Norman, R., Pang, J., Ference, B., Liew, D., Sijbrands, E., et al. (2019). Cc1 cost-effectiveness of screening and treating children with familial hypercholesterolemia early in life from A Dutch healthcare perspective. *Value Health* 22, S405. doi:10.1016/j.jval.2019.09.045

Ademi, Z., Norman, R., Pang, J., Liew, D., Zoungas, S., Sijbrands, E., et al. (2020). Health economic evaluation of screening and treating children with familial hypercholesterolemia early in life: Many happy returns on investment? *Atherosclerosis* 304, 1–8. doi:10.1016/j.atherosclerosis.2020.05.007

Ahnen, D. J., Wade, S. W., Jones, W. F., Sifri, R., Mendoza Silveiras, J., Greenamyer, J., et al. (2014). The increasing incidence of young-onset colorectal cancer: a call to action. *Mayo Clin. Proc.* 89 (2), 216–224. doi:10.1016/j.mayocp.2013.09.006

Bansal, A., Jones, L., Hao, J., Crosslin, D., and Veenstra, D. L. Aim 2 analysis.

Beauchamp, T. L., and Childress, J. F. (2001). *Principles of biomedical ethics*. USA: Oxford University Press.

Beheshti, S., Madsen, C. M., Varbo, A., Benn, M., and Nordestgaard, B. G. (2018). Relationship of familial hypercholesterolemia and high low-density lipoprotein cholesterol to ischemic stroke: Copenhagen general population study. *Circulation* 138 (6), 578–589. doi:10.1161/CIRCULATIONAHA.118.033470

Benn, M., Watts, G. F., Tybjærg-Hansen, A., and Nordestgaard, B. G. (2016). Mutations causative of familial hypercholesterolaemia: Screening of 98 098 individuals from the Copenhagen General Population Study estimated a prevalence of 1 in 217. *Eur. Heart J.* 37, 1384–1394. doi:10.1093/eurheartj/ehw028

Bensend, T. A., Veach, P. M., and Niendorf, K. B. (2014). What's the harm? Genetic counselor perceptions of adverse effects of genetics service provision by non-genetics professionals. *J. Genet. Couns.* 23 (1), 48–63. doi:10.1007/s10897-013-9605-3

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., et al. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *Jama* 305 (22), 2304–2310. doi:10.1001/jama.2011.743

Bowen, M. S., Kolor, K., Dotson, W. D., Ned, R. M., and Khoury, M. J. (2012). Public health action in genomics is now needed beyond newborn screening. *Public health genomics* 15 (6), 327–334. doi:10.1159/000341889

Burke, W., Tarini, B., Press, N. A., and Evans, J. P. (2011). Genetic screening. *Epidemiol. Rev.* 33 (1), 148–164. doi:10.1093/epirev/mxr008

Burke, W., Antommaria, A. H. M., Bennett, R., Botkin, J., Clayton, E. W., Henderson, G. E., et al. (2013). Recommendations for returning genomic incidental findings? We need to talk! *Genet. Med.* 15 (11), 854–859. doi:10.1038/gim.2013.113

Centers for Disease Control and Prevention (2014). *Tier 1 genomics applications and their importance to public health*. Georgia: Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/genomics/implementation/toolkit/tier1.htm.

Centers for Disease Control and Prevention (2020). *Familial hypercholesterolemia*. Georgia: Centers for Disease Control and Prevention. Retrieved from https://www.cdc.gov/genomics/disease/fh/FH.htm.

Chowdhury, S., Dent, T., Pashayan, N., Hall, A., Lyratzopoulos, G., Hallowell, N., et al. (2013). Incorporating genomics into breast and prostate cancer screening: assessing the implications. *Genet. Med.* 15 (6), 423–432. doi:10.1038/gim.2012.167

Clayton, E. W., McCullough, L. B., Biesecker, L. G., Joffe, S., Ross, L. F., Wolf, S. M., et al. (2014). Addressing the ethical challenges in genetic testing and sequencing of children. *Am. J. Bioeth.* 14 (3), 3–9. doi:10.1080/15265161.2013.879945

Cleveland Clinic (2022). Lynch syndrome & HNPCC: Symptoms, causes, tests and treatments. Retrieved from https://my.clevelandclinic.org/health/diseases/17195-lynch-syndrome–hnpcc.

Collier, R. (2012). "The downside of genetic screening.". *CMAJ Can. Med. Assoc. J. = J. de l'Association medicale Can.* 184 (8), 862–864. doi:10.1503/cmaj.109-4169

Committee on Bioethics, Committee on Genetics, ACMG Genomics SocialEthical and Legal Issues Committee (2013). Ethical and policy issues in genetic testing and screening of children. *Pediatrics* 131, 620–622.

Daly, M. B., Pilarski, R., Yurgelun, M. B., Berry, M. P., Buys, S. S., Dickson, P., et al. (2020). NCCN guidelines insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 1.2020. *J. Natl. Compr. Canc. Netw.* 18 (4), 380–391. doi:10.6004/jnccn.2020.0017

Davidson, K. W., Barry, M. J., Mangione, C. M., Cabana, M., Caughey, A. B., Davis, E. M., et al. (2021). Screening for colorectal cancer: US preventive services Task Force recommendation statement. *Jama* 325 (19), 1965–1977. doi:10.1001/jama.2021.6238

Degoma, E. M., Ahmad, Z. S., O'Brien, E. C., Kindt, I., Shrader, P., Newman, C. B., et al. (2016). Treatment gaps in adults with heterozygous familial hypercholesterolemia in the United States: data from the CASCADE-FH registry. *Circ. Cardiovasc. Genet.* 9 (3), 240–249. doi:10.1161/CIRCGENETICS.116.001381

Dewey, F. E., Murray, M. F., Overton, J. D., Habegger, L., Leader, J. B., Fetterolf, S. N., et al. (2016). Distribution and clinical impact of functional variants in 50, 726 whole-exome sequences from the DiscovEHR Study. *Science* 354, aaf6814. doi:10.1126/science.aaf6814

Domchek, S. M., Friebel, T. M., Singer, C. F., Evans, D. G., Lynch, H. T., Isaacs, C., et al. (2010). Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA* 304 (9), 967–975. doi:10.1001/jama.2010.1237

Dominguez-Valentin, M., Sampson, J. R., Seppälä, T. T., Ten Broeke, S. W., Plazzer, J. P., Nakken, S., et al. (2020). Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the prospective Lynch syndrome database. *Genet. Med.* 22 (1), 15–25. doi:10.1038/s41436-019-0596-9

Driver, J. (2014). The history of Utilitarianism. *Stanf. Encycl. Philosophy*. Retrieved from https://plato.stanford.edu/entries/utilitarianism-history/.

George, R., Kovak, K., and Cox, S. L. (2015). Aligning policy to promote cascade genetic screening for prevention and early diagnosis of heritable diseases. *J. Genet. Couns.* 24 (3), 388–399. doi:10.1007/s10897-014-9805-5

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., et al. (2014). Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society Task Force on colorectal cancer. *Gastroenterology* 147 (2), 502–526. doi:10.1053/j.gastro.2014.04.001

Goldberg, A. C., Hopkins, P. N., Toth, P. P., Ballantyne, C. M., Rader, D. J., Robinson, J. G., et al. (2011). Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the national lipid association expert panel on familial hypercholesterolemia. *J. Clin. Lipidol.* 5 (3), 133–140. doi:10.1016/j.jacl.2011.03.001

Green, R. C., Berg, J. S., Grody, W. W., Kalia, S. S., Korf, B. R., Martin, C. L., et al. (2013). ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet. Med.* 15 (7), 565–574. doi:10.1038/gim.2013.73

Green, R. F., Dotson, W. D., Bowen, S., Kolor, K., and Khoury, M. J. (2015). "Genomics in public health: perspective from the office of public health genomics at the centers for disease Control and prevention (CDC)," in *Healthcare* (Switzerland: Multidisciplinary Digital Publishing Institute), 3, 830–837.

Guglielmo, A., Staropoli, N., Giancotti, M., and Mauro, M. (2018). Personalized medicine in colorectal cancer diagnosis and treatment: a systematic review of health economic evaluations. *Cost. Eff. Resour. Alloc.* 16 (1), 2–14. doi:10.1186/s12962-018-0085-z

Guzauskas, G. F., Garbett, S., Zhou, Z., Spencer, S. J., Smith, H. S., Hao, J., et al. (2020). Cost-effectiveness of population-wide genomic screening for hereditary breast and ovarian cancer in the United States. *JAMA Netw. Open* 3 (10), e2022874. doi:10.1001/jamanetworkopen.2020.22874

Hamilton, J. G., Genoff, M. C., Salerno, M., Amoroso, K., Boyar, S. R., Sheehan, M., et al. (2017). Psychosocial factors associated with the uptake of contralateral prophylactic mastectomy among BRCA1/2 mutation noncarriers with newly diagnosed breast cancer. *Breast Cancer Res. Treat.* 162 (2), 297–306. doi:10.1007/s10549-017-4123-x

Hampel, H., Frankel, W. L., Martin, E., Arnold, M., Khanduja, K., Kuebler, P., et al. (2008). Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J. Clin. Oncol.* 26 (35), 5783–5788. doi:10.1200/JCO.2008.17.5950

Howard, A., Bottorff, J. L., Balneaves, L. G., and Kim-Sing, C. (2010). Women's constructions of the'right time'to consider decisions about risk-reducing mastectomy and risk-reducing oophorectomy. *BMC women's health* 10 (1), 24–12. doi:10.1186/1472-6874-10-24

Jasperson, K. W., Vu, T. M., Schwab, A. L., Neklason, D. W., Rodriguez-Bigas, M. A., Burt, R. W., et al. (2010). Evaluating Lynch syndrome in very early onset colorectal cancer probands without apparent polyposis. *Fam. Cancer* 9 (2), 99–107. doi:10.1007/s10689-009-9290-4

Kastrinos, F., Stoffel, E. M., Balmaña, J., Steyerberg, E. W., Mercado, R., and Syngal, S. (2008). Phenotype comparison of MLH1 and MSH2 mutation carriers in a cohort of 1, 914 individuals undergoing clinical genetic testing in the United States. *Cancer Epidemiol. Biomarkers Prev.* 17 (8), 2044–2051. doi:10.1158/1055-9965.EPI-08-0301

Katz, L. H., Advani, S., Burton-Chase, A. M., Fellman, B., Polivka, K. M., Yuan, Y., et al. (2017). Cancer screening behaviors and risk perceptions among family members of colorectal cancer patients with unexplained mismatch repair deficiency. *Fam. Cancer* 16 (2), 231–237. doi:10.1007/s10689-016-9947-8

Kenen, R. H., Shapiro, P. J., Hantsoo, L., Friedman, S., and Coyne, J. C. (2007). Women with BRCA1 or BRCA2 mutations renegotiating a post-prophylactic mastectomy identity: self-image and self-disclosure. *J. Genet. Couns.* 16 (6), 789–798. doi:10.1007/s10897-007-9112-5

Khera, A. V., Won, H. H., Peloso, G. M., Lawson, K. S., Bartz, T. M., Deng, X., et al. (2016). Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J. Am. Coll. Cardiol.* 67 (22), 2578–2589. doi:10.1016/j.jacc.2016.03.520

Khoury, M. (2013). *How can we use genetic testing in population screening for common diseases?* Georgia: Centers for Disease Control and Prevention. Retrieved from https://blogs.cdc.gov/genomics/2013/02/21/how-can-we-use-genetic-testing/.

Koçan, S., and Gürsoy, A. (2016). Body image of women with breast cancer after mastectomy: A qualitative research. *J. Breast Health* 12 (4), 145–150. doi:10.5152/tjbh.2016.2913

Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., et al. (2017). *BRCA1* and *BRCA2* Cohort Consortium. Risks of breast, ovarian, and contralateral breast cancer for *BRCA1* and *BRCA2*mutation carriers. *JAMA* 317 (23), 2402–2416. doi:10.1001/jama.2017.7112

Legal Information Institute *Legal age*. New York: Legal Information Institute. Retrieved from https://www.law.cornell.edu/wex/legal_age.

Lokich, E., Stuckey, A., Raker, C., Wilbur, J. S., Laprise, J., and Gass, J. (2014). Preoperative genetic testing affects surgical decision making in breast cancer patients. *Gynecol. Oncol.* 134 (2), 326–330. doi:10.1016/j.ygyno.2014.05.028

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome sequencing–based screening for *BRCA1/2* expected pathogenic variants among adult biobank participants. *JAMA Netw. Open* 1 (5), e182140. doi:10.1001/jamanetworkopen.2018.2140

Marseille, E., and Kahn, J. G. (2019). Utilitarianism and the ethical foundations of cost-effectiveness analysis in resource allocation for global health. *Philos. Ethics Humanit. Med.* 14 (1), 5–7. doi:10.1186/s13010-019-0074-7

Marshall, C. R., Chowdhury, S., Taft, R. J., Lebo, M. S., Buchan, J. G., Harrison, S. M., et al. (2020). Best practices for the analytical validation of clinical whole-genome sequencing intended for the diagnosis of germline disease. *NPJ Genom. Med.* 5 (1), 47–12. doi:10.1038/s41525-020-00154-9

McGowan, M. P., Dehkordi, H., Moriarty, P. M., and Duell, P. B. (2019). Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J. Am. Heart Assoc.* 8, e013225. doi:10.1161/JAHA.119.013225

MD Anderson Cancer Center (2010). *Q&A: Understanding and managing Lynch syndrome*. Texas: MD Anderson Cancer Center. Retrieved from https://www.mdanderson.org/cancerwise/qa-understanding-and-managing-lynch-syndrome.h00-158589789.html.

Møller, P., Seppälä, T., Bernstein, I., Holinski-Feder, E., Sala, P., Evans, D. G., et al. (2017). Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. *Gut* 66 (3), 464–472. doi:10.1136/gutjnl-2015-309675

Moreira, L., Balaguer, F., Lindor, N., de la Chapelle, A., Hampel, H., Aaltonen, L. A., et al. (2012). Identification of Lynch syndrome among patients with colorectal cancer. *Jama* 308 (15), 1555–1565. doi:10.1001/jama.2012.13088

Murray, M. F., Evans, J. P., Angrist, M., Chan, K., Uhlmann, W. R., Doyle, D. L., et al. (2018). A proposed approach for implementing genomics-based screening programs for healthy adults. *NAM Perspect.* doi:10.31478/201812a

National Cancer Institute. Hereditary breast and ovarian cancer (2021). Retrieved from https://www.cancer.net/cancer-types/hereditary-breast-and-ovarian-cancer.

National Comprehensive Cancer Network (2021). Genetic/familial high-risk assessment: Colorectal (version 1.2021). Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf

Nelson, H. D., Pappas, M., Cantor, A., Haney, E., and Holmes, R. (2019). Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: updated evidence report and systematic review for the US preventive services Task Force. *Jama* 322 (7), 666–685. doi:10.1001/jama.2019.8430

Newman, C. B., Preiss, D., Tobert, J. A., Jacobson, T. A., Page, R. L., Goldstein, L. B., et al. (2019). Statin safety and associated adverse events: a scientific statement from the American heart association. *Arterioscler. Thromb. Vasc. Biol.* 39 (2), e38–e81. doi:10.1161/ATV.0000000000000073

NIH Familial hypercholesterolemia - genetics home reference - NIH Retrieved from https://ghr.nlm.nih.gov/condition/familial-hypercholesterolemia

Oliveri, S., Ferrari, F., Manfrinati, A., and Pravettoni, G. (2018). A systematic review of the psychological implications of genetic testing: a comparative analysis among cardiovascular, neurodegenerative and cancer diseases. *Front. Genet.* 9, 624. doi:10.3389/fgene.2018.00624

Pal, T., and Vadaparampil, S. T. (2012). Genetic risk assessments in individuals at high risk for inherited breast cancer in the breast oncology care setting. *Cancer control.* 19 (4), 255–266. doi:10.1177/107327481201900402

Petrucelli, N., Daly, M. B., and Pal, T. (2016). BRCA1-and BRCA2-associated hereditary breast and ovarian cancer. GeneReviews®[Internet].

Rendle, K. A., Halley, M. C., May, S. G., and Frosch, D. L. (2015). Redefining risk and benefit: understanding the decision to undergo contralateral prophylactic mastectomy. *Qual. Health Res.* 25 (9), 1251–1259. doi:10.1177/1049732314557085

Research on Genomics, National Academies of Sciences, Engineering, and Medicine (2018). Implementing and evaluating genomic screening programs in health care systems: Proceedings of a workshop.

Ross, L. F., Saal, H. M., David, K. L., and Anderson, R. R. (2013). Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet. Med.* 15 (3), 234–245. doi:10.1038/gim.2012.176

Shugar, A. (2017). Teaching genetic counseling skills: Incorporating a genetic counseling adaptation continuum model to address psychosocial complexity. *J. Genet. Couns.* 26 (2), 215–223. doi:10.1007/s10897-016-0042-y

Simon Broome Register Group (1991). Risk of fatal coronary heart disease in familial hypercholesterolaemia. *BMJ Br. Med. J.* 893–896.

Sjouke, B., Kusters, D. M., Kindt, I., Besseling, J., Defesche, J. C., Sijbrands, E. J. G., et al. (2015). Homozygous autosomal dominant hypercholesterolaemia in

the Netherlands: Prevalence, genotype–phenotype relationship, and clinical outcome. *Eur. Heart J.* 36, 560–565. doi:10.1093/eurheartj/ehu058

Sturm, A. C., Knowles, J. W., Gidding, S. S., Ahmad, Z. S., Ahmed, C. D., Ballantyne, C. M., et al. (2018). Clinical genetic testing for familial hypercholesterolemia: JACC scientific expert panel. *J. Am. Coll. Cardiol.* 72 (6), 662–680. doi:10.1016/j.jacc.2018.05.044

ten Broeke, S. W., Brohet, R. M., Tops, C. M., van der Klift, H. M., Velthuizen, M. E., Bernstein, I., et al. (2015). Lynch syndrome caused by germline PMS2 mutations: delineating the cancer risk. *J. Clin. Oncol.* 33 (4), 319–325. doi:10.1200/JCO.2014.57.8088

US Preventive Services Task Force (2019). Breast cancer: medication use to reduce risk. Published September 3, 2019. Available at: https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/breast-cancer-medications-for-risk-reduction

Vasen, H. F., Blanco, I., Aktan-Collan, K., Gopie, J. P., Alonso, A., Aretz, S., et al. (2013). Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 62 (6), 812–823. doi:10.1136/gutjnl-2012-304356

Wert, G. (2005). Cascade Screening: Whose information is it anyway? *Eur. J. Hum. Genet.* 13, 397–398. doi:10.1038/sj.ejhg.5201373

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A mixed-methods protocol to develop and validate a stewardship maturity matrix for human genomic data in the cloud

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This article describes a mixed-methods protocol to develop and test the implementation of a stewardship maturity matrix (SMM) for repositories which govern access to human genomic data in the cloud. It is anticipated that the cloud will host most human genomic and related health datasets generated as part of publicly funded research in the coming years. However, repository managers lack practical tools for identifying what stewardship outcomes matter most to key stakeholders as well as how to track progress on their stewardship goals over time. In this article we describe a protocol that combines Delphi survey methods with SMM modeling first introduced in the earth and planetary sciences to develop a stewardship impact assessment tool for repositories that manage access to human genomic data. We discuss the strengths and limitations of this mixed-methods design and offer points to consider for wrangling both quantitative and qualitative data to enhance rigor and representativeness. We conclude with how the empirical methods bridged in this protocol have potential to improve evaluation of data stewardship systems and better align them with diverse stakeholder values in genomic data science.

KEYWORDS

stewardship, human genomics, ELSI (ethical, legal, and social implications), data governance, cloud, Delphi

1 Introduction

Genomics is a data-intensive science requiring extensive research collaboration across institutions and international borders. Research institutions face mounting pressure co-locate secure access, use and exchange of data to drive innovation in genomics (Langmead and Nellore, 2018). In addition to decentralized and federated access models, national

Abbreviations: ELSI—Ethical, legal, and social issues. FAIR—Findable, Accessible, Interoperable, Reusable. IQR—interquartile range. PaaS—Platform as a service. SMM—stewardship maturity matrix. SaaS—Software as a service.

research agencies are heavily invested in cloud technologies to enable controlled data access (Stein et al., 2015). This migration to the cloud represents an important shift not only in how data repositories stand up their privacy and security infrastructures, but also in how repository managers steward the data resources generated by research supported through public funds (Grzesik et al., 2021). Genomic data are uniquely identifying not only for the individual about whom data specifically relate, but also for their biological relatives and communities (Song et al., 2022) in which they live and work. Sharing genomic data also comes with increased risk of re-identification. Recent studies have shown, for example, that individuals can be re-identified from aggregate datasets with few record linkages (Dwork et al., 2017). These properties affect how genomic and related data are collected, regulated, and shared.

We refer to data repositories in this article as entities which store, organize, validate, archive, preserve and distribute genomic and related health data submitted by the community related to particular system(s) in compliance with the FAIR (findable, accessible, reusable and interoperable) Data Principles (NIH, 2022a). At a minimum, data stewardship can refer to the institutional practices and policies meant to calibrate appropriate data protection with compliant data access and use. Data stewardship is thus integral to well-functioning data governance systems (Boeckhout et al., 2018) that requires practical frameworks for compliance as well as stakeholder-engaged research on values and priorities.

Yet while commitments to responsible stewardship are outlined in repository data sharing policies, and methods for evaluating stewardship impact have been proposed (Wilkinson et al., 2016), these are largely underdeveloped for cloud-native environments with few exceptions [see for example access policies for the research analysis platform of the United Kingdom Biobank (UK Biobank, 2022) and NIH Cloud Guidebook (NIH, 2022b)].

We lack empirical data, for example, on what stewardship outcomes matter most to key stakeholders and how we should measure them over time. Examples of stewardship outcomes could include concordance between consent permissions and data use restrictions, ethics review of proposed data uses, processing times for data access requests, and the number of successful data access requests among researchers working in low-and middle-income countries. According to its access procedures, for example, United Kingdom Biobank's cloud services charges fees for tiered access as well as data storage and analysis of data. While reduced access options are available, it is unclear whether pay-for-access policies affect who can afford to conduct the research in the first place.

In this article we describe a mixed-methods study design to identify stewardship outcomes and develop assessment criteria for assessing them in cloud-native environments. We first discuss the unique properties of genomic data and the ethical, legal and social issues of migrating such data to the cloud. We then explain how current genomic data management and access challenges the ways that repositories practice responsible stewardship in these new computing environments. In response to these practical challenges, we describe how a modified Delphi together with stewardship maturity modeling can be used to develop, validate and test the implementation of a stewardship impact assessment tool for global repositories which host data in the cloud. Next, we discuss analytical approaches for wrangling both quantitative and qualitative data generated in the proposed study, raising points to consider for ensuring rigor and representativeness. We conclude with how adapting SMMs for tracking progress on data stewardship can advance a new research agenda for evidence-based stewardship in human genomics as computing capabilities evolve.

1.1 Cloud infrastructures and the need to store, analyze and share human genomic data at enterprise scale

New digital infrastructures powered by cloud technologies transform how researchers interact with, analyze, and share data at scale including in clinical areas such as cancer (Langmead and Nellore, 2018) (Lau et al., 2017) and rare disease (Zurek et al., 2021). Using cloud services as infrastructure to host the largescale genomic data collections—one of four distinct types of cloud service separate from software as service (SaaS), platform as service (PaaS) and serverless (O'Driscoll et al., 2013)—offers powerful advantages (Stein, 2010). These include simplifying management (Schatz et al., 2022), overcoming security risks associated with traditional copy and download, and making data available in organized, searchable formats which reduce time and resource burdens (Kudtarkar et al., 2010).

However unique features of these computing environments compel new ethical, legal and social questions about how to responsibly access and steward genomic data in the cloud (Carter, 2019) (Filippi and Vieira, 2014). For example, data protection laws are jurisdiction-specific while actual data users may be based all over the world. This complicates which data protections regulations should principally apply: those in the jurisdiction where the repository is based, where the user resides, or both? Many repositories purchase cloud services from commercial providers (e.g., Google, Amazon Web Services), raising some concerns about the dependence on third parties and potential for interference (Molnár-Gábor et al., 2017). As Philipps and colleagues argue, "service outages caused by technical problems, changes to the company"s terms of service or even sudden closure of the company could block researchers' access to data at any time. Also, it is often unclear to what extent researchers using cloud services can ensure that their data are not

TABLE 1 Data stewardship frameworks.

Stewardship framework	Stewardship focus	
FAIR (Wilkinson et al., 2016)	Findable, Accessible, Interoperable, Reusable,	Datasets
TRUST (Lin et al., 2020)	Trust, Respect, User-focused, Sustainability, Technology	Data repositories
CARE (Carroll et al., 2021)	Contribute, Attribute, Release, Empower	Data stakeholders (e.g. data users, creators, regulators, contributors)

TABLE 2 Template stewardship maturity matrix that charts n stewardship outcomes of interest onto five descriptive layers of organizational development.

	Outcome n	Outcome n + 1	Outcome n + 2
Ad hoc (not managed)	Ad hoc criteria for outcome 1	Ad hoc criteria for outcome 2	Ad hoc criteria for outcome 3
Minimal (limit-managed, not defined)	Minimal criteria for outcome 1	Minimal criteria for outcome 2	Minimal criteria for outcome 3
Intermediate (managed, defined, partially implemented)	Intermediate criteria for outcome 1	Intermediate criteria for outcome 2	Intermediate criteria for outcome 3
Advanced (well-managed, well-defined, fully implemented)	Advanced criteria for outcome 1	Advanced criteria for outcome 2	Advanced criteria for outcome 3
Optimal (measured, controlled, audited)	Optimal criteria for outcome 1	Optimal criteria for outcome 2	Optimal criteria for outcome 3

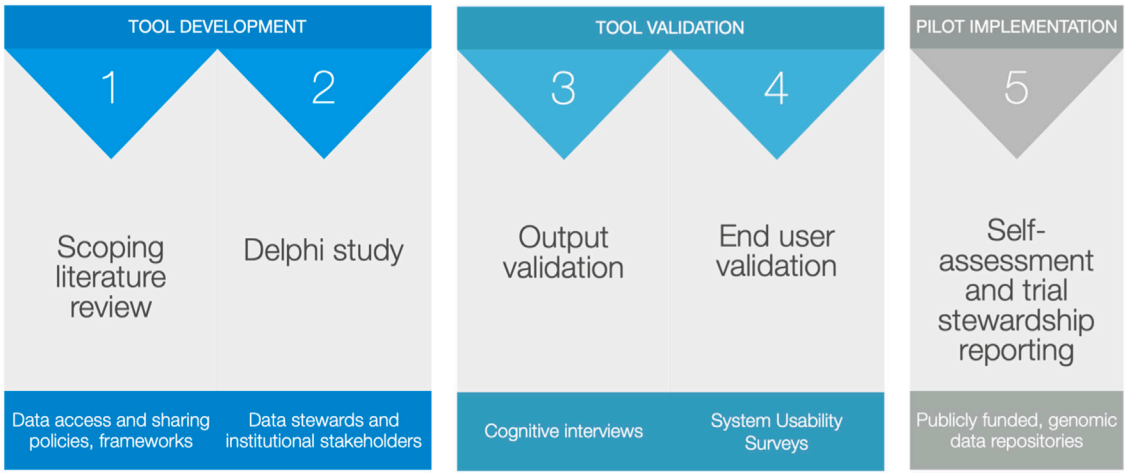

FIGURE 1
Step-by-step outline of a protocol to develop, validate and pilot the implementation of a stewardship maturity matrix tool to track progress on human genomic data stewarded in the cloud.

disclosed to third parties, such as those conducting abusive state-level "surveillance" (Phillips et al., 2020).

While there is broad consensus on data stewardship principles outlined in frameworks such as FAIR, TRUST, and CARE (Table 1), their assessment has been computationally difficult to perform in practice (Anjaria, 2020). It has been shown how modeling a stewardship maturity matrix (SMM) can be effective at capturing the FAIRness of datasets and TRUSTworthiness of repositories in the earth and planetary sciences (Downs et al., 2015) (22). SMMs are often presented by a two dimensional array mapping n stewardship outcomes of interest onto various levels of organizational development (Peng et al., 2015): ad hoc, minimal, intermediate, advanced and optimal. A sample SMM is presented in Table 2. Across the rows of the matrix reflect "various facets of core stewardship functionality, (e.g., data management), while the columns describe typical behaviours representing increasing maturity in practices and capability against each aspect, ranging from a poorly-managed

TABLE 3 Materials and equipment used in the protocol organized by study phase.

Research phase	Materials and equipment used
	Laptop computer, internet access
Phase 1: Identifying core outcomes of genomic data stewardship	• Library services/access and librarian support
Phase 2. Developing the stewardship maturity matrix	• Online survey platform, with optional software applications specific to Delphi surveys (e.g. Welphi available at https://www.welphi.com/en/Home.html
	• Qualitative data analysis software (e.g. Dedoose, NVivo)
	• Quantitative data analysis programs (e.g. R, STATA)
Phase 3. Validation of the stewardship maturity matrix tool	• Video conferencing services
	• Qualitative data analysis software (e.g. Dedoose, NVivo)
	• Quantitative data analysis programs (e.g. R, STATA)

or no-capability state to an advanced, well-managed state" (23). Once developed, the SMM "can be used not only as a guide to users about the rigour of data stewardship practices, but also as a tool for monitoring and improving aspects of organizational performance in producing, managing, or servicing climate data" (Dunn et al., 2021).

Several reasons justify exploring how SMMs can be adapted to study human genomic data stewardship outcomes. First, advances in human genomics, like earth and planetary sciences, depend on sharing high quality and well managed data resources. Second, large, publicly funded repositories are among the primary sources where researchers access the data they need to conduct rigorous genomics research. Therefore data access and release activities catalyzed by repositories makes them strategic focal points for assessing stewardship outcomes (Dunn et al., 2021).

2 Methods

In the sections that follow, we provide methods and instructions for how to first develop (phase 1) validate (phase 2) and then test the implementation (phase 3) of a SMM for human genomic and related health data managed in the cloud. An overview of the protocol, as well as the specific materials and equipment used are provided in Figure 1 and Table 3, respectively. First, a scoping review of data sharing, management and access policies inform an initial core outcomes set for responsible data stewardship bespoke to cloud-native repositories. These core outcomes are then evaluated and further refined by actual repository managers, privacy officers and other institutional data stewards in a Delphi study. Institutional stakeholders engaged in the Delphi will also work to develop assessment criteria specific to each core outcome in a process that will result in a draft SMM. The SMM will be field tested with topic experts and piloted within repositories that currently host genomic data in the cloud.

2.1 Phase 1: Identifying core outcomes of genomic data stewardship

The objective of Phase 1 is to inform a core outcomes set (COS) for genomic data stewarded in the cloud following a scoping literature review of data sharing, management and access policies (see for example Ethics and Governance Framework for the United Kingdom Biobank); published data stewardship frameworks, empirical studies, guidelines, and best practices. A detailed search strategy will be developed with guidance from a reference librarian, and which will include relevant search terms such as "genomic data," "stewardship," "cloud," "infrastructure," "data sharing," "outcomes" among others to best capture existing stewardship measurements and approaches. An example search strategy is provided in the Supplementary Material S1.

2.2 Phase 2. Developing the stewardship maturity matrix

Findings from the literature review will inform an initial COS that will be refined in a three-round Delphi survey involving institutional data stewards, repository managers and other data access and privacy officers working at genomic data repositories globally.

Delphi methods are particularly well suited to refining COS and have been used in previous bioethics work to guide genomics policy (Stevens Smith et al., 2020). Delphi studies engage informed stakeholders through iterative rounds of structured communication and feedback (Banno et al., 2019). A Delphi facilitator collects panel responses, usually anonymously, and statistically aggregates and analyzes them (Rowe et al., 2001). The facilitator then provides summaries back to panelists who are invited to re-evaluate their position after considering responses from fellow panelists. This process is iterated across several rounds until reaching a pre-specified threshold indicating a consensus pattern.

TABLE 4 Practical guidance for planning an expert Delphi panel.

Attribute	Questions to consider	Useful indicators	Protocol-specific guidance
Relevant expertise	o What professionals are involved in or implicated by the policy topic?	o Degree credentials	Professionals with relevant expertise could include
	o What industries are affected?	o Professional background and training	o Data stewards
	o What community groups are affected?	o Job description	o Data producers
		o Employer	o Data access committees
			o Repository managers
			o Data infrastructure designers
			o Software engineers
			o Cloud service providers
			o Policy and governance leads
Availability	o Do you have a pre-existing relationship with the prospective panelist or their professional community?	o Informational interview with prospective panelists	o Schedule interviews before/after work hours
	o Are there constraints on the panelists' time?	o Publicly available contact information	o Compensate panelists for afterhours participation
	o Can they be contacted?		o Avoid participation during peak holiday months
	o Can they access communication channels?		
	o Are they willing to sustain their participation?		
Representativeness	o Is the demographic distribution of prospective panelists reflective of the stakeholder community?	o Published literature	o Leverage members in existing professional networks/societies (e.g. Global Alliance for Genomics)
	o What is the demographic distribution of panelists in terms of age, gender, profession, years of experience, race/ethnicity/ religion	o Demographic reports	o Consider oversampling from underrepresented groups
		o Census data	o Conduct online search of active human genomic data repositories globally

The Delphi survey will enable panelists to evaluate each outcome for its relative importance and feasibility, suggest new outcomes and vote to eliminate those that are either infeasible to implement or unable to be measured in practice. In the final round of the Delphi, panelists will convene to develop assessment criteria specific to each core outcome and map these onto a two-dimensional array shown in Table 2.

2.2.1 Phase 2 participant selection

Prospective panelists should represent institutional stakeholders with expertise in data management and data access review (e.g., data access committee members, privacy officers, managers) across repositories which currently use cloud services or plan to in the future. Panel membership is critical to the external validity of the resulting SMM. We will therefore carefully consider personal attributes such as relevant expertise, experience, availability, and representativeness to guide recruitment decisions using Table 4 as a guide. Published studies also reported that offering incentives improved panel retention and enhanced the quality of participation (Belton et al., 2019) without unduly pressuring participation. As is customary, we plan to compensate Delphi panelists using rates typical of professional consultation in their respective fields.

2.2.2 Phase 2 data collection

In Round 1 of the Delphi, we will capture panelists' perspectives on the relative importance and feasibility of each core outcome (Sinha et al., 2011) and allow panelists the opportunity to contribute additional outcomes. We intend to pilot each round of surveys among a group of topic-naïve experts to ensure overall comprehension. To discourage ambivalent responses, we will adopt a three point Likert scale for rating exercises (Lange et al., 2020). Embedding free text responses in the survey will allow us to triangulate quantitative survey data with qualitative analysis of the rationales panelists provide for each core outcome. In Round 2 of the Delphi, panelists will re-rate outcomes that failed to reach consensus in Round 1 after reviewing the results and panel summaries. A summary report of survey results and qualitative rationales from Round 2 will be given to panelists prior to a 60 min virtual consensus workshop in Round 3. During the workshop, panelists will provide input on draft assessment criteria specific to core outcomes deemed to be essential after Rounds 1 and 2. We will use a progressive maturity scale—the capability maturity model integration™ (Carnegie Mellon University, 2001)—to match core outcomes with assessment criteria.

2.2.3 Phase 2 data analysis

Practical guidance is limited on developing core outcome sets for organizations rather than individuals such as clinicians or policy makers (Sinha et al., 2011). We will therefore look to consensus building frameworks and psychometrically-validated tools used in the clinical (Kirkham et al., 2017) and other data science research contexts for guidance (Board, 2019). Descriptive statistics–including median, mean, interquartile range and standard deviation—will benchmark consensus on the core outcomes set (von der Gracht, 2012) when there is >70% agreement on one rating, or 80% agreement across two contiguous ratings (Needham and de Loe, 1990). We will generate a core-outcomes set from those outcomes which are considered essential via panel consensus and which demonstrate low to no polarity based on IQRs less than 1 (Raskin, 1994; Rayens and Hahn, 2000).

2.3 Phase 3 validation of the stewardship maturity matrix tool

Borrowing from approaches used in the environmental impact assessment literature (Bockstaller and Girardin, 2003), two validation exercises will serve to test the tool's "output" and "usability" among prospective end users.

2.3.1 Phase 3 data collection

We will first develop hypothetical vignettes of stewardship practices that correspond to each of the five stewardship maturity levels outlined in the SMM and assign reference scores to them. Next, we will conduct cognitive interviews with prospective end users to validate how well user scores align with the reference (output validation). Cognitive interviewing is a specific approach to structured interviewing during which we will capture real-time feedback on user experience (Willis et al., 2004; Willis, 2005; Boeije and Willis, 2013). Interviewees 'think aloud' as they apply the SMM to assign an overall stewardship maturity score to each vignette until assessments reach a recommended interrater reliability score of 0.8 (Burla et al., 2008). Following the interviews participants will complete a System Usability Survey (Bangor et al., 2008; Lewis, 2018) to complement output validation data about the tool's overall ease of use (user validation).

2.3.2 Phase 3 participation selection

Interviewees will be purposively recruited from expert communities who have experience developing data management and release policies, standards and executable data access workflows in cloud environments.

2.3.3 Phase 3 data analysis

We expect the validation exercises to generate quantitative as well as qualitative data. Both datasets will require their own analytical approaches. Pearson's chi square test will enable us to compare reference scores with scores assigned by end users. User experience themes will also be synthesized from qualitative data emerging from the cognitive interviews using a content analysis approach. To enhance rigor, independent coders will develop an initial codebook from analyzing a sample of interview transcripts. Coders will then meet to resolve any discrepancies and revise the codebook as appropriate.

2.4 Pilot testing and implementation

Should we fail to reach interrater consensus during the cognitive interviews, or the usability tests reveal issues with internal validity, we will re-engage Delphi participants to further refine the SMM based on feedback from the validation studies. Upon successfully demonstrating the tool's output validity and usability, we will pursue a pilot program with repository managers affiliated with cloud-native repositories. Pilot testing will inform the organizational factors to consider for implementation.

3 Limitations

The mixed-methods study design described in this protocol should be considered in light of several limitations and considerations. Delphi studies can be both time and resource intensive. It is possible that panelists are lost to attrition, which may skew the rating distributions. Second, engaging primarily institutional stakeholders to help develop the tool, may not adequately capture the perspectives and experiences of data contributors. Researchers could consider adapting the protocol in the future to solicit input directly from individuals who have previously shared their data, or plan to contribute their genomic data to cloud-native repositories in the future. Third, cloud computing and software engineering professionals skew largely white, European and male. Therefore, oversampling participants from groups commonly underrepresented in these technical fields, particularly during the Phase 2 validation phase, is critically important for promoting equity and representation as well as to ensuring external validity. Fourth, usability testing may not capture all relevant errors end users could make. Participants' unfamiliarity with the concepts measured in Phase 2—for example ethics, stewardship and governance, time spent working in one's role—as well as biases that can carry over from institutional environments are among the most common reasons why usability testing fails.

4 Conclusion and future directions

The development, validation, and implementation of an impact assessment tool is an important practical solution to a growing infrastructure problem for institutions that endeavor to

track progress on genomic data stewardship in the cloud. This article outlines a mixed-methods protocol to rigorously develop and validate an assessment tool to monitor human genomic data stewardship in novel cloud environments. Research and development of a SMM for genomic data stewardship is especially timely as government investment in cloud-based data infrastructures expands (e.g., NIH STRIDES Initiative, https://cloud.nih.gov/about-strides/). Both institutional and public stakeholders benefit from transparent reporting of stewardship outcomes at the repository level. A reliable and usable SMM tool allows data managers, data access committee members, privacy officers, and other institutional officials to self-assess stewardship practices early and often. Scores generated from periodic assessment using the SMM tool could enable data stewards to identify "'quick wins" where higher ratings for some aspects require little effort to obtain" (Dunn et al., 2021). With the stewardship assessment criteria in mind, genomic researchers could proactively practice good stewardship when sharing or curating data they generate in their work. Researchers could also use stewardship scores to help guide their choices about which datasets to use for their projects. Finally, periodic assessment and routine reporting of stewardship outcomes using a standard SMM tool can improve repository practices in the long term while helping to sustain public trust in publicly funded genomic research in the future.

Future work will be needed to determine repository preparedness for implementing stewardship assessments as part of their annual reporting. Rigorous studies investigating the effects of transparent reporting of stewardship outcomes on more diverse data stakeholders (e.g., individual and community data contributors) are also needed. Cloud-native repositories could in the future seek certification for their commitment to responsible stewardship practice through programs sponsored under the CoreTrustSeal (https://www.coretrustseal.org/) and strike an advisory committee to review and assess new data infrastructure proposals. "If cloud technology is the future of biomedical science then, for genomics, the future is already here" (44). It is incumbent on data producers, users and regulators alike to prepare for this future in ways that are concordant with diverse value systems and as computer science and genomic data discovery evolve.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

VR conceptualized the study and developed the protocol with supervisory input from authors GP and MC. VR prepared initial drafts of this manuscript. All authors reviewed and approved the submitted version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fgene.2022.876869/full#supplementary-material

References

Anjaria, K. A. (2020). Computational implementation and formalism of FAIR data stewardship principles. *DTA* 54 (2), 193–214. doi:10.1108/dta-09-2019-0164

Bangor, A., Kortum, P. T., and Miller, J. T. (2008). An empirical evaluation of the system usability scale. *Int. J. Human–Computer Interact.* 24 (6), 574–594. doi:10.1080/10447310802205776

Banno, M., Tsujimoto, Y., and Kataoka, Y. (2019). Reporting quality of the Delphi technique in reporting guidelines: A protocol for a systematic analysis of the EQUATOR network library. *BMJ Open* 9 (4), e024942. doi:10.1136/bmjopen-2018-024942

Belton, I., MacDonald, A., Wright, G., and Hamlin, I. (2019). Improving the practical application of the Delphi method in group-based judgment: A six-step prescription for a well-founded and defensible process. *Technol. Forecast. Soc. Change* 147, 72–82. doi:10.1016/j.techfore.2019.07.002

Board, C. S. (2019). CoreTrustSeal trustworthy data repositories requirements: Extended guidance 2020–2022. Available from: https://zenodo.org/record/3632533 (accessed on May 17, 2022).

Bockstaller, C., and Girardin, P. (2003). How to validate environmental indicators. *Agric. Syst.* 76 (2), 639–653. doi:10.1016/s0308-521x(02)00053-7

Boeckhout, M., Zielhuis, G. A., and Bredenoord, A. L. (2018). The FAIR guiding principles for data stewardship: Fair enough? *Eur. J. Hum. Genet.* 26 (7), 931–936. doi:10.1038/s41431-018-0160-0

Boeije, H., and Willis, G. (2013). The cognitive interviewing reporting framework (CIRF): Towards the harmonization of cognitive testing reports. *Methodology* 9 (3), 87–95. doi:10.1027/1614-2241/a000075

Burla, L., Knierim, B., Barth, J., Liewald, K., Duetz, M., and Abel, T. (2008). From text to codings: Intercoder reliability assessment in qualitative content analysis. *Nurs. Res.* 57 (2), 113–117. doi:10.1097/01.NNR.0000313482.33917.7d

Carnegie Mellon University (2001). *Capability maturity model integration (CMMISM), version 1.1. Continuous representation*. Pittsburgh, United States: Carnegie Mellon University, 645.

Carroll, S. R., Herczog, E., Hudson, M., Russell, K., and Stall, S. (2021). Operationalizing the CARE and FAIR principles for indigenous data futures. *Sci. Data* 8 (1), 108. doi:10.1038/s41597-021-00892-0

Carter, A. B. (2019). Considerations for genomic data privacy and security when working in the cloud. *J. Mol. Diagn.* 21 (4), 542–552. doi:10.1016/j.jmoldx.2018.07.009

Downs, R. R., Duerr, R., Hills, D. J., and Ramapriyan, H. K. (2015). *Data stewardship in the earth sciences* 21 (7/8). D-Lib Magazine.

Dunn, R., Lief, C., Peng, G., Wright, W., Baddour, O., Donat, M., et al. (2021). Stewardship maturity assessment tools for modernization of climate data management. *Data Sci. J.* 20, 7. doi:10.5334/dsj-2021-007

Dwork, C., Smith, A., Steinke, T., and Ullman, J. (2017). Exposed! A survey of attacks on private data. *Annu. Rev. Stat. Appl.* 4 (1), 61–84. doi:10.1146/annurev-statistics-060116-054123

Filippi, P. D., and Vieira, M. S. (2014). THe commodification of information commons: The case of cloud computing. *Sci. Tech. L. Rev* 102, 42.

Grzesik, P., Augustyn, D. R., Wyciślik, Ł., and Mrozek, D. (2021). Serverless computing in omics data analysis and integration. *Briefings Bioinforma.* 23, bbab349. doi:10.1093/bib/bbab349

Kirkham, J. J., Davis, K., Altman, D. G., Blazeby, J. M., Clarke, M., Tunis, S., et al. (2017). Core outcome set-STAndards for development: The COS-STAD recommendations. *PLoS Med.* 14 (11), e1002447. doi:10.1371/journal.pmed.1002447

Kudtarkar, P., DeLuca, T. F., Fusaro, V. A., Tonellato, P. J., and Wall, D. P. (2010). Cost-effective cloud computing: A case study using the comparative genomics tool, roundup. *Evol. Bioinform Online* 6, 197–203. doi:10.4137/EBO.S6259

Lange, T., Kopkow, C., Lützner, J., Günther, K. P., Gravius, S., Scharf, H. P., et al. (2020). Comparison of different rating scales for the use in Delphi studies: Different scales lead to different consensus and show different test-retest reliability. *BMC Med. Res. Methodol.* 20 (1), 28. doi:10.1186/s12874-020-0912-8

Langmead, B., and Nellore, A. (2018). Cloud computing for genomic data analysis and collaboration. *Nat. Rev. Genet.* 19 (4), 208–219. doi:10.1038/nrg.2017.113

Lau, J. W., Lehnert, E., Sethi, A., Malhotra, R., Kaushik, G., Onder, Z., et al. (2017). The cancer genomics cloud: Collaborative, reproducible, and democratized—a new paradigm in large-scale computational research. *Cancer Res.* 77 (21), e3–e6. doi:10.1158/0008-5472.CAN-17-0387

Lewis, J. R. (2018). The system usability scale: Past, present, and future. *Int. J. Human–Computer. Interact.* 34 (7), 577–590. doi:10.1080/10447318.2018.1455307

Lin, D., Crabtree, J., Dillo, I., Downs, R. R., Edmunds, R., Giaretta, D., et al. (2020). The TRUST Principles for digital repositories. *Sci. Data* 7 (1), 144. doi:10.1038/s41597-020-0486-7

Molnár-Gábor, F., Lueck, R., Yakneen, S., and Korbel, J. O. (2017). Computing patient data in the cloud: Practical and legal considerations for genetics and genomics research in europe and internationally. *Genome Med.* 9 (1), 58. doi:10.1186/s13073-017-0449-6

Needham, R. D., and de Loe, R. C. (1990). The policy Delphi: Purpose, structure and application. *Can. Geogr.* 34 (2), 133–142. doi:10.1111/j.1541-0064.1990.tb01258.x

NIH (2022). Biomedical data repositories and knowledgebases. Available from: https://datascience.nih.gov/data-ecosystem/biomedical-data-repositories-and-knowledgebases#repositories.

NIH (2022). Cloud Guidebook. Available from: http://nih-data-commons.us/cloud-guidebook/.

O'Driscoll, A., Daugelaite, J., and Sleator, R. D. (2013). 'Big data', Hadoop and cloud computing in genomics. *J. Biomed. Inf.* 46 (5), 774–781. doi:10.1016/j.jbi.2013.07.001

Peng, G., Privette, J. L., Kearns, E. J., Ritchey, N. A., and Ansari, S. (2015). A unified framework for measuring stewardship practices applied to digital environmental datasets. *Data Sci. J.* 13 (0), 231–252. doi:10.2481/dsj.14-049

Phillips, M., Molnár-gábor, F., Korbel, J. O., Thorogood, A., Joly, Y., Chalmers, D., et al. (2020). Genomics: data sharing needs an international code of conduct. *Nature.* 578, 31–33.

Raskin, M. S. (1994). The Delphi study in field instruction revisited: Expert consensus on issues and research priorities. *J. Soc. Work Educ.* 30 (1), 75–89. doi:10.1080/10437797.1994.10672215

Rayens, M. K., and Hahn, E. J. (2000). Building consensus using the policy Delphi method. *Policy, Polit. Nurs. Pract.* 1 (4), 308–315. doi:10.1177/152715440000100409

Rowe, G., and Wright, G. (2001). "Expert opinions in forecasting: The role of the Delphi technique," in *International series in operations research & management science; vol. 30*. Editor F. S. Hillier (Boston, MA: Springer US), 125–144.

Schatz, M. C., Philippakis, A. A., Afgan, E., Banks, E., Carey, V. J., Carroll, R. J., et al. (2022). Inverting the model of genomics data sharing with the NHGRI Genomic Data Science Analysis, Visualization, and Informatics Lab-space. *Cell Genomics*. 2, 100085. doi:10.1016/j.xgen.2021.100085

Sinha, I. P., Smyth, R. L., and Williamson, P. R. (2011). Using the Delphi technique to determine which outcomes to measure in clinical trials: Recommendations for the future based on a systematic review of existing studies. *PLoS Med.* 8 (1), e1000393. doi:10.1371/journal.pmed.1000393

Song, L., Liu, H., Brinkman, F. S. L., Gill, E., Griffiths, E. J., Hsiao, W. W. L., et al. (2022). Addressing privacy concerns in sharing viral sequences and minimum contextual data in a public repository during the COVID-19 pandemic. *Front. Genet.* 12, 716541. doi:10.3389/fgene.2021.716541

Stein, L. D., Knoppers, B. M., Campbell, P., and Korbel, J. O. (2015). Data analysis: Create a cloud commons. *Nature* 523, 149–151. doi:10.1038/523149a

Stein, L. D. (2010). The case for cloud computing in genome informatics. *Genome Biol.* 11 (5), 207. doi:10.1186/gb-2010-11-5-207

Stevens Smith, H., Russell, H. V., Lee, B. H., and Morain, S. R. (2020). Using the Delphi method to identify clinicians' perceived importance of pediatric exome sequencing results. *Genet. Med.* 22 (1), 69–76. doi:10.1038/s41436-019-0601-3

UK Biobank (2022). UK Biobank access procedures: Application and review procedures for access to the UK Biobank resource. Available from: https://www.ukbiobank.ac.uk/media/hfnf2w0f/20220722-access-procedures-v2-1-final.pdf.

Van der Auwera, G., and O'Connor, B. (2020). *Genomics in the cloud: Using docker, GATK, and WDL in terra*. 1st ed. California, United States: O'Reilly Media.

von der Gracht, H. A. (2012). Consensus measurement in Delphi studies. *Technol. Forecast. Soc. Change* 79 (8), 1525–1536. doi:10.1016/j.techfore.2012.04.013

Wilkinson, M. D., Dumontier, M., Aalbersberg, IjJ., Appleton, G., Axton, M., Baak, A., et al. (2016). Comment: The FAIR Guiding Principles for scientific data management and stewardship. *Sci. Data* 3, 160018–160019. doi:10.1038/sdata.2016.18

Willis, G. (2005). *Cognitive interviewing*. California, United States: SAGE Publications, Inc.

Willis, G. B. (2004). "Cognitive interviewing revisited: A useful technique, in theory?," in *Wiley series in survey methodology*. S. Presser, J. M. Rothgeb, M. P. Couper, J. T. Lessler, E. Martin, J. Martin, et al. (Hoboken, NJ, USA: John Wiley & Sons), 23–43.

Zurek, B., Ellwanger, K., Vissers, L. E. L. M., Schüle, R., Synofzik, M., Töpf, A., et al. (2021). Solve-RD: Systematic pan-European data sharing and collaborative analysis to solve rare diseases. *Eur. J. Hum. Genet.* 29 (9), 1325–1331. doi:10.1038/s41431-021-00859-0

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From the patient to the population: Use of genomics for population screening

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Genomic medicine is expanding from a focus on diagnosis at the patient level to prevention at the population level given the ongoing under-ascertainment of high-risk and actionable genetic conditions using current strategies, particularly hereditary breast and ovarian cancer (HBOC), Lynch Syndrome (LS) and familial hypercholesterolemia (FH). The availability of large-scale next-generation sequencing strategies and preventive options for these conditions makes it increasingly feasible to screen pre-symptomatic individuals through public health-based approaches, rather than restricting testing to high-risk groups. This raises anew, and with urgency, questions about the limits of screening as well as the moral authority and capacity to screen for genetic conditions at a population level. We aimed to answer some of these critical questions by using the WHO Wilson and Jungner criteria to guide a synthesis of current evidence on population genomic screening for HBOC, LS, and FH.

KEYWORDS

population screening, tier 1 conditions, hereditary breast and ovarian cancer (HBOC), lynch syndrome, familial hypercholestelemia, genetic testing

Introduction

Genomic medicine is expanding from a focus on diagnosis at the patient level to prevention at the population level. As test costs fall, it could become feasible to screen pre-symptomatic individuals through public health-based approaches, rather than restricting testing to high-risk groups. Indeed, pilot initiatives in which hundreds of thousands of individuals will undergo genomic screening are being launched in health systems in the United States (U.S.) (Carey et al., 2016; Schwartz et al., 2018; Lacaze et al., 2019; Grzymski et al., 2020), the United Kingdom (U.K.) (Genomics England, 2021), and Australia (Rowley et al., 2019; Lacaze et al., 2022). Leading hereditary conditions for consideration in population screening include hereditary breast and ovarian cancer syndrome (HBOC), Lynch syndrome (LS), and familial hypercholesterolemia (FH). These conditions are prioritized for screening due to their under-ascertainment using current screening approaches and the availability of

TABLE 1 Wilson and Jungner's principles for disease screening (Wilson and Jungner, 1968).

#	Principle
1	The condition sought should be an important health problem
2	There should be an accepted treatment for patients with recognized disease
3	Facilities for diagnosis and treatment should be available
4	There should be a recognizable latent or early symptomatic stage
5	There should be a suitable test or examination
6	The test should be acceptable to the population
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood
8	There should be an agreed policy on whom to treat as patients
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
10	Case-finding should be a continuing process and not a "once and for all" project

evidence-based interventions to reduce morbidity and mortality (Centers for Disease Control and Prevention OoPHG, 2022).

Traditional methods to identify cases with HBOC, LS, and FH include genetic testing for patients meeting clinical, ethnicity or family-history based criteria (Hampel et al., 2008; Schofield et al., 2014; Klančar et al., 2015; Tognetto et al., 2017; Groselj et al., 2018; Gupta et al., 2019; Daly et al., 2020; Kunnackal John et al., 2021; Zuurbier et al., 2021). However, these targeted approaches have been found to miss a substantial proportion of individuals who harbor pathogenic variants. For example, >50% of individuals with pathogenic *BRCA1* and *BRCA2* (*BRCA1/2*) variants are missed by family history-based criteria (Metcalfe et al., 2010a; Gabai-Kapara et al., 2014; Manchanda et al., 2015a). The availability of large-scale next-generation sequencing (NGS) strategies and preventive options for these conditions makes it increasingly feasible to screen pre-symptomatic individuals through public health-based approaches, rather than restricting testing to high-risk groups.

This raises anew, and with urgency, questions about the limits of screening as well as the capacity to screen for genetic conditions at a population level, or in other words, population genomic screening. We use the term "population genomic screening" to refer to germline DNA testing among an unselected, asymptomatic population with the aim of identifying individuals with pathogenic/likely pathogenic (henceforth, "pathogenic") variants. Key issues to scaling up population genomic screening include the optimal testing approach, penetrance of these conditions in the general population, clinical effectiveness, cost-effectiveness, acceptability, health system capacity to implement such a program, ethical issues such as overdiagnosis, access challenges and equity.

Decisions about screening are expected to align with the World Health Organization principles of screening. These criteria, developed by Wilson and Jungner in 1968, inform decision-making around disease screening and generally include considerations of the nature of the disease, test characteristics, and the availability, effectiveness and acceptability of preventive interventions or treatments (Table 1) (Wilson and Jungner, 1968). Since its publication, Wilson and Jungner's criteria have been widely accepted, modified and used by decision-makers across the world to guide screening decisions. Whereas the Wilson and Jungner criteria were developed for programs aiming to enable early detection and intervention for individuals with early stages of a disease, population genomic screening programs would identify those with a genetic predisposition to disease. The identification of a pathogenic variant in an asymptomatic individual through genetic screening is not equivalent to a clinical diagnosis of the associated disease (Murray, 2016; Murray et al., 2021). Given the complexity of policy decision-making for genetic tests and genetic screening programs, various frameworks and sets of decision criteria have been developed to guide these decisions (Sanderson et al., 2005; Burke and Zimmern, 2007; Andermann et al., 2008; Teutsch et al., 2009; Andermann et al., 2011; National Academies of Sciences Engineering and Medicine, 2017; Pitini et al., 2019). While these newer frameworks and decision criteria share core elements with Wilson and Jungner such as those related to the natural history of the condition, the effectiveness of the test, and effectiveness of preventive interventions, newer frameworks extend Wilson and Jungner's criteria to include considerations related to implementation issues such as health service delivery, ethics, and equity. However, these more recent criteria for genomic evaluation have not been universally adopted, and different health systems vary in which criteria are used in policy decisions, if any. Given the lack of a universally accepted set of decision criteria for genomic screening, and the continued relevance of the fundamental principles of

Wilson and Jungner, we will use the Wilson and Jungner criteria to guide a synthesis of the current evidence on population genomic screening for leading gene-condition pairs. In addition, we also discuss ethical and equity considerations. While these are absent from the original Wilson and Jungner criteria, they are increasingly important in decision frameworks for genomic screening programs (Andermann et al., 2008; Pitini et al., 2019) and are commonly considered across various frameworks and sets of decision criteria for genomic technologies (Burke and Zimmern, 2007; Andermann et al., 2008; Teutsch et al., 2009; Andermann et al., 2010; Botkin et al., 2010; Andermann et al., 2011). We highlight policy and practice issues as well as future research priorities to inform the design of population genomic screening programs to maximize population benefits and minimize harms.

Is the condition sought an important health problem?

HBOC, LS and FH are characterized by their high penetrance, evidence-based interventions for prevention/treatment and subsequent benefits from the early detection, in line with fundamental principles of screening. The CDC Office of Public Health Genomics (OPHG) designates screening for HBOC, LS, and FH as Tier 1 genomic applications (Centers for Disease Control and Prevention OoPHG, 2022). Tier 1 genomic applications are those which could have a substantial, positive impact on public health based on: 1) A high prevalence of 1 in 200 for HBOC, 1 in 340 for LS and in 1 in 250 for FH in the general populations (exact frequency may vary in certain populations); 2) the under-ascertainment of current strategies; and, 3) established risk-reducing interventions that reduce morbidity and mortality (Abul-Husn et al., 2016; Akioyamen et al., 2017; Manickam et al., 2018; Grzymski et al., 2020; Manickam et al., 2021).

Is the natural history of the condition adequately understood?

The natural histories of HBOC, LS, and FH are relatively well understood. HBOC is caused by pathogenic variants in *BRCA1/2* which confer substantially elevated risks for female breast cancer, ovarian cancer, and male breast cancer (in particular for *BRCA2* carriers), in addition to increased risks for pancreatic cancer, prostate cancer, and melanoma (The Breast Cancer Linkage Consortium, 1999; Brose et al., 2002; Levine et al., 2003; Lindor et al., 2008; Lynch et al., 2009; Moran et al., 2012; Mavaddat et al., 2013; McKay et al., 2016). While pathogenic variants in other genes including *PALB2, RAD51C, RAD51D*, and *BRIP1* also cause hereditary breast and ovarian cancer, we focus this review on *BRCA1/2* because of the higher frequency of pathogenic variants in the population in these genes, and established clinical management guidelines (Manickam et al., 2018; National Comprehensive Cancer Network (NCCN), 2021a). LS is caused by pathogenic variants in mismatch repair (MMR) genes *MLH1, MSH2, MSH6*, and *PMS2*, as well as deletions in *EPCAM* which lead to silencing of *MSH2*. Affected individuals are at increased risk for colorectal cancer (CRC), endometrial cancer, ovarian cancer, and other cancers (Lindor et al., 2008; Senter et al., 2008; Baglietto et al., 2010; Bonadona et al., 2011; Giardiello et al., 2014). FH, caused by pathogenic variants in *LDLR, PCSK9*, and *APOB*, is characterized by elevated plasma low-density lipoprotein cholesterol (LDL-C) levels, which leads to risks for cardiovascular disease and premature mortality (Youngblom et al., 2016).

Two key issues that inform natural history are penetrance and age of onset. HBOC, LS and FH exhibit high but incomplete penetrance. Although the penetrance (the chance that an individual with the condition will manifest particular features) of the causative genes has been estimated in cohorts ascertained with strong personal and family history of disease, it has yet to be well-established in the general population (Murray et al., 2021). Some studies suggest penetrance in the general population may vary from estimates from family-based studies (Forrest et al., 2022). However, the risk to those identified through population screening will likely still be high enough to warrant clinical intervention, at least in *BRCA*1/2 carriers where there is substantial evidence demonstrating high penetrance even among unselected cases (Chatterjee et al., 2001; Chatterjee and Wacholder, 2001; Antoniou et al., 2005; Chatterjee et al., 2006; Kuchenbaecker et al., 2017; Chen et al., 2020). These studies highlight the importance of evaluating the appropriateness of population genomic screening and subsequent interventions, given the potential for overdiagnosis and overtreatment (to be discussed in a subsequent section, *Ethical considerations*). Adding another layer of complexity to risk prediction, other genetic factors, such as polygenic background, and non-genetic risk factors (e.g., diet, environmental exposures, and clinical risk factors) can also influence the penetrance of these conditions (Fahed et al., 2020).

Based on the age of onset and availability of age-appropriate preventive interventions, the optimal age to initiate screening will vary across target conditions. For example, surveillance and risk-reducing surgeries for HBOC and LS are recommended in adulthood (National Comprehensive Cancer Network (NCCN), 2021a; National Comprehensive Cancer Network (NCCN), 2021b), while pharmacologic treatment of FH can begin in childhood (Gidding et al., 2015). The health outcomes and costs of population screening programs will likely vary depending on the age at which screening and intervention is initiated. Specific considerations related to the target population for

each condition are provided throughout the subsequent sections.

Is there a suitable test or examination?

One element of test performance is validity, which encompasses both "analytic validity" (accuracy in detecting the target genetic variant) and "clinical validity" (accuracy in identifying patients with the target condition) (Bombard et al., 2013). Test selection for population genomic screening should consider what type of genetic variation primarily causes the target condition, and testing laboratories should be equipped to manage gene-specific technical challenges [e.g., *PMS2* pseudogenes (Hegde et al., 2014; Li et al., 2015; Lee et al., 2021a)]. Several laboratory considerations for population genomic screening include whether to perform full gene sequencing or targeted variant testing, whether to test for only known pathogenic variants or also novel variants, and whether to perform deletion/duplication analysis in addition to sequence analysis; each of these decisions will impact test costs and post-test residual risk (Lu et al., 2019). NGS has very high analytic sensitivity and specificity for detecting single-nucleotide variants and small insertions/deletions (Baudhuin et al., 2015; Judkins et al., 2015; Toland et al., 2018), and could be coupled with gene-targeted deletion/duplication analysis to increase detection of disease-causing variants for HBOC, LS and FH (Petrucelli et al., 1998; Idos et al., 2004; Ison et al., 2014). Deletion/duplication analysis is necessary to identify disease-causing variants in *EPCAM*. The use of array-based genotyping in population genomic screening has been found to result in false positives and false negatives compared to NGS or Sanger sequencing (Blout Zawatsky et al., 2021; Bowling et al., 2021). For HBOC, in the Ashkenazi Jewish (AJ) population, there are three founder variants (*BRCA1* c.68_69delAG, *BRCA1* c.5266dupC and *BRCA2* c.5946delT) which are prevalent in ~2.5% (Roa et al., 1996) of the population. While these variants do account for the majority of pathogenic *BRCA1/2* variants in the AJ population (Walsh et al., 2017), some *BRCA1/2* carriers would be missed if targeted founder variant testing as opposed to NGS was used in population genomic screening among the AJ population (Rosenthal et al., 2015; Solano et al., 2018).

Another aspect of genetic test performance is variant interpretation (Richards et al., 2015). Key issues related to variant interpretation include variants of uncertain significance (VUS) (Burke et al., 192022), discordant variant interpretations between diagnostic laboratories (Garber et al., 2016; Harrison et al., 2017; Iacocca et al., 2018; Lebo et al., 2018; Amendola et al., 2020; Mighton et al., 2021a), variant reclassification over time (Macklin et al., 2018; Mersch et al., 2018; Slavin et al., 2018; Turner et al., 2018; Esterling et al., 2020; Chiang et al., 2021) and recontacting patients with updated results (e.g., changes from VUS to likely pathogenic or pathogenic which may warrant medical follow-up) (Otten et al., 2015; El Mecky et al., 2019). While these issues exist in standard clinical genetic testing, they will be magnified if genomic screening is conducted at a population scale, and will need to be considered in program design/implementation.

A further aspect of test performance is the positive predictive value (PPV), the probability that a patient with a positive result (a reported pathogenic or likely pathogenic variant) has the associated condition (Hagenkord et al., 2020). PPV depends on test characteristics (specificity, sensitivity) and condition prevalence (Akobeng, 2007; Oleske, 2010; Hagenkord et al., 2020). As HBOC, FH, and LS have a lower prevalence in the general population compared to populations ascertained based on family history, this would reduce the PPV of a positive result obtained from population genomic screening compared to a positive result from genomic testing among high-risk populations (Hagenkord et al., 2020). Estimates of PPV for Tier 1 conditions range from 80% to 91%, assuming 99.95% specificity and that one-third of the overall positive rate is likely pathogenic variants and two-thirds are pathogenic variants (Hagenkord et al., 2020). Increasing test specificity can increase the PPV, which laboratories could accomplish by adjusting the reporting cut-off between a positive and a negative result (Lu et al., 2019; Hagenkord et al., 2020). For example, reporting only high confidence likely pathogenic variants can increase specificity (Hagenkord et al., 2020).

Is there a recognizable latent or early symptomatic stage?

Among these three conditions, there is a pre-symptomatic state that is identifiable by molecular testing for pathogenic variants in the relevant genes (Youngblom et al., 2016; Petrucelli et al., 2022). Therefore, population genomic screening for HBOC, LS, and FH can be used to identify individuals with pathogenic variants in the causative genes who would not otherwise be identified through routine clinical care and could gain benefits from early intervention (Grzymski et al., 2020). Multiple studies have found that population genomic screening identifies carriers of pathogenic variants for HBOC, LS, and FH who were previously unaware of their variant (Buchanan et al., 2020; Grzymski et al., 2020; Abul-Husn et al., 2021; Lee et al., 2021b; Blout Zawatsky et al., 2021).

Hereditary breast and ovarian cancer

Population genomic screening methods have been found to identify a higher proportion of *BRCA1/2* carriers than family-history and clinical criteria-based methods (Manchanda et al., 2015a; Manickam et al., 2018; Abul-Husn et al., 2019). In addition to their improved detection rate, *BRCA1/2* screening programs suggest that penetrance of cancer in families of Ashkenazi Jewish ancestry identified through population screening programs is just as high as in families identified through traditional family history based or clinical criteria methods (Gabai-Kapara et al., 2014).

Lynch syndrome

Compared to traditional approaches for clinically ascertaining LS cases (e.g., tumor testing followed by germline testing among affected patients or family history-based approaches for unaffected cases (Hampel et al., 2008; Batte et al., 2014; Tognetto et al., 2017; Kahn et al., 2019), a potential benefit of population genomic screening is the identification of a greater number of pre-symptomatic patients which could allow for cancer prevention through enhanced surveillance, chemoprevention with aspirin, and surgical prevention with hysterectomy and bilateral salpingo-oophorectomy. Several studies have found that population genomic screening identified pre-symptomatic individuals with pathogenic variants in LS genes who were unaware of their variant and would be missed by standard approaches to case identification (Buchanan et al., 2020; Grzymski et al., 2020; Abul-Husn et al., 2021; Lee et al., 2021b; Blout Zawatsky et al., 2021).

Familial hypercholesterolemia

Evidence from clinical testing programs and population-based studies suggest that population genomic screening for FH will lead to benefits. These include increased case detection and short-term improvements, especially when conducted during the pediatric period, given the potential for early intervention through dietary cholesterol reduction, medication, and screening intensity (Smith et al., 2016). Systematic reviews and observational studies have found that universal lipid screening for FH among children and adolescents followed by targeted genetic testing, and cascade testing of relatives, are effective methods for identifying FH cases (Lozano et al., 2016a; Wald et al., 2016; Groselj et al., 2018; Lee et al., 2019; Matsunaga et al., 2021; Zuurbier et al., 2021). The availability and lower costs of lipid screening approaches raises questions about the necessity of using genomic screening as a first tier test to identify FH cases.

Are there accepted options for surveillance and prevention for high-risk populations?

There are various surveillance and prevention options endorsed by clinical practice guidelines to guide the management of individuals with HBOC, LS and FH.

Hereditary breast and ovarian cancer syndrome

Although there are guidelines for the management of patients with pathogenic variants in various HBOC genes (National Comprehensive Cancer Network (NCCN), 2021a; Tischkowitz et al., 2021; Manchanda et al., 2022), we are focusing on the Tier 1 genes, *BRCA1* and *BRCA2*. In terms of prevention, bilateral prophylactic mastectomy and risk-reducing salpingo-oophorectomy are highly effective in preventing breast cancer and ovarian/fallopian tube cancers respectively in addition to reducing mortality, though a small residual risk for primary peritoneal cancer remains (National Comprehensive Cancer Network (NCCN), 2021a; Li et al., 2016; Honold and Camus, 2018; Finch et al., 2014).

Among females who decline or defer surgery, early detection options for female carriers of a disease-causing *BRCA1/2* variant usually comprise of a combination of routine mammograms and breast MRIs for breast cancer risks, which are effective at detecting breast cancer among *BRCA1/2*-positive females. MRI is more sensitive than mammography in high-risk females (National Comprehensive Cancer Network (NCCN), 2021a; Warner et al., 2004; Kriege et al., 2004; Leach et al., 2005; Kuhl et al., 2005; Riedl et al., 2007; Sardanelli et al., 2007; Lowry et al., 2012; Lehman et al., 2016). Among high-risk females, MRI in combination with mammography has been found to be more sensitive than either modality alone (Warner et al., 2008; Mann et al., 2019) and to improve overall survival relative to mammography alone (Bae et al., 2020). In an observational cohort study of MRI in combination with mammography among unaffected female *BRCA1/2* heterozygotes, the probability of dying of breast cancer within 20 years was 2% (Warner et al., 2020). For ovarian cancer risks, guidelines from the National Comprehensive Cancer Network (NCCN) suggest that transvaginal ultrasound and CA-125 may be offered at the clinician's discretion to *BRCA1/2* carriers who have not elected for risk-reducing salpingo-oophorectomy (National Comprehensive Cancer Network (NCCN), 2021a). However, these interventions are of uncertain benefit (National Comprehensive Cancer Network (NCCN), 2021a; Jacobs et al., 2016; Menon et al., 2009) and ovarian cancer screening with transvaginal ultrasound and CA-125 has not been demonstrated to reduce mortality (Menon et al., 2021).

Chemopreventive options are routinely offered in clinical practice given the evidence that they reduce breast cancer risk for all at-risk populations, including *BRCA1/2* carriers (National Comprehensive Cancer Network (NCCN), 2021a; Gronwald et al., 2006; Narod et al., 2000).

For male carriers of *BRCA1*/2 pathogenic variants, recommendations consist of yearly screening with a digital rectal exam and prostate-specific antigen (PSA) blood test initiated by age 40–45 however limited data exists to support the effectiveness of additional screening (breast cancer) (National Comprehensive Cancer Network (NCCN), 2021a; Gao et al., 2019).

Studies with female AJ *BRCA1*/2 carriers identified through population screening indicate acceptability for and high uptake of risk-reducing strategies (Metcalfe et al., 2012; Lieberman et al., 2017). Long-term follow up supports improvements in psychological outcomes such as anxiety (Metcalfe et al., 2012; Manchanda et al., 2015a; Manchanda et al., 2020a; Morgan et al., 2021). In the general population, there is less evidence on the uptake of preventive strategies or outcomes. Several studies indicate that many *BRCA1*/2 carriers identified through population screening do undergo risk-reducing procedures such as surveillance or prophylactic surgery (Buchanan et al., 2020; Lee et al., 2021b; Elhanan et al., 2022). In some cases, HBOC-associated cancers were diagnosed because of the screening initiated based on the genomic screening results (Buchanan et al., 2020).

Lynch syndrome

For Lynch syndrome, there are strategies for early detection or prevention of CRC and gynaecological cancers. Early detection strategies in LS include recommendations for colonoscopy, endoscopy, and total body examinations (National Comprehensive Cancer Network (NCCN), 2021b; Stjepanovic et al., 2019). Surveillance colonoscopy is effective at reducing CRC burden and improving survival among LS patients (Dove-Edwin et al., 2002; Järvinen et al., 2009; Ladabaum et al., 2015; Stjepanovic et al., 2019), though the optimal intervals for surveillance and age to initiate screening are still areas of investigation (National Comprehensive Cancer Network (NCCN), 2021b; Stjepanovic et al., 2019; Järvinen et al., 2009; Dove-Edwin et al., 2002; Jenkins et al., 2015), especially among patients with *PMS2* variants which may have lower penetrance (National Comprehensive Cancer Network (NCCN), 2021b; Lindor et al., 2006). There is observational evidence that prophylactic hysterectomy and/or bilateral salpingo-oophorectomy effectively reduce the incidence of gynaecological cancers among females with LS (Schmeler et al., 2006) and is routinely recommended for at-risk females (Crosbie et al., 2019); however, evidence on mortality is lacking. Chemoprevention with aspirin is also an option for LS risk management as there is evidence that aspirin reduces risk for CRC and other LS-associated cancers (Burn et al., 2011; Ait Ouakrim et al., 2015), however there is no evidence on the effect of aspirin on mortality (Rubenstein et al., 2015). Endometrial cancer screening has not been proven to benefit LS patients (National Comprehensive Cancer Network (NCCN), 2021b). However, it may be considered at the discretion of the clinician every 1–2 years in conjunction with endometrial biopsy, which is considered a sensitive and specific diagnostic test (National Comprehensive Cancer Network (NCCN), 2021b). Transvaginal ultrasound can be considered among postmenopausal females (National Comprehensive Cancer Network (NCCN), 2021b).

Evidence on the outcomes of population genomic screening for LS beyond detection rate is limited. Several studies of population genomic screening for LS have found that a proportion of individuals with pathogenic LS variants underwent risk-reducing procedures, including colonoscopy and prophylactic surgery (Buchanan et al., 2020; Lee et al., 2021b; Elhanan et al., 2022). Several individuals were diagnosed with LS-associated cancers because of follow-up initiated based on their genomic screening results (Buchanan et al., 2020). However, there is some literature that suggests the uptake of risk-reducing strategies is very low (< 10%) when patients are responsible for communicating their results to their clinicians (Elhanan et al., 2022).

Familial hypercholesterolemia

Management of heterozygous FH is aimed at primary prevention of atherosclerotic cardiovascular disease through lipid lowering pharmacological therapy, using statins, ezetimibe or PCSK9 inhibitors or other LDL lowering medications, with guidelines recommending initiation at ages 8–10 or earlier based on severity (Carroll et al., 2008; Gidding et al., 2015; Defesche et al., 2017; Kim et al., 2021). Trials have yet to directly compare cardiovascular disease outcomes associated with different pharmacologic treatments for heterozygous FH, and treatment recommendations therefore are based on surrogate outcomes including LDL cholesterol lowering and arterial imaging (Defesche et al., 2017). For example, a systematic review found that statins were effective at lowering LDL-C and total cholesterol (TC) concentration, but there was no evidence on the effect of screening on long term outcomes, such as lipid concentrations or cardiovascular outcomes in adulthood (Lozano et al., 2016a).

Evidence of clinical outcomes of population genomic screening for FH is emerging, but limited to short-term outcomes. Several studies have found that population genomic screening identified individuals with clinical manifestations of FH who were previously unaware of their condition (Buchanan et al., 2020; Lee et al., 2021b; Elhanan et al., 2022). In these

studies, a proportion of individuals with pathogenic FH variants initiated risk-reducing strategies such as LDL-lowering medications (Buchanan et al., 2020; Lee et al., 2021b; Elhanan et al., 2022). In one study in which patients were tasked with informing their healthcare provider of their population genomic screening results, LDL-C levels improved in the short term for only 9% of patients with pathogenic FH-related variants, while the remainder exhibited no change in their clinical management (Elhanan et al., 2022).

Is there an agreed policy on whom to treat as patients?

There are evidence-based clinical practice guidelines for the management of individuals with pathogenic variants in genes for HBOC, LS, and FH, as described above. It is important to consider that the evidence used to develop these guidelines is largely from cases ascertained through standard diagnostic approaches, as opposed to through population screening-based ascertainment (Murray et al., 2021). Over time, as evidence on penetrance in unselected populations accumulates, management guidelines may need to be updated with specifications for how to manage individuals with disease risk identified through population genomic screening, given the potential reduced penetrance (Murray et al., 2021). This is less likely to be necessary for the genes included in this review than for moderate penetrance genes, given that the penetrance is likely still high in unselected populations and sufficient to warrant clinical intervention.

Is the test acceptable to the population?

Views among founder populations

Much of the evidence base for population-based genomic screening is from the three *BRCA1/2* founder variants' screening in the AJ population. Unselected population-based *BRCA1/2*-screening in the AJ population conducted in Israel (Gabai-Kapara et al., 2014; Lieberman et al., 2017a), Canada (Metcalfe et al., 2013), and the UK (Manchanda et al., 2015a) were found to be safe, acceptable, and feasible. In Israel, Poland, and the UK (Manchanda et al., 2019; Reisel et al., 2022), *BRCA1/2*-screening in the AJ population demonstrates high uptake (> 67%) and satisfaction rates (> 90%), with participants expressing positive attitudes towards the screening experience (Lieberman et al., 2017a). Within the AJ population, motivators for participation were reassurance, decreasing uncertainty, health empowerment, opportunity for risk reduction, and family planning (Lieberman et al., 2017b). Barriers for participation were fear of social and insurance discrimination, stigma, anxiety, and lack of physician awareness and support (Lehmann et al., 2002; Lieberman et al., 2017b). Established founder mutations for LS and FH may also offer a feasible opportunity for population-based genetic screening, however, very limited, if any, research has been done in those populations to determine the acceptability of such programs (Lahtinen et al., 2015; Ponti et al., 2015).

General public views

Current debate centers around whether the same screening principles and findings for populations with founder mutations can be expanded to all populations (Yurgelun et al., 2015; Foulkes et al., 2016). Outside of the AJ population, there is a paucity of research addressing public views and acceptability of a population-based genetic screening program for HBOC, LS, and FH. For HBOC, surveys of unselected females in the US (Rubinsak et al., 2019) and UK (Meisel et al., 2016) demonstrate high interest (> 82%) and acceptability for population-based *BRCA1/2* screening. Quantitative and qualitative data from a pilot population genomic screening study predicting ovarian cancer risk demonstrate acceptability, feasibility, reduced cancer worry, and no adverse psychological impact (Gaba et al., 2020; Gaba et al., 2022). Universal genetic and cholesterol screening programs for FH in children demonstrated high uptake within the UK (Wald et al., 2016), and were acceptable to the Australian public (Bowman et al., 2019). Public and patient survey and qualitative interview results from the North America (Graham et al., 1998; Watkins et al., 2011), Europe (Berth et al., 2002), and Australia (Dunlop et al., 2021) indicate support for adult population genomic screening for LS.

Motivators for screening participation include eligibility for increased surveillance and treatment, and the benefits for family members (Ten Haaf et al., 2017). Barriers for screening participation include cost, genetic discrimination, test accuracy, and data confidentiality (Ten Haaf et al., 2017). Genetic discrimination, particularly in the context of insurance, employment, and social relationships (Wauters and Van Hoyweghen, 2016), remains a pervasive deterrent to screening amongst the public, despite the existence of policies to protect sensitive genetic information from misuse worldwide (Joly et al., 2017; Kim et al., 2021).

Providers' view

Reported attitudes and views of population genomic screening at the provider level are scarce. Many international studies report that non-genetics specialist healthcare providers (Batra et al., 2002; Carroll et al., 2008; Menzin et al., 2010; Klitzman et al., 2013; Hauser et al., 2018) feel ill-equipped to discuss the benefits, limitations, and health implications of genetic testing for HBOC, LS (Hamilton et al., 2017; Laforest et al., 2019), and FH (Haga et al., 2019; Pang et al., 2020; Watts et al., 2021). Additional reported barriers to population genomic

screening include implementation costs, misinterpretation of results, and the potential for increased patient anxiety (Shkedi-Rafid et al., 2013; De Simone et al., 2021). A potential benefit of population genomic screening is the removal of genetic testing eligibility criteria, which providers find overly complex (Klitzman et al., 2013; Laforest et al., 2019).

Is the cost of case-finding economically balanced in relation to possible expenditure on medical care as a whole?

Hereditary breast and ovarian cancer

Multiple modeling studies suggest population-based testing for *BRCA1/2* would be more cost-effective than testing based on clinical criteria or family history from a health system perspective in high- and upper-middle income countries (Manchanda et al., 2018; Zhang et al., 2019; Manchanda et al., 2020b; Guzauskas et al., 2020), and cost-saving from a societal perspective (Manchanda et al., 2020b) in high- and upper-middle-income countries. In lower-middle income countries, cost-effectiveness depended on the cost of the test (Manchanda et al., 2020b; Meshkani et al., 2021). Models suggest it may be most cost-effective to initiate population screening among younger individuals (Zhang et al., 2019; Guzauskas et al., 2020). In the AJ population, economic evaluations indicate population genomic screening for *BRCA1/2* variants would be cost-effective (Manchanda et al., 2015b; Manchanda et al., 2017).

Lynch Syndrome

For LS, economic evidence on population genomic screening among unaffected individuals is limited. A recent U.S.-based economic evaluation suggests that adult population genomic screening among unselected 30-years-old individuals for LS variants would likely be cost-effective at a $150,000 willingness-to-pay threshold (Guzauskas et al., 2022). In contrast, another study found that population genomic screening for LS in unaffected individuals at age 20, followed by cascade testing of first-degree relatives, would not be cost-effective compared to current practices (Dinh et al., 2011). An Australian economic evaluation found that population genomic screening for *MLH1* and *MSH2* for LS would be cost-effective if conducted as part of a multigene panel including *BRCA1/2*, but not if performed in isolation (Zhang et al., 2019).

Familial hypercholesterolemia

Multiple economic evaluations from the UK, Poland, Spain and Australia have found that population genomic screening for FH would be cost-effective from a healthcare system perspective (Marks et al., 2002; Lázaro et al., 2017; Pelczarska et al., 2018; Marquina et al., 2021), and one Australia-based evaluation suggests it would be cost saving from a societal perspective (Marquina et al., 2021). There is some evidence to suggest that greatest health gains could achieved by screening the youngest probands, however this would also be more costly (Pelczarska et al., 2018). Cascade testing of first- and second-degree relatives of identified patients with FH is also recommended and has been found to be highly cost-effective (Marks et al., 2002; Wonderling et al., 2004; Oliva et al., 2009; Nherera et al., 2011).

Are facilities for diagnosis and treatment available?

Current models of genetics care are personnel- and time-intensive and not feasible at a population-scale. Key challenges include critical workforce shortages, which contribute to long wait times, a lack of genetics education among non-genetics specialist healthcare providers, and fragmentation of care (Suther and Kiros, 2009; Hann et al., 2017; Office of the Auditor General, 2017; Hoskovec et al., 2018; Stoll et al., 2018; Dragojlovic et al., 2020). These challenges persist in urban areas and are exacerbated in remote and under-served communities (Office of the Auditor General, 2017). Capacity to sustain population genomic screening must also include laboratory infrastructure, secure data storage, as well as bioinformatic and analytic pipelines to support population-scale genomic analyses (Kelly et al., 2021). There is a paucity of data on the availability and distribution of laboratory infrastructure and personnel including clinical laboratory geneticists and medical laboratory technicians (Dragojlovic et al., 2020). This is critical to understand as it will be variable across jurisdictions and will be important for decision-makers to determine how to deliver the program (i.e. the distribution of testing centres).

Is case finding a continuing process?

The possibility for variants to be reclassified over time means that case finding must be an ongoing process. Most reclassifications are from VUS to likely benign or benign, and reclassification of variants initially classified as pathogenic/likely pathogenic is very rare (Macklin et al., 2018; Mersch et al., 2018; Mighton et al., 2019). In the context of population genomic screening, reclassifications from VUS to pathogenic/likely pathogenic are particularly relevant, as an upgrade from VUS to pathogenic/likely pathogenic could impact medical management. This raises questions about the need for periodic reanalysis and recontact of patients for the return of updated results. The issues of reclassification and recontact already present practical and resource challenges in the context of targeted, clinical testing (Otten et al., 2015; El

Mecky et al., 2019), and would be magnified if testing were implemented at the population scale. This is critical to note as non-European populations consistently have higher VUS rates due to lack of representation in databases, leading to higher rates of reclassification and the need for recontact in these populations (Popejoy and Fullerton, 2016; Slavin et al., 2019; Buchanan et al., 2020; Popejoy et al., 2020). There are currently variation in recontact guidelines and practices across jurisdictions, laboratories, and health systems (Bombard and Mighton, 2018; Sirchia et al., 2018), despite recontact being expected by patients (Linderman et al., 2016; Mighton et al., 2021b).

Ethical considerations

It is important to consider the potential harms and unintended consequences of population genomic screening. Early detection and preventive strategies for HBOC, LS, and FH such as high intensity surveillance, prophylactic surgeries, and pharmacotherapy are not without risks including exposure to radiation, false positives, surgical complications, and adverse drug reactions.

For HBOC, there is some observational evidence to suggest that exposure to diagnostic radiation, including mammography, at a young age is associated with increased risk for breast cancer among females with disease-causing *BRCA1/2* variants (Pijpe et al., 2012). A systematic review of the harms of breast cancer screening among average-risk females found that harms included overdiagnosis (at rates of 11%–22% from randomized controlled trials [RCTs]) and false positive results which were associated with elevated anxiety, distress, and breast-cancer specific worry; however, the review only included females at average-risk and excluded those with pathogenic *BRCA1/2* variants (Nelson et al., 2016). Psychological harms have been identified among *BRCA1/2* carriers, related to false positives and living at risk for disease (Metcalfe et al., 2020). With respect to LS, a systematic review of colorectal cancer screening among average-risk individuals found serious adverse events from colonoscopy including perforations and major bleeds, but these events were uncommon in average-risk populations (Lin et al., 2021). However, high-risk patients such as those with LS were excluded from the review (Lin et al., 2021). For FH, the safety profile differs across pharmacologic therapies. For statins and PCSK9 inhibitors, RCTs have found that treatment-related adverse events did not significantly differ between therapy and placebo (Kastelein et al., 2015; Lozano et al., 2016b), though for statins there are sporadic reports of systemic, immunologic, and pain-related adverse events (Lozano et al., 2016b). Bile acid sequestrants have been commonly associated with adverse GI symptoms, and poor palatability (Lozano et al., 2016b).

Across all conditions, potential harms include genetic discrimination which can arise in a variety of settings. This includes insurance discrimination, which is especially relevant in countries such as the U.S. where much of the population must purchase private health insurances (Ridic et al., 2012; Maynard, 2013). Harms may also be caused when carriers face challenges in accessing risk-reducing strategies in jurisdictions without universal healthcare coverage or among historically underserved populations (e.g., rural populations) (Nguyen-Pham et al., 2014; Chandak et al., 2019; Villegas and Haga, 2019). This raises the question of whether it is ethical to offer population genomic screening in the absence of universal coverage of downstream risk-reducing management. Patient harm may also arise if patients who receive negative results from screening are falsely reassured and forego recommended scheduled screening for average risk populations (i.e., age- and family history-recommended screening) although recent evidence suggests this risk may be minimal (Burnell et al., 2022). Conversely, false positive results may lead to overdiagnosis and overtreatment, where patients and family members may undergo unnecessary investigations and potentially life-altering procedures such as prophylactic surgeries. Although these issues also affect patients undergoing family-history based testing, the higher rates of false positive results associated with population screening coupled with a larger number of patients undergoing genetic testing translates to a larger volume of patients who may receive inappropriate and unnecessary medical care.

At present, the balance of benefits and harms of population genomic screening are not well-characterized. This calls into question whether and to what degree the balance of benefits and harms of screening and subsequent interventions for HBOC, LS and FH should be discussed with patients to ensure informed decision-making. Likewise, it remains unclear how to meaningfully obtain informed consent at the population level given the diversity of literacy, health literacy, socioeconomic status, geography, and culture among screened populations. Genomic screening might not be desirable for all people based on their values and preferences, further highlighting the importance of informed decision-making.

Return of results at the population level presents a further issue. Genomic information is uncertain and complex; delivering this information may lead to adverse psychological outcomes (Mighton et al., 2021c). Among patients receiving positive results after genetic testing, there is evidence of increased risk of anxiety, distress and depression (Rew et al., 2010; Wade et al., 2010; Wade, 2019). Certain populations may face additional risks, such as children feeling a loss of autonomy and women who feel burdened with the responsibility of sharing results with relatives (Gaff et al., 2007; Wade et al., 2010; Wade, 2019). Moreover, parents become overprotective of genetically at-risk children and recognize a disruption of the parent-child relationship (Rew et al., 2010). Although these harms are typically rare and transient, genomic screening at a population level will result in a large number of individuals with psychological harms. In addition to high-quality genetic counseling support, there will

TABLE 2 Summary of key points and gaps.

	BRCA1/2-associated HBOC	LS	FH
Natural history	Caused by pathogenic variants in *BRCA1/2*. Other genes cause breast and ovarian cancer, however, they are out of scope of this manuscript.	Caused by pathogenic variants in the mismatch repair genes *MLH1, MSH2, MSH6, PMS2*, as well as deletions in *EPCAM*.	Caused primarily by pathogenic variants in *LDLR*, *PCSK9*, and *APOB*.
	High penetrance for female breast, and ovarian cancers among others.	High penetrance for CRC, endometrial cancer, and ovarian cancer among others.	Elevated low-density lipoprotein cholesterol (LDL-C), which leads to risks for cardiovascular disease and premature mortality.
	All conditions: Underdiagnosed in the general population. Limited evidence on penetrance in the general population.		
Test and intervention characteristics	NGS is effective, and could be coupled with gene-targeted deletion/duplication analysis to increase detection of pathogenic variants.	NGS is effective, and could be coupled with gene-targeted deletion/duplication analysis to increase detection of pathogenic variants. *PMS2* testing should be carried out by experienced laboratories as homologous pseudogenes present challenges and variants require validation. Deletion/duplication analysis is required for detecting disease-causing *EPCAM* variants.	NGS is effective, and could be coupled with deletion/duplication analysis to increase detection of pathogenic variants.
	There are guideline-endorsed, effective options for risk-reduction: prophylactic bilateral mastectomy, prophylactic bilateral salpingo-oophorectomy, surveillance with MRI and mammography, chemoprevention.	There are guideline-endorsed, effective options for risk-reduction: surveillance colonoscopy, prophylatic, hysterectomy, prophylactic, bilateral salpingo-oophorectomy, chemoprevention with aspirin.	There are guideline-endorsed, effective options for risk-reduction; Guideline-endorsed, effective options for risk reduction: pharmacologic treatments which are effective at reducing LDL-C levels.
Clinical and cost-effectiveness	Population genomic screening increases detection rate vs. family history-based approaches.	Population screening increases detection rate vs. family history-based approaches.	Population genomic screening increases detection rate vs. family history-based approaches.
	Improved short-term outcomes from high-risk screening or prophylactic surgeries, and some long-term psychological outcomes for AJ populations.	One cost-effectiveness analysis suggests that population genomic screening for LS in US context would be cost-effective at $150,000 USD threshold; an Australian analysis suggests population genomic screening for LS genes (*MLH1, MSH2*) alongside HBOC genes would be cost-effective, but would not be cost-effective in isolation.	Modelling studies suggest that universal cholesterol screening followed by genomic testing and cascade testing of relatives would be cost-effective from a health system perspective and cost saving from a societal perspective.
	Economic models suggest population screening would be cost-effective in the general population compared to family history/clinical criteria-based screening in high- and middle-income countries, and cost-effective or cost-saving in the AJ population.		
Next steps/needs in order to advance population screening	There is evidence to support population genomic screening in the AJ population.	There is some limited evidence that population genomic screening for LS leads to uptake of risk reducing strategies, however more evidence on clinical outcomes is needed, as well as cost-effectiveness models from jurisdictions other than the US.	There is some evidence that population genomic screening for FH improves detection rate and short-term outcomes, and cost-effectiveness models suggest it would be cost-effective, however evidence on long-term health outcomes of population screening (cardiovascular events, mortality) is needed.
	Pilot implementation studies in the general population have been initiated in Australia and the UK; (Lacaze et al., 2022; Yorkshire Cancer Research, 2022) more are needed in other jurisdictions.		
	All conditions: Prior to implementing population screening, public engagement with rigorous, evidence-based approaches is needed, and economic evaluations should be conducted in context of the healthcare system in which screening implementation is being considered. Population genomic screening will require major investments in infrastructure and workforce capacity-building; decision makers will need to determine how population genomic screening should be prioritized relative to other healthcare programs.		

also be a need for mental health professionals to support these patients and their families. Furthermore, how to manage VUS in population screening remains unresolved, though there is growing consensus that VUS should not be reported in screening contexts (Murray et al., 2021; Burke et al., 192022). An alternative approach is to examine strategies for return of VUS findings, reclassification, and follow-up, a focus of current investigation.

Equity

Equity is an important consideration. There are currently disparities in access to and outcomes of genetics services. Racialized and underserved populations often have lower referral rates, differential rates of service uptake, more frequent misdiagnoses or inconclusive test results, older age and more advanced disease stage of diagnosis, and higher mortality rates (Armstrong et al., 2005; Maddison et al., 2011; Cragun et al., 2015; Kerner et al., 2015; Purificacion et al., 2015; Manrai et al., 2016; Vohnout et al., 2016; Amrock et al., 2017; Landry and Rehm, 2018; Muller et al., 2018; Hendricks-Sturrup and Lu, 2019; Ndugga-Kabuye and Issaka, 2019; Ehrenberg et al., 2021). These disparities are present worldwide, highlighting the pervasiveness of health inequities and an urgency for strategies to address them prior to adoption of population screening, to avoid exacerbating these issues. In addition, many underserved populations have limited guidelines on risk factors or treatment recommendations, making it difficult for clinicians to provide appropriate and effective care (Hann et al., 2017). For example, there is a scarcity of guidelines for breast cancer screening in transgender individuals undergoing gender-affirming hormone therapy (Berro et al., 2020; Rolle et al., 2021).

Furthermore, availability of risk-reducing strategies is not consistent across jurisdictions. For example, the extent (if any) of reimbursement for these interventions will vary by healthcare systems, leading to out-of-pocket costs for high-risk individuals, likely exacerbating existing inequities for underserved populations and undermining the effectiveness of the screening program.

Gaps, future research, and key implications for practice and policy

Clinical effectiveness

There is considerable evidence that population genomic screening improves detection of individuals with pathogenic variants for HBOC, LS, and FH compared to family history or clinical criteria-based approaches, identifying individuals who would otherwise be missed. However, with the exception of *BRCA1/2* screening in the AJ population, evidence on whether the improved detection rate translates into improved health outcomes (morbidity, mortality) is lacking (Table 2: Summary of key points and gaps). While there are guideline-endorsed, evidence-based strategies to reduce morbidity and mortality for these conditions, several studies suggest that only a proportion of individuals with pathogenic variants identified through population genomic screening approaches actually uptake the associated risk-reducing interventions (Elhanan et al., 2022). Furthermore, studies on clinical effectiveness and ongoing pilot studies (Foss et al., 2022) have primarily employed observational or retrospective designs which suffer from multiple sources of bias (e.g., missing data, loss to follow up) that could reduce the quality of the evidence. However, among the AJ population, there is substantial evidence to support population screening for *BRCA1/2,* including high acceptability, satisfaction, uptake of preventive strategies, in addition to improvements in long term outcomes and reduced costs (Metcalfe et al., 2010a; Metcalfe et al., 2010b; Metcalfe et al., 2012; Metcalfe et al., 2013; Gabai-Kapara et al., 2014; Manchanda et al., 2015a; Manchanda et al., 2015b; Manchanda et al., 2016; Lieberman et al., 2017a; Lieberman et al., 2017b; Manchanda et al., 2017; Manchanda et al., 2019; Manchanda et al., 2020a; Manchanda et al., 2020c; Reisel et al., 2022). Another gap in the literature is that some data has been generated from biobanks and return of secondary findings, which is not reflective of population genomic screening and its outcomes. There is a need for large-scale, prospective, purpose-built population genomic screening pilot studies designed to capture long-term outcomes (Table 3: Recommendations/future directions). While RCTs provide a higher level of evidence than observational studies (Brozek et al., 2009), it may not be warranted to screen only half the population given a lack of equipoise. However, RCTs could be conducted where appropriate, such as for refining the strategy of undertaking testing (e.g., comparing different models for obtaining consent or returning results).

Acceptability

Successful implementation of population genomic screening depends on its acceptability to both the participants and providers, as it can reveal critical issues that can impact uptake, and program compliance (Screening programmes: A short guide, 2020). Much of the current evidence remains within the context of the AJ population for HBOC, which limits the transferability of these findings to the general population and for LS and FH contexts. Rigorous, evidence-based approaches to engage with the public and providers can include public deliberation (Siegel et al., 2013), discrete choice experiments (DCE) (Reed Johnson et al., 2013; Miller et al., 2015; Hauber et al., 2016; Marshall et al., 2016; Terris-Prestholt et al., 2019; Mighton et al., 2021b), or interviews and focus groups (Abelson et al., 2003). Diverse views on expectations and acceptance for the entire trajectory of population genomic screening (e.g., from invitation for screening to follow-up care) within the target jurisdiction, are required to justify the need and to inform the design and implementation of a public health program of this magnitude.

Economic evaluation

Economic evaluations of population genomic screening have had some limitations. Most have been conducted from the health

TABLE 3 Recommendations and future directions.

Recommendation	Considerations
Future programs and research should consider equity	Consider equity at all points in the care pathway
	Representation of the diverse voices within the population is crucial to inform the design and implementation of a population screening program and necessary for the full potential of genomic screening to be realized
Long term, high quality, studies of clinical effectiveness are needed	To date, most studies have reported on short-term, surrogate outcomes. Longer term studies that assess morbidity and mortality are needed
Cost-effectiveness is context-specific; economic evaluations should be conducted from the perspective of the health care system considering implementing screening	Most economic evaluations of genomic technologies have employed modeling or been conducted within the AJ population. Real-world data in other populations is needed
	Pilot population genomic screening programs and research studies should include concurrent cost-effectiveness analyses
Optimize capacity/workforce	There are critical shortages in the genetics workforce and laboratory infrastructure
	Scaling up the genetics workforce, capacity-building for non-genetics healthcare providers will be needed to support population screening
	Use of digital tools and automation can promote efficiency and enable capacity for population screening
Large-scale studies are needed to characterize penetrance of Tier 1 conditions in unselected populations	The cohorts under study should include individuals of diverse ancestries
	Future work is needed to assess the contributions of polygenic, monogenic, and other risk factors to disease risk in order to improve risk prediction
	Risk prediction should incorporate complex modeling (e.g., BOADICEA) to incorporate multiple risk factors
Implement population-based *BRCA1/2* testing in the AJ population	There is sufficient evidence to support population screening for *BRCA1/2* in the AJ population
	Pilot implementation studies in the (non-AJ) general population are needed

system payer perspective, which is the perspective which typically informs health system decision-making. However, economic evaluations from a health system perspective do not capture out-of-pocket or indirect costs to patients and family members. More economic evaluations from societal perspectives that capture out-of-pocket and indirect costs borne by patients and family members are needed given the impact of results on relatives and their spill-over effects (Caro et al., 2012; Drummond et al., 2015; Husereau et al., 2022). Important contextual factors to consider include test costs and funding and implementation of healthcare (e.g., single-payer/universal healthcare systems vs. private health insurers). For example, in the US, where a large portion of funding is provided by various private insurers, implementation of a coordinated, public health screening program for the entire country will face challenges. Existing economic evaluations have used modeling to evaluate cost-effectiveness; yet models are limited by their assumptions and model inputs. Real-world evidence on the economic impacts of population genomic screening, is therefore needed. Furthermore, variations in cost-effectiveness thresholds exist between jurisdictions (e.g., $100,000/QALY gained). Decisions about population screening are highly context specific, and decision makers will also need to consider what the greatest public health priorities are in their jurisdiction.

Programme infrastructure and workforce

In order for population genomic screening to be feasible, there is a need to scale up the genomics workforce, build capacity among non-genetics healthcare providers, and incorporate alternative models of service delivery (Cragun et al., 2015; Peterson et al., 2020) such as mainstreaming (Hamilton et al., 2021; Scheinberg et al., 2021; McCuaig et al., 2021; Yoon et al., 2021; Piedimonte et al., 2020; O'Shea et al., 2021; Ramsey et al., 2022) and the use of digital tools (Manchanda et al., 2016; Bombard and Hayeems, 2020; Shickh et al., 2021; Lee et al., 2022). The use of digital decision support tools is particularly promising. There is increasing evidence that when combined with a brief genetic counseling session, they perform as well, if not better than traditional counseling at improving knowledge, satisfaction, risk perception, and communication between family members, while reducing time spent with HCP and costs (Manchanda et al., 2016; Bombard et al., 2020; Solomon et al., 2020; Bangash et al., 2022; Pande et al., 2022). Although tools have been developed for all three Tier 1 conditions, there are a larger number of tools, at more advanced stages of development and implementation for *BRCA1/2* testing, compared to FH and Lynch syndrome (Manchanda et al., 2016; Bangash et al., 2022; Pande et al., 2022). Moreover, improvements in information technology infrastructure, bioinformatics pipelines, data security and corresponding workforce training would improve the

management of population scale genetic data (Khoury et al., 2016; Kelly et al., 2021). It is critical that future research incorporates evaluations of alternative service delivery models, coordination and access of a putative population genomic screening program along with follow up care, both of which have been neglected in evaluation frameworks and the literature, but will inform the ultimate success of the programs (Andermann et al., 2008; Andermann et al., 2010; Pitini et al., 2019).

Equity

There are currently inequities in access to clinical genetics services, and any additional screening or innovations will only continue to serve populations with access to these services unless deliberate focus is placed on engagement and collaboration (Ford and Airhihenbuwa, 2010a; Ford and Airhihenbuwa, 2010b) across underserved populations. Representation of the diversity within the population is crucial to informing the design and implementation of a population screening program that is centered in the margins. Improvements in transparency, representation, and community collaboration must be prioritized at the outset (Lemke et al., 2010; Caulfield et al., 2014). Designing and implementing an accessible and inclusive population screening program offers opportunities to overcome well-characterized barriers of current genetic service models fueled by structural racism, medical distrust, and a history of eugenics (Fine et al., 2005; Ontario Ministry of Health and Long-Term Care, 2018; Fraiman and Wojcik, 2021). With more diverse participants engaging in genetic research, the diversity of genetic databases can improve, leading to more accurate variant interpretation and higher carrier identification for diverse communities (Landry et al., 2018). Until the benefits of screening are accessible to communities who have been historically underserved and marginalized, the full potential of population genomic screening cannot be realized.

Limitations

Our review has several limitations. This was not a systematic review, nor was a formal quality appraisal of studies conducted. Moreover, this review was limited to Tier 1 conditions-future research and evidence synthesis will be needed to address other actionable gene-condition pairs (e.g., other genes for hereditary breast and ovarian cancer including *PALB2, RAD51C, RAD51D,* and *BRIP1* (Manchanda et al., 2018); *TTR* for hereditary transthyretin amyloidosis (Soper et al., 2021); endocrine tumour genes (Savatt et al., 2022); arrhythmia syndrome genes (Walsh et al., 2022)) and their suitability for population genomic screening.

Conclusion

Despite these limitations, our review suggests that there is evidence that population genomic screening for HBOC, LS, and FH would improve detection of individuals with pathogenic variants in the causative genes compared to traditional approaches to case ascertainment. For outcomes beyond detection rate, HBOC has the strongest support for population genomic screening, with evidence demonstrating clinical and cost-effectiveness in the general population; real world implementation studies in the general population are needed. In the AJ population, there is substantial evidence on acceptability, satisfaction, different models of implementation, psychological/quality of life outcomes, uptake of preventive strategies, and cost-effectiveness in support of population *BRCA1/2* screening.

LS and FH both have preliminary evidence supporting population genomic screening, but major gaps remain in the literature. For FH, although there is evidence suggesting population genomic screening programs would have clinical and cost-effectiveness, the evidence on long-term outcomes is limited. Furthermore, the evidence on cost-effectiveness is limited to modelling studies. Real-world studies establishing cost-effectiveness and clinical effectiveness over longer follow-up periods are needed. Economic models suggest population genomic screening for LS may only be cost-effective at a very high cost-effectiveness threshold. Further evidence is critical to establish clinical effectiveness of screening for LS in asymptomatic individuals and cost-effectiveness in lower- and middle-income jurisdictions.

In addition to filling in the evidence gaps, ethical concerns such as potential overdiagnosis, as well as issues related to equity and access to testing and follow-up interventions will need to be considered at the program design stage. Adoption of population genomic screening will require major restructuring and investments to scale up the workforce, build capacity in non-genetics providers, adapt alternative delivery models (mainstreaming, digital tools), optimize IT infrastructure and prioritize an approach that is inclusive of historically underrepresented populations to ensure the full potential of population genomic screening can be realized.

Author contributions

All authors contributed to conceptualizing, writing, editing and finalizing the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Abelson, J., Forest, P. G., Eyles, J., Smith, P., Martin, E., and Gauvin, F. P. (2003). Deliberations about deliberative methods: Issues in the design and evaluation of public participation processes. *Soc. Sci. Med.* 57 (2), 239–251. doi:10.1016/s0277-9536(02)00343-x

Abul-Husn, N. S., Manickam, K., Jones, L. K., Wright, E. A., Hartzel, D. N., Gonzaga-Jauregui, C., et al. (2016). Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science* 354 (6319), aaf7000. doi:10.1126/science.aaf7000

Abul-Husn, N. S., Soper, E. R., Braganza, G. T., Rodriguez, J. E., Zeid, N., Cullina, S., et al. (2021). Implementing genomic screening in diverse populations. *Genome Med.* 13 (1), 17. doi:10.1186/s13073-021-00832-y

Abul-Husn, N. S., Soper, E. R., Odgis, J. A., Cullina, S., Bobo, D., Moscati, A., et al. (2019). Exome sequencing reveals a high prevalence of BRCA1 and BRCA2 founder variants in a diverse population-based biobank. *Genome Med.* 1212 (1), 2. doi:10.1186/s13073-019-0691-1

Ait Ouakrim, D., Dashti, S. G., Chau, R., Buchanan, D. D., Clendenning, M., Rosty, C., et al. (2015). Aspirin, Ibuprofen, and the risk of colorectal cancer in lynch syndrome. *J. Natl. Cancer Inst.* 107 (9), djv170. doi:10.1093/jnci/djv170

Akioyamen, L. E., Genest, J., Shan, S. D., Reel, R. L., Albaum, J. M., Chu, A., et al. (2017). Estimating the prevalence of heterozygous familial hypercholesterolaemia: A systematic review and meta-analysis. *BMJ Open* 7 (9), e016461. doi:10.1136/bmjopen-2017-016461

Akobeng, A. K. (2007). Understanding diagnostic tests 1: Sensitivity, specificity and predictive values. *Acta Paediatr. Acta Paediatr.* 96 (3), 338–341. doi:10.1111/j.1651-2227.2006.00180.x

Amendola, L. M., Muenzen, K., Biesecker, L. G., Bowling, K. M., Cooper, G. M., Dorschner, M. O., et al. (2020). Variant classification concordance using the ACMG-AMP variant interpretation guidelines across nine genomic implementation research studies. *Am. J. Hum. Genet.* 11107 (5), 932–941. doi:10.1016/j.ajhg.2020.09.011

Amrock, S. M., Duell, P. B., Knickelbine, T., Martin, S. S., O'Brien, E. C., Watson, K. E., et al. (2017). Health disparities among adult patients with a phenotypic diagnosis of familial hypercholesterolemia in the CASCADE-FH™ patient registry. *Atherosclerosis* 267, 19–26. doi:10.1016/j.atherosclerosis.2017.10.006

Andermann, A., Blancquaert, I., Beauchamp, S., and Costea, I. (2011). Guiding policy decisions for genetic screening: Developing a systematic and transparent approach. *Public Health Genomics* 14 (1), 9–16. doi:10.1159/000272898

Andermann, A., Blancquaert, I., Beauchamp, S., and Déry, V. (2008). Revisiting Wilson and Jungner in the genomic age: A review of screening criteria over the past 40 years. *Bull. World Health Organ.* 86 (4), 317–319. doi:10.2471/blt.07.050112

Andermann, A., Blancquaert, I., and Déry, V. (2010). Genetic screening: A conceptual framework for programmes and policy-making. *J. Health Serv. Res. Policy* 15 (2), 90–97. doi:10.1258/jhsrp.2009.009084

Antoniou, A. C., Pharoah, P. D., Narod, S., Risch, H. A., Eyfjord, J. E., Hopper, J. L., et al. (2005). Breast and ovarian cancer risks to carriers of the BRCA1 5382insC and 185delAG and BRCA2 6174delT mutations: A combined analysis of 22 population based studies. *J. Med. Genet.* 42 (7), 602–603. doi:10.1136/jmg.2004.024133

Armstrong, K., Micco, E., Carney, A., Stopfer, J., and Putt, M. (2005). Racial differences in the use of BRCA1/2 testing among women with a family history of breast or ovarian cancer. *JAMA.* 293 (14), 1729–1736. doi:10.1001/jama.293.14.1729

Bae, M. S., Sung, J. S., Bernard-Davila, B., Sutton, E. J., Comstock, C. E., and Morris, E. A. (2020). Survival outcomes of screening with breast MRI in women at elevated risk of breast cancer. *J breast imaging. Radiology* 2 (1), 29–30. doi:10.1148/radiol.2019192339

Baglietto, L., Lindor, N. M., Dowty, J. G., White, D. M., Wagner, A., Gomez Garcia, E. B., et al. (2010). Risks of Lynch syndrome cancers for MSH6 mutation carriers. *J. Natl. Cancer Inst.* 102 (3), 193–201. doi:10.1093/jnci/djp473

Bangash, H., Makkawy, A., Gundelach, J. H., Miller, A. A., Jacobson, K. A., and Kullo, I. J. (2022). Web-based tool (FH family share) to increase uptake of cascade testing for familial hypercholesterolemia: Development and evaluation. *JMIR Hum. Factors* 9 (1), e32568. doi:10.2196/32568

Batra, S., Valdimarsdottir, H., McGovern, M., Itzkowitz, S., and Brown, K. (2002). Awareness of genetic testing for colorectal cancer predisposition among specialists in gastroenterology. *Am. J. Gastroenterol.* 97 (3), 729–733. doi:10.1111/j.1572-0241.2002.05556.x

Batte, B. A., Bruegl, A. S., Daniels, M. S., Ring, K. L., Dempsey, K. M., Djordjevic, B., et al. (2014). Consequences of universal MSI/IHC in screening ENDOMETRIAL cancer patients for Lynch syndrome. *Gynecol. Oncol.* 134 (2), 319–325. doi:10.1016/j.ygyno.2014.06.009

Baudhuin, L. M., Lagerstedt, S. A., Klee, E. W., Fadra, N., Oglesbee, D., Ferber, M. J., et al. (2014). Confirming variants in next-generation sequencing panel testing by sanger sequencing. *J. Mol. Diagn* 17 (4), 456–461. doi:10.1016/j.jmoldx.2015.03.004

Berro, T., Zayhowski, K., Field, T., Channaoui, N., and Sotelo, J. (2020). Genetic counselors' comfort and knowledge of cancer risk assessment for transgender patients. *J. Genet. Couns.* 29 (3), 342–351. doi:10.1002/jgc4.1172

Berth, H., Balck, F., and Dinkel, A. (2002). Attitudes toward genetic testing in patients at risk for HNPCC/FAP and the German population. *Genet. Test.* 6 (4), 273–280. doi:10.1089/10906570260471804

Blout Zawatsky, C. L., Shah, N., Machini, K., Perez, E., Christensen, K. D., Zouk, H., et al. (2021). Returning actionable genomic results in a research biobank: Analytic validity, clinical implementation, and resource utilization. *Am. J. Hum. Genet.* 108 (12), 2224–2237. doi:10.1016/j.ajhg.2021.10.005

Bombard, Y., Bach, P. B., and Offit, K. (2013). Translating genomics in cancer care. *J. Natl. Compr. Canc. Netw.* 11 (11), 1343–1353. doi:10.6004/jnccn.2013.0158

Bombard, Y., Clausen, M., Shickh, S., Mighton, C., Casalino, S., Kim, T. H. M., et al. (2020). Effectiveness of the genomics ADvISER decision aid for the selection of secondary findings from genomic sequencing: A randomized clinical trial. *Genet. Med.* 22 (4), 727–735. doi:10.1038/s41436-019-0702-z

Bombard, Y., and Hayeems, R. Z. (2020). How digital tools can advance quality and equity in genomic medicine. *Nat. Rev. Genet.* 21 (9), 505–506. doi:10.1038/s41576-020-0260-x

Bombard, Y., and Mighton, C. (2018). Recontacting clinical genetics patients with reclassified results: Equity and policy challenges. *Eur. J. Hum. Genet.* 27, 505–506. doi:10.1038/s41431-018-0313-1

Bonadona, V., Bonaïti, B., Olschwang, S., Grandjouan, S., Huiart, L., Longy, M., et al. (2011). Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA.* 305 (22), 2304–2310. doi:10.1001/jama.2011.743

Botkin, J. R., Teutsch, S. M., Kaye, C. I., Hayes, M., Haddow, J. E., Bradley, L. A., et al. (2010). Outcomes of interest in evidence-based evaluations of genetic tests. *Genet. Med.* 12 (4), 228–235. doi:10.1097/GIM.0b013e3181cdde04

Bowling, K. M., Thompson, M. L., Gray, D. E., Lawlor, J. M. J., Williams, K., East, K. M., et al. (2021). Identifying rare, medically relevant variation via population-based genomic screening in Alabama: Opportunities and pitfalls. *Genet. Med.* 23 (2), 280–288. doi:10.1038/s41436-020-00976-z

Bowman, F. L., Molster, C. M., Lister, K. J., Bauskis, A. T., Garton-Smith, J., Vickery, A. W., et al. (2019). Identifying perceptions and preferences of the general public concerning universal screening of children for familial hypercholesterolaemia. *Public Health Genomics* 22 (1-2), 25–35. doi:10.1159/000501463

Brose, M. S., Rebbeck, T. R., Calzone, K. A., Stopfer, J. E., Nathanson, K. L., and Weber, B. L. (2002). Cancer risk estimates for BRCA1 mutation carriers identified in a risk evaluation program. *J. Natl. Cancer Inst.* 94 (18), 1365–1372. doi:10.1093/jnci/94.18.1365

Brozek, J. L., Akl, E. A., Alonso-Coello, P., Lang, D., Jaeschke, R., Williams, J. W., et al. (2009). Grading quality of evidence and strength of recommendations in clinical practice guidelines. Part 1 of 3. An overview of the GRADE approach and grading quality of evidence about interventions. *Allergy* 64 (5), 669–677. doi:10.1111/j.1398-9995.2009.01973.x

Buchanan, A. H., Lester Kirchner, H., Schwartz, M. L. B., Kelly, M. A., Schmidlen, T., Jones, L. K., et al. (2020). Clinical outcomes of a genomic screening program for

actionable genetic conditions. *Genet. Med.* 1122 (11), 1874–1882. doi:10.1038/s41436-020-0876-4

Burke, W., Parens, E., Chung, W. K., Berger, S. M., and Appelbaum, P. S. (1920). The challenge of genetic variants of uncertain clinical significance : A narrative review. *Ann. Intern. Med.* 175, 994–1000. doi:10.7326/M21-4109

Burke, W., and Zimmern, R. (2007). *Moving beyond ACCE: An expanded framework for genetic test evaluation*. Cambridge, United Kingdom: PHG Foundation. Available at: https://www.phgfoundation.org/report/moving-beyond-acce-an-expanded-framework-for-genetic-test-evaluation.

Burn, J., Gerdes, A. M., Macrae, F., Mecklin, J. P., Moeslein, G., Olschwang, S., et al. (2011). Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: An analysis from the CAPP2 randomised controlled trial. *Lancet* 378 (9809), 2081–2087. doi:10.1016/S0140-6736(11)61049-0

Burnell, M., Gaba, F., Sobocan, M., Desai, R., Sanderson, S., Loggenberg, K., et al. (2022). Randomised trial of population-based *BRCA* testing in Ashkenazi jews: Long-term secondary lifestyle behavioural outcomes. *BJOG*. doi:10.1111/1471-0528.17253

Carey, D. J., Fetterolf, S. N., Davis, F. D., Faucett, W. A., Kirchner, H. L., Mirshahi, U., et al. (2016). The Geisinger MyCode community health initiative: An electronic health record-linked biobank for precision medicine research. *Genet. Med.* 18 (9), 906–913. doi:10.1038/gim.2015.187

Caro, J. J., Briggs, A. H., Siebert, U., and Kuntz, K. M. (2012). Modeling good research practices--overview: A report of the ISPOR-SMDM modeling good research practices task force-1. *Med. Decis. Mak.* 32 (5), 667–677. doi:10.1177/0272989X12454577

Carroll, J. C., Cappelli, M., Miller, F., Wilson, B. J., GrunfEld, E., Peeters, C., et al. (2008). Genetic services for hereditary breast/ovarian and colorectal cancers - physicians' awareness, use and satisfaction. *Community Genet.* 11 (1), 43–51. doi:10.1159/000111639

Caulfield, T., Burningham, S., Joly, Y., Master, Z., Shabani, M., Borry, P., et al. (2014). A review of the key issues associated with the commercialization of biobanks. *J. Law Biosci.* 1 (1), 94–110. doi:10.1093/jlb/lst004

Centers for Disease Control and Prevention OoPHG (2022). *Tier 1 genomics applications and their importance to public health*.

Chandak, A., Nayar, P., and Lin, G. (2019). Rural-urban disparities in access to breast cancer screening: A Spatial Clustering analysis. *J. Rural. Health* 35 (2), 229–235. doi:10.1111/jrh.12308

Chatterjee, N., Kalaylioglu, Z., Shih, J. H., and Gail, M. H. (2006). Case-control and case-only designs with genotype and family history data: Estimating relative risk, residual familial aggregation, and cumulative risk. *Biometrics* 62 (1), 36–48. doi:10.1111/j.1541-0420.2005.00442.x

Chatterjee, N., Shih, J., Hartge, P., Brody, L., Tucker, M., and Wacholder, S. (2001). Association and aggregation analysis using kin-cohort designs with applications to genotype and family history data from the Washington Ashkenazi Study. *Genet. Epidemiol.* 21 (2), 123–138. doi:10.1002/gepi.1022

Chatterjee, N., and Wacholder, S. (2001). A marginal likelihood approach for estimating penetrance from kin-cohort designs. *Biometrics* 57 (1), 245–252. doi:10.1111/j.0006-341x.2001.00245.x

Chen, J., Bae, E., Zhang, L., Hughes, K., Parmigiani, G., Braun, D., et al. (2020). Penetrance of breast and ovarian cancer in women who carry a BRCA1/2 mutation and do not use risk-reducing salpingo-oophorectomy: An updated meta-analysis. *JNCI Cancer Spectr.* 4 (4), pkaa029. doi:10.1093/jncics/pkaa029

Chiang, J., Chia, T. H., Yuen, J., Shaw, T., Li, S. T., Binte Ishak, N. D., et al. (2021). Impact of variant reclassification in cancer predisposition genes on clinical care. *JCO Precis. Oncol.* (5), 577–584. doi:10.1200/po.20.00399

Cragun, D., Bonner, D., Kim, J., Akbari, M. R., Narod, S. A., Gomez-Fuego, A., et al. (2015). Factors associated with genetic counseling and BRCA testing in a population-based sample of young Black women with breast cancer. *Breast Cancer Res. Treat.* 151 (1), 169–176. doi:10.1007/s10549-015-3374-7

Crosbie, E. J., Ryan, N. A. J., Arends, M. J., Bosse, T., Burn, J., Cornes, J. M., et al. (2019). The Manchester International Consensus Group recommendations for the management of gynecological cancers in Lynch syndrome. *Genet. Med.* 21 (10), 2390–2400. doi:10.1038/s41436-019-0489-y

Daly, M. B., Pilarski, R., Yurgelun, M. B., Berry, M. P., Buys, S. S., Dickson, P., et al. (2020). NCCN guidelines Insights: Genetic/familial high-risk assessment: Breast, ovarian, and pancreatic, version 1.2020. *J. Natl. Compr. Canc. Netw.* 18 (4), 380–391. doi:10.6004/jnccn.2020.0017

De Simone, L. M., Arjunan, A., Vogel Postula, K. J., Maga, T., and Bucheit, L. A. (2021). Genetic counselors' perspectives on population-based screening for BRCA-related hereditary breast and ovarian cancer and Lynch syndrome. *J. Genet. Couns.* 30 (1), 158–169. doi:10.1002/jgc4.1305

Defesche, J. C., Gidding, S. S., Harada-Shiba, M., Hegele, R. A., Santos, R. D., and Wierzbicki, A. S. (2017). Familial hypercholesterolaemia. *Nat. Rev. Dis. Prim.* 3, 17093. doi:10.1038/nrdp.2017.93

Dinh, T. A., Rosner, B. I., Atwood, J. C., Boland, C. R., Syngal, S., Vasen, H. F. A., et al. (2011). Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population. *Cancer Prev. Res.* 4 (1), 9–22. doi:10.1158/1940-6207.CAPR-10-0262

Dove-Edwin, I., Boks, D., Goff, S., Kenter, G. G., Carpenter, R., Vasen, H. F. A., et al. (2002). The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. *Cancer* 94 (6), 1708–1712. doi:10.1002/cncr.10380

Dragojlovic, N., Borle, K., Kopac, N., Ellis, U., Birch, P., Adam, S., et al. (2020). The composition and capacity of the clinical genetics workforce in high-income countries: A scoping review. *Genet. Med.* 22 (9), 1437–1449. doi:10.1038/s41436-020-0825-2

Drummond, M., Sculpher, M., Claxton, K., Stoddart, G., and Torrance, G. (2015). *Methods for the economic evaluation of health care programmes*. 4th ed. Oxford University Press.

Dunlop, K., Rankin, N. M., Smit, A. K., Salgado, Z., Newson, A. J., Keogh, L., et al. (2021). Acceptability of risk-stratified population screening across cancer types: Qualitative interviews with the Australian public. *Health Expect.* 24 (4), 1326–1336. doi:10.1111/hex.13267

Ehrenberg, S., Walsh Vockley, C., Nelson, E., Baker, J., Arcieri, M., Lindenberger, J., et al. (2021). Under-referral of Plain community members for genetic services despite being qualified for genetic evaluation. *J. Genet. Couns.* 30, 1084–1090. doi:10.1002/jgc4.1395

El Mecky, J., Johansson, L., Plantinga, M., Fenwick, A., Lucassen, A., Dijkhuizen, T., et al. (2019). Reinterpretation, reclassification, and its downstream effects: Challenges for clinical laboratory geneticists. *BMC Med. Genomics* 1112 (1), 170. doi:10.1186/s12920-019-0612-6 29

Elhanan, G., Kiser, D., Neveux, I., Dabe, S., Bolze, A., Metcalf, W. J., et al. (2022). Incomplete penetrance of population-based genetic screening results in electronic health record. *Front. Genet.* 13, 866169. doi:10.3389/fgene.2022.866169

Esterling, L., Wijayatunge, R., Brown, K., Morris, B., Hughes, E., Pruss, D., et al. (2020). Impact of a cancer gene variant reclassification program over a 20-year period. *JCO Precis. Oncol.* 4doi, 944–954. doi:10.1200/PO.20.00020

Fahed, A. C., Wang, M., Homburger, J. R., Patel, A. P., Bick, A. G., Neben, C. L., et al. (2020). Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat. Commun.* 11 (1), 3635. doi:10.1038/s41467-020-17374-3

Finch, A. P., Lubinski, J., Moller, P., Singer, C. F., Karlan, B., Senter, L., et al. (2014). Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *J. Clin. Oncol.* 32 (15), 1547–1553. doi:10.1200/JCO.2013.53.2820

Fine, M. J., Ibrahim, S. A., and Thomas, S. B. (2005). The role of race and genetics in health disparities research. *Am. J. Public Health* 95 (12), 2125–2128. doi:10.2105/AJPH.2005.076588

Ford, C. L., and Airhihenbuwa, C. O. (2010). Critical race theory, race equity, and public health: Toward antiracism praxis. *Am. J. Public Health* 100 (1), S30–S35. doi:10.2105/AJPH.2009.171058

Ford, C. L., and Airhihenbuwa, C. O. (2010). The public health critical race methodology: Praxis for antiracism research. *Soc. Sci. Med.* 71 (8), 1390–1398. doi:10.1016/j.socscimed.2010.07.030

Forrest, I. S., Chaudhary, K., Vy, H. M. T., Petrazzini, B. O., Bafna, S., Jordan, D. M., et al. (2022). Population-based penetrance of deleterious clinical variants. *JAMA* 327 (4), 350–359. doi:10.1001/jama.2021.23686

Foss, K. S., O'Daniel, J. M., and Berg, J. S. (2022). The rise of population genomic screening: Characteristics of current programs and the need for evidence regarding optimal implementation. *J. Pers. Med.* 12 (5), 692. doi:10.3390/jpm12050692

Foulkes, W. D., Knoppers, B. M., and Turnbull, C. (2016). Population genetic testing for cancer susceptibility: Founder mutations to genomes. *Nat. Rev. Clin. Oncol.* 13 (1), 41–54. doi:10.1038/nrclinonc.2015.173

Fraiman, Y. S., and Wojcik, M. H. (2021). The influence of social determinants of health on the genetic diagnostic odyssey: Who remains undiagnosed, why, and to what effect? *Pediatr. Res.* 89 (2), 295–300. doi:10.1038/s41390-020-01151-5

Gaba, F., Blyuss, O., Liu, X., Goyal, S., Lahoti, N., Chandrasekaran, D., et al. (2020). Population study of ovarian cancer risk prediction for targeted screening and prevention. *Cancers (Basel)* 12 (5), E1241. doi:10.3390/cancers12051241

Gaba, F., Oxley, S., Liu, X., Yang, X., Chandrasekaran, D., Kalsi, J., et al. (2022). Unselected population genetic testing for personalised ovarian cancer risk prediction: A qualitative study using semi-structured interviews. *Diagn. (Basel)* 12 (5), 1028. doi:10.3390/diagnostics12051028

Gabai-Kapara, E., Lahad, A., Kaufman, B., Friedman, E., Segev, S., Renbaum, P., et al. (2014). Population-based screening for breast and ovarian cancer risk due to

BRCA1 and BRCA2. *Proc. Natl. Acad. Sci. U. S. A.* 111 (39), 14205–14210. doi:10.1073/pnas.1415979111

Gaff, C. L., Clarke, A. J., Atkinson, P., Sivell, S., Elwyn, G., Iredale, R., et al. (2007). Process and outcome in communication of genetic information within families: A systematic review. *Eur. J. Hum. Genet.* 15 (10), 999–1011. doi:10.1038/sj.ejhg.5201883

Gao, Y., Goldberg, J. E., Young, T. K., Babb, J. S., Moy, L., and Heller, S. L. (2019). Breast cancer screening in high-risk men: A 12-year longitudinal observational study of male breast imaging utilization and outcomes. *Radiology* 11293 (2), 282–291. doi:10.1148/radiol.2019190971

Garber, K. B., Vincent, L. M., Alexander, J. J., Bean, L. J. H., Bale, S., and Hegde, M. (2016). Reassessment of genomic sequence variation to harmonize interpretation for personalized medicine. *Am. J. Hum. Genet.* 99 (5), 1140–1149. doi:10.1016/j.ajhg.2016.09.015

Genomics England (2021). *Newborn Genomes programme. Genomics England*. Available at: https://www.genomicsengland.co.uk/initiatives/newborns.

Giardiello, F. M., Allen, J. I., Axilbund, J. E., Boland, C. R., Burke, C. A., Burt, R. W., et al. (2014). Guidelines on genetic evaluation and management of lynch syndrome: A consensus statement by the US multi-society task force on colorectal cancer. *Am. J. Gastroenterol.* 109 (8), 1159–1179. doi:10.1038/ajg.2014.186

Gidding, S. S., Champagne, M. A., de Ferranti, S. D., Defesche, J., Ito, M. K., Knowles, J. W., et al. (2015). The agenda for familial hypercholesterolemia: A scientific statement from the American heart association. *Circulation* 132 (22), 2167–2192. doi:10.1161/CIR.0000000000000297

Graham, I. D., Logan, D. M., Hughes-Benzie, R., Evans, W. K., Perras, H., McAuley, L. M., et al. (1998). How interested is the public in genetic testing for colon cancer susceptibility? Report of a cross-sectional population survey. *Cancer Prev. Control* 2 (4), 167–172.

Gronwald, J., Tung, N., Foulkes, W. D., Offit, K., Gershoni, R., Daly, M., et al. (2006). Tamoxifen and contralateral breast cancer in BRCA1 and BRCA2 carriers: An update. *Int. J. Cancer* 118 (9), 2281–2284. doi:10.1002/ijc.21536

Groselj, U., Kovac, J., Sustar, U., Mlinaric, M., Fras, Z., Podkrajsek, K. T., et al. (2018). Universal screening for familial hypercholesterolemia in children: The Slovenian model and literature review. *Atherosclerosis* 277, 383–391. doi:10.1016/j.atherosclerosis.2018.06.858

Grzymski, J. J., Elhanan, G., Morales Rosado, J. A., Smith, E., Schlauch, K. A., Read, R., et al. (2020). Population genetic screening efficiently identifies carriers of autosomal dominant diseases. *Nat. Med.* 26 (8), 1235–1239. doi:10.1038/s41591-020-0982-5

Gupta, S., Provenzale, D., Llor, X., Halverson, A. L., Grady, W., Chung, D. C., et al. (2019). NCCN guidelines Insights: Genetic/familial high-risk assessment: Colorectal, version 2.2019. *J. Natl. Compr. Canc. Netw.* 17 (9), 1032–1041. doi:10.6004/jnccn.2019.0044

Guzauskas, G. F., Garbett, S., Zhou, Z., Spencer, S. J., Smith, H. S., Hao, J., et al. (2020). Cost-effectiveness of population-wide genomic screening for hereditary breast and ovarian cancer in the United States. *JAMA Netw. Open* 3 (10), e2022874. doi:10.1001/jamanetworkopen.2020.22874

Guzauskas, G. F., Jiang, S., Garbett, S., Zhou, Z., Spencer, S. J., Snyder, S. R., et al. (2022). Cost-effectiveness of population-wide genomic screening for Lynch syndrome in the United States. *Genet. Med.* 24, 1017–1026. doi:10.1016/j.gim.2022.01.017

Haga, S. B., Kim, E., Myers, R. A., and Ginsburg, G. S. (2019). Primary care physicians' knowledge, attitudes, and experience with personal genetic testing. *J. Pers. Med.* 9 (2), E29. doi:10.3390/jpm9020029

Hagenkord, J., Funke, B., Qian, E., Hegde, M., Jacobs, K. B., Ferber, M., et al. (2020). Design and reporting considerations for genetic screening tests. *J. Mol. Diagn.* 22 (5), 599–609. doi:10.1016/j.jmoldx.2020.01.014

Hamilton, J. G., Abdiwahab, E., Edwards, H. M., Fang, M. L., Jdayani, A., and Breslau, E. S. (2017). Primary care providers' cancer genetic testing-related knowledge, attitudes, and communication behaviors: A systematic review and research agenda. *J. Gen. Intern. Med.* 32 (3), 315–324. doi:10.1007/s11606-016-3943-4

Hamilton, J. G., Symecko, H., Spielman, K., Breen, K., Mueller, R., Catchings, A., et al. (2021). Uptake and acceptability of a mainstreaming model of hereditary cancer multigene panel testing among patients with ovarian, pancreatic, and prostate cancer. *Genet. Med.* 1123 (11), 2105–2113. doi:10.1038/s41436-021-01262-2

Hampel, H., Frankel, W. L., Martin, E., Arnold, M., Khanduja, K., Kuebler, P., et al. (2008). Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J. Clin. Oncol.* 26 (35), 5783–5788. doi:10.1200/JCO.2008.17.5950

Hann, K. E. J., Freeman, M., Fraser, L., Waller, J., Sanderson, S. C., Rahman, B., et al. (2017). Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: A systematic review. *BMC Public Health* 17 (1), 503. doi:10.1186/s12889-017-4375-8

Harrison, S. M., Dolinsky, J. S., Knight Johnson, A. E., Pesaran, T., Azzariti, D. R., Bale, S., et al. (2017). Clinical laboratories collaborate to resolve differences in variant interpretations submitted to ClinVar. *Genet. Med.* 19 (10), 1096–1104. doi:10.1038/gim.2017.14

Hauber, A. B., González, J. M., Groothuis-Oudshoorn, C. G., Prior, T., Marshall, D. A., Cunningham, C., et al. (2016). Statistical methods for the analysis of discrete choice experiments: A report of the ISPOR conjoint analysis good research practices task force. *Value Health* 19 (4), 300–315. doi:10.1016/j.jval.2016.04.004

Hauser, D., Obeng, A. O., Fei, K., Ramos, M. A., and Horowitz, C. R. (2018). Views of primary care providers on testing patients for genetic risks for common chronic diseases. *Health Aff.* 37 (5), 793–800. doi:10.1377/hlthaff.2017.1548

Hegde, M., Ferber, M., Mao, R., Samowitz, W., and Ganguly, A. (2014). ACMG technical standards and guidelines for genetic testing for inherited colorectal cancer (Lynch syndrome, familial adenomatous polyposis, and MYH-associated polyposis). *Genet. Med.* 16 (1), 101–116. doi:10.1038/gim.2013.166

Hendricks-Sturrup, R. M., and Lu, C. Y. (2019). Understanding implementation challenges to genetic testing for familial hypercholesterolemia in the United States. *J. Pers. Med.* 9 (1). doi:10.3390/jpm9010009

Honold, F., and Camus, M. (2018). Prophylactic mastectomy versus surveillance for the prevention of breast cancer in women's BRCA carriers. *Medwave* 18 (4), e7161. doi:10.5867/medwave.2018.04.7160

Hoskovec, J. M., Bennett, R. L., Carey, M. E., DaVanzo, J. E., DoughertyM.Hahn, S. E., et al. (2018). Projecting the supply and demand for certified genetic counselors: A workforce study. *J. Genet. Couns.* 27 (1), 16–20. doi:10.1007/s10897-017-0158-8

Husereau, D., Drummond, M., Augustovski, F., de Bekker-Grob, E., Briggs, A. H., Carswell, C., et al. (2022). Consolidated health economic evaluation reporting standards (CHEERS) 2022 explanation and elaboration: A report of the ISPOR CHEERS II good practices task force. *Value Health.* 25 (1), 10–31. doi:10.1016/j.jval.2021.10.008

Iacocca, M. A., Chora, J. R., Carrié, A., Freiberger, T., Leigh, S. E., Defesche, J. C., et al. (2018). ClinVar database of global familial hypercholesterolemia-associated DNA variants. *Hum. Mutat.* 1139 (11), 1631–1640. doi:10.1002/humu.23634

Ison, H. E., Clarke, S. L., and Knowles, J. W. (2014). "Familial hypercholesterolemia," in *GeneReviews® [Internet]*. Editors M. P. Adam, D. B. Everman, and G. M. Mirzaa (Seattle, WA: University of Washington, Seattle), 1993–2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK174884/

Idos, G., and Valle, L. (2004). "Lynch Syndrome," in *GeneReviews® [Internet]*. Editors M. P. Adam, D. B. Everman, and G. M. Mirzaa (Seattle, WA: University of Washington, Seattle), 1993–2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1211/

Jacobs, I. J., Menon, U., Ryan, A., Gentry-Maharaj, A., Burnell, M., Kalsi, J. K., et al. (2016). Ovarian cancer screening and mortality in the UK collaborative trial of ovarian cancer screening (UKCTOCS): A randomised controlled trial. *Lancet* 387 (10022), 945–956. doi:10.1016/S0140-6736(15)01224-6

Järvinen, H. J., Renkonen-Sinisalo, L., Aktán-Collán, K., Peltomäki, P., Aaltonen, L. A., and Mecklin, J. P. (2009). Ten years after mutation testing for lynch syndrome: Cancer incidence and outcome in mutation-positive and mutation-negative family members. *J. Clin. Oncol.* 27 (28), 4793–4797. doi:10.1200/JCO.2009.23.7784

Jenkins, M. A., Dowty, J. G., Ait Ouakrim, D., Mathews, J. D., Hopper, J. L., Drouet, Y., et al. (2015). Short-term risk of colorectal cancer in individuals with lynch syndrome: A meta-analysis. *J. Clin. Oncol.* 33 (4), 326–331. doi:10.1200/JCO.2014.55.8536

Joly, Y., Feze, I. N., Song, L., and Knoppers, B. M. (2017). Comparative approaches to genetic discrimination: Chasing Shadows? *Trends Genet.* 33 (5), 299–302. doi:10.1016/j.tig.2017.02.002

Judkins, T., Leclair, B., Bowles, K., Gutin, N., Trost, J., McCulloch, J., et al. (2015). Development and analytical validation of a 25-gene next generation sequencing panel that includes the BRCA1 and BRCA2 genes to assess hereditary cancer risk *BMC Cancer* 15 (5), 299–302. doi:10.1186/s12885-015-1224-y

Kahn, R. M., Gordhandas, S., Maddy, B. P., Baltich Nelson, B., Askin, G., Christos, P. J., et al. (2019). Universal endometrial cancer tumor typing: How much has immunohistochemistry, microsatellite instability, and MLH1 methylation improved the diagnosis of Lynch syndrome across the population? *Cancer* 125 (18), 3172–3183. doi:10.1002/cncr.32203

Kastelein, J. J., Ginsberg, H. N., Langslet, G., Hovingh, G. K., Ceska, R., Dufour, R., et al. (2015). ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur. Heart J.* 1436 (43), 2996–3003. doi:10.1093/eurheartj/ehv370

Kelly, M. A., Leader, J. B., Wain, K. E., Bodian, D., Oetjens, M. T., Ledbetter, D. H., et al. (2021). Leveraging population-based exome screening to impact clinical care:

The evolution of variant assessment in the Geisinger MyCode research project. *Am. J. Med. Genet. C Semin. Med. Genet.* 187 (1), 83–94. doi:10.1002/ajmg.c.31887

Kerner, J., Liu, J., Wang, K., Fung, S., Landry, C., Lockwood, G., et al. (2015). Canadian cancer screening disparities: A recent historical perspective. *Curr. Oncol.* 22 (2), 156–163. doi:10.3747/co.22.2539

Khoury, M. J., Iademarco, M. F., and Riley, W. T. (2016). Precision public health for the era of precision medicine. *Am. J. Prev. Med.* 50 (3), 398–401. doi:10.1016/j.amepre.2015.08.031

Kim, H., Ho, C. W. L., Ho, C. H., Athira, P. S., Kato, K., De Castro, L., et al. (2021). Genetic discrimination: Introducing the asian perspective to the debate. *NPJ Genom. Med.* 6 (1), 54. doi:10.1038/s41525-021-00218-4

Klančar, G., Grošelj, U., and Kovač, J. (2015). Universal screening for familial hypercholesterolemia in children. *J. Am. Coll. Cardiol.* 66 (11), 1250–1257. doi:10.1016/j.jacc.2015.07.017

Klitzman, R., Chung, W., Marder, K., Shanmugham, A., Chin, L. J., Stark, M., et al. (2013). Attitudes and practices among internists concerning genetic testing. *J. Genet. Couns.* 22 (1), 90–100. doi:10.1007/s10897-012-9504-z

Kriege, M., Brekelmans, C. T., Boetes, C., Besnard, P. E., Zonderland, H. M., Obdeijn, I. M., et al. (2004). Efficacy of MRI and mammography for breast-cancer screening in women with a familial or genetic predisposition. *N. Engl. J. Med.* 351 (5), 427–437. doi:10.1056/NEJMoa031759

Kuchenbaecker, K. B., Hopper, J. L., Barnes, D. R., Phillips, K. A., Mooij, T. M., Roos-Blom, M. J., et al. (2017). Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. *JAMA* 317 (23), 2402–2416. doi:10.1001/jama.2017.7112

Kuhl, C. K., Schrading, S., Leutner, C. C., Morakkabati-Spitz, N., Wardelmann, E., Fimmers, R., et al. (2005). Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. *J. Clin. Oncol.* 23 (33), 8469–8476. doi:10.1200/JCO.2004.00.4960

Kunnackal John, G., Das Villgran, V., Caufield-Noll, C., and Giardiello, F. (2021). Worldwide variation in lynch syndrome screening: Case for universal screening in low colorectal cancer prevalence areas. *Fam. Cancer* 20 (2), 145–156. doi:10.1007/s10689-020-00206-0

Lacaze, P., Tiller, J., and Winship, I. (2019). Healthcare system-funded preventive genomic screening: Challenges for Australia and other single-payer systems. *Public Health Genomics* 22 (3-4), 140–144. doi:10.1159/000502917

Lacaze, P. A., Tiller, J., Winship, I., and Group, D. S. I. (2022). Population DNA screening for medically actionable disease risk in adults. *Med. J. Aust.* 216 (6), 278–280. doi:10.5694/mja2.51454

Ladabaum, U., Ford, J. M., Martel, M., and Barkun, A. N. (2015). American gastroenterological association technical review on the diagnosis and management of lynch syndrome. *Gastroenterology* 149 (3), 783–813. e20. doi:10.1053/j.gastro.2015.07.037

Laforest, F., Kirkegaard, P., Mann, B., and Edwards, A. (2019). Genetic cancer risk assessment in general practice: Systematic review of tools available, clinician attitudes, and patient outcomes. *Br. J. Gen. Pract.* 69 (679), e97–e105. doi:10.3399/bjgp18X700265

Lahtinen, A. M., Havulinna, A. S., Jula, A., Salomaa, V., and Kontula, K. (2015). Prevalence and clinical correlates of familial hypercholesterolemia founder mutations in the general population. *Atherosclerosis* 238 (1), 64–69. doi:10.1016/j.atherosclerosis.2014.11.015

Landry, L. G., Ali, N., Williams, D. R., Rehm, H. L., and Bonham, V. L. (2018). Lack of diversity in genomic databases is A barrier to translating precision medicine research into practice. *Health Aff.* 37 (5), 780–785. doi:10.1377/hlthaff.2017.1595

Landry, L. G., and Rehm, H. L. (2018). Association of racial/ethnic categories with the ability of genetic tests to detect a cause of cardiomyopathy. *JAMA Cardiol.* 3 (4), 341–345. doi:10.1001/jamacardio.2017.5333

Lázaro, P., Pérez de Isla, L., Watts, G. F., Alonso, R., Norman, R., Muniz, O., et al. (20172017). Cost-effectiveness of a cascade screening program for the early detection of familial hypercholesterolemia. *J. Clin. Lipidol.* 11 (1), 260–271. doi:10.1016/j.jacl.2017.01.002

Leach, M. O., Boggis, C. R., Dixon, A. K., Easton, D. F., Eeles, R. A., Evans, D. G. R., et al. (20052005). Screening with magnetic resonance imaging and mammography of a UK population at high familial risk of breast cancer: A prospective multicentre cohort study (MARIBS). *Lancet* 365 (9473), 1769–1778. doi:10.1016/S0140-6736(05)66481-1

Lebo, M. S., Zakoor, K. R., Chun, K., Speevak, M. D., Waye, J. S., McCready, E., et al. (2018). Data sharing as a national quality improvement program: Reporting on BRCA1 and BRCA2 variant-interpretation comparisons through the Canadian open genetics Repository (COGR). *Genet. Med.* 20 (3), 294–302. doi:10.1038/gim.2017.80

Lee, C., Elsekaily, O., Kochan, D. C., Alhalabi, L., Faizee, F., Sharp, R., et al. (2021). Penetrance and outcomes at 1-year following return of actionable variants identified by genome sequencing. *Genet. Med.* 23 (7), 1192–1201. doi:10.1038/s41436-021-01142-9

Lee, C., Rivera-Valerio, M., Bangash, H., Prokop, L., and Kullo, I. J. (2019). New case detection by cascade testing in familial hypercholesterolemia: A systematic review of the literature. *Circ. Genom. Precis. Med.* 1112 (11), e002723. doi:10.1161/CIRCGEN.119.002723

Lee, C. Y., Yen, H. Y., Zhong, A. W., and Gao, H. (2021). Resolving misalignment interference for NGS-based clinical diagnostics. *Hum. Genet.* 140 (3), 477–492. doi:10.1007/s00439-020-02216-5

Lee, W., Shickh, S., Assamad, D., Luca, S., Clausen, M., Somerville, C., et al. (2022). Patient-facing digital tools for delivering genetic services: a systematic review. *J. Med. Genet.*. doi:10.1136/jmg-2022-108653

Lehman, C. D., Lee, J. M., DeMartini, W. B., Hippe, D. S., Rendi, M. H., Kalish, G., et al. (2016). Screening MRI in women with a personal history of breast cancer. *J. Natl. Cancer Inst.* 108 (3), djv349. doi:10.1093/jnci/djv349

Lehmann, L. S., Weeks, J. C., Klar, N., and Garber, J. E. (20022002). A population-based study of Ashkenazi Jewish women's attitudes toward genetic discrimination and BRCA1/2 testing. *Genet. Med.* 4 (5), 346–352. doi:10.1097/00125817-200209000-00005

Lemke, A. A., Wolf, W. A., Hebert-Beirne, J., and Smith, M. E. (2010). Public and biobank participant attitudes toward genetic research participation and data sharing. *Public Health Genomics* 13 (6), 368–377. doi:10.1159/000276767

Levine, D. A., Argenta, P. A., Yee, C. J., Marshall, D. S., Olvera, N., Bogomolniy, F., et al. (2003). Fallopian tube and primary peritoneal carcinomas associated with BRCA mutations. *J. Clin. Oncol.* 21 (22), 4222–4227. doi:10.1200/JCO.2003.04.131

Li, J., Dai, H., Feng, Y., Tang, J., Chen, S., Tian, X., et al. (2015). A comprehensive strategy for accurate mutation detection of the highly homologous PMS2. *J. Mol. Diagn.* 17 (5), 545–553. doi:10.1016/j.jmoldx.2015.04.001

Li, X., You, R., Wang, X., Liu, C., Xu, Z., Zhou, J., et al. (2016). Effectiveness of prophylactic surgeries in BRCA1 or BRCA2 mutation carriers: A meta-analysis and systematic review. *Clin. Cancer Res.* 22 (15), 3971–3981. doi:10.1158/1078-0432.CCR-15-1465

Lieberman, S., Lahad, A., Tomer, A., Cohen, C., Levy-Lahad, E., and Raz, A. (2017). Population screening for BRCA1/BRCA2 mutations: Lessons from qualitative analysis of the screening experience. *Genet. Med.* 19 (6), 628–634. doi:10.1038/gim.2016.175

Lieberman, S., Tomer, A., Ben-Chetrit, A., Olsha, O., Strano, S., Beeri, R., et al. (2017). Population screening for BRCA1/BRCA2 founder mutations in Ashkenazi Jews: Proactive recruitment compared with self-referral. *Genet. Med.* 19 (7), 754–762. doi:10.1038/gim.2016.182

Lin, J. S., Perdue, L. A., Henrikson, N. B., Bean, S. I., and Blasi, P. R. (2021). Screening for colorectal cancer: Updated evidence report and systematic review for the US preventive services task force. *JAMA* 325 (19), 1978–1998. doi:10.1001/jama.2021.4417

Linderman, M. D., Nielsen, D. E., and Green, R. C. (2016). Personal genome sequencing in Ostensibly Healthy individuals and the PeopleSeq Consortium. *J. Pers. Med.* 6 (2), E14. doi:10.3390/jpm6020014

Lindor, N. M., McMaster, M. L., Lindor, C. J., and Greene, M. H. (2008). Concise handbook of familial cancer susceptibility syndromes - second edition. *JNCI Monogr.* (38), 3–93. doi:10.1093/jncimonographs/lgn001

Lindor, N. M., Petersen, G. M., Hadley, D. W., Kinney, A. Y., Miesfeldt, S., Lu, K. H., et al. (2006). Recommendations for the care of individuals with an inherited predisposition to lynch syndrome: A systematic review. *JAMA.* 296 (12), 1507–1517. doi:10.1001/jama.296.12.1507

Lowry, K. P., Lee, J. M., Kong, C. Y., McMahon, P. M., Gilmore, M. E., Cott Chubiz, J. E., et al. (2012). Annual screening strategies in BRCA1 and BRCA2 gene mutation carriers: A comparative effectiveness analysis. *Cancer* 118 (8), 2021–2030. doi:10.1002/cncr.26424

Lozano, P., Henrikson, N. B., and Dunn, J. (2016). *Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: A systematic evidence review for the U.S. Preventive services task force.*

Lozano, P., Henrikson, N. B., Dunn, J., Morrison, C. C., Nguyen, M., Blasi, P. R., et al. (2016). Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: Evidence report and systematic review for the US preventive services task force. *JAMA.* 316 (6), 645–655. doi:10.1001/jama.2016.6176

Lu, J. T., Ferber, M., Hagenkord, J., Levin, E., South, S., Kang, H. P., et al. (2019). Evaluation for genetic Disorders in the absence of a clinical indication for testing: Elective genomic testing. *J. Mol. Diagn.* 21 (1), 3–12. doi:10.1016/j.jmoldx.2018.09.006

Lynch, H. T., Casey, M. J., Snyder, C. L., Bewtra, C., Lynch, J. F., Butts, M., et al. (2009). Hereditary ovarian carcinoma: Heterogeneity, molecular genetics, pathology, and management. *Mol. Oncol.* 3 (2), 97–137. doi:10.1016/j.molonc.2009.02.004

Macklin, S., Durand, N., Atwal, P., and Hines, S. (2018). Observed frequency and challenges of variant reclassification in a hereditary cancer clinic. *Genet. Med.* 20 (3), 346–350. doi:10.1038/gim.2017.207

Maddison, A. R., Asada, Y., and Urquhart, R. (2011). Inequity in access to cancer care: A review of the Canadian literature. *Cancer Causes Control* 22 (3), 359–366. doi:10.1007/s10552-010-9722-3

Manchanda, R., Burnell, M., Gaba, F., Desai, R., Wardle, J., GeSSler, S., et al. (2020). Randomised trial of population-based BRCA testing in Ashkenazi jews: Long-term outcomes. *BJOG.* 127 (3), 364–375. doi:10.1111/1471-0528.15905

Manchanda, R., Burnell, M., Gaba, F., SanderSon, S., Loggenberg, K., GeSSler, S., et al. (2019). Attitude towards and factors affecting uptake of population-based BRCA testing in the Ashkenazi jewish population: A cohort study. *BJOG.* 126 (6), 784–794. doi:10.1111/1471-0528.15654

Manchanda, R., Burnell, M., Loggenberg, K., Desai, R., Wardle, J., Sanderson, S. C., et al. (2016). Cluster-randomised non-inferiority trial comparing DVD-assisted and traditional genetic counselling in systematic population testing for BRCA1/2 mutations. *J. Med. Genet.* 53 (7), 472–480. doi:10.1136/jmedgenet-2015-103740

Manchanda, R., Gaba, F., Talaulikar, V., Pundir, J., Gessler, S., Davies, M., et al. (2022). Risk-reducing salpingo-oophorectomy and the use of hormone replacement therapy below the age of natural menopause: Scientific impact Paper No. 66 october 2021: Scientific impact paper No. 66. *BJOG* 129 (1), e16–e34. doi:10.1111/1471-0528.16896

Manchanda, R., Legood, R., Burnell, M., McGuire, A., Raikou, M., Loggenberg, K., et al. (2015). Cost-effectiveness of population screening for BRCA mutations in Ashkenazi jewish women compared with family history-based testing. *J. Natl. Cancer Inst.* 107 (1), 380. doi:10.1093/jnci/dju380

Manchanda, R., Lieberman, S., Gaba, F., Lahad, A., and Levy-Lahad, E. (2020). Population screening for inherited predisposition to breast and ovarian cancer. *Annu. Rev. Genomics Hum. Genet.* 3121, 373–412. doi:10.1146/annurev-genom-083118-015253

Manchanda, R., Loggenberg, K., Sanderson, S., Burnell, M., Wardle, J., Gessler, S., et al. (2015). Population testing for cancer predisposing BRCA1/BRCA2 mutations in the ashkenazi-jewish community: A randomized controlled trial. *J. Natl. Cancer Inst.* 107 (1), 379. doi:10.1093/jnci/dju379

Manchanda, R., Patel, S., Antoniou, A. C., Levy-Lahad, E., Turnbull, C., Evans, D. G., et al. (2017). Cost-effectiveness of population based BRCA testing with varying Ashkenazi Jewish ancestry. *Am. J. Obstet. Gynecol.* 11217 (5), e1–e1578. e12. doi:10.1016/j.ajog.2017.06.038

Manchanda, R., Patel, S., Gordeev, V. S., Antoniou, A. C., Smith, S., Lee, A., et al. (2018). Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. *J. Natl. Cancer Inst.* 110 (7), 714–725. doi:10.1093/jnci/djx265

Manchanda, R., Sun, L., Patel, S., Evans, O., Wilschut, J., De Freitas Lopes, A. C., et al. (2020). Economic evaluation of population-based BRCA1/BRCA2 mutation testing across multiple countries and health systems. *Cancers (Basel)* 12 (7), E1929. doi:10.3390/cancers12071929

Manickam, K., Buchanan, A. H., Schwartz, M. L. B., Hallquist, M. L. G., Williams, J. L., Rahm, A. K., et al. (2018). Exome sequencing-based screening for BRCA1/2 expected pathogenic variants among adult biobank participants. *JAMA Netw. Open* 1 (5), e182140. doi:10.1001/jamanetworkopen.2018.2140

Manickam, K., McClain, M. R., Demmer, L. A., Biswas, S., Kearney, H. M., Malinowski, J., et al. (2021). Exome and genome sequencing for pediatric patients with congenital anomalies or intellectual disability: An evidence-based clinical guideline of the American College of medical genetics and genomics (ACMG). *Genet. Med.* 1123 (11), 2029–2037. doi:10.1038/s41436-021-01242-6

Mann, R. M., Kuhl, C. K., and Moy, L. (2019). Contrast-enhanced MRI for breast cancer screening. *J. Magn. Reson. Imaging* 50 (2), 377–390. doi:10.1002/jmri.26654

Manrai, A. K., Funke, B. H., Rehm, H. L., Olesen, M. S., Maron, B. A., Szolovits, P., et al. (2016). Genetic misdiagnoses and the potential for health disparities. *N. Engl. J. Med.* 375 (7), 655–665. doi:10.1056/NEJMsa1507092

Marks, D., Wonderling, D., Thorogood, M., Lambert, H., Humphries, S. E., and Neil, H. A. (2002). Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. *BMJ* 324 (7349), 1303. doi:10.1136/bmj.324.7349.1303

Marquina, C., Lacaze, P., Tiller, J., Riaz, M., Sturm, A. C., Nelson, M. R., et al. (2021). Population genomic screening of young adults for familial hypercholesterolaemia: A cost-effectiveness analysis. *Eur. Heart J.* 11, 3243–3254. doi:10.1093/eurheartj/ehab770

Marshall, D. A., Deal, K., Bombard, Y., Leighl, N., MacDonald, K. V., and Trudeau, M. (2016). How do women trade-off benefits and risks in chemotherapy treatment decisions based on gene expression profiling for early-stage breast cancer? A discrete choice experiment. *BMJ Open* 6 (6), e010981. doi:10.1136/bmjopen-2015-010981

Matsunaga, K., Mizobuchi, A., Fu, H. Y., Ishikawa, S., Tada, H., Kawashiri, M. A., et al. (2021). Universal screening for familial hypercholesterolemia in children in kagawa, Japan. *J. Atheroscler. Thromb.* 29, 839–849. doi:10.5551/jat.62780

Mavaddat, N., Peock, S., Frost, D., Ellis, S., Platte, R., Fineberg, E., et al. (2013). Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. *J. Natl. Cancer Inst.* 105 (11), 812–822. doi:10.1093/jnci/djt095

Maynard, A. (2013). Health care rationing: Doing it better in public and private health care systems. *J. Health Polit. Policy Law* 38 (6), 1103–1127. doi:10.1215/03616878-2373157

McCuaig, J. M., Thain, E., Malcolmson, J., Keshavarzi, S., Armel, S. R., and Kim, R. H. (2021). A comparison of patient-reported outcomes following consent for genetic testing using an oncologist- or genetic counselor-mediated model of care. *Curr. Oncol.* 28 (2), 1459–1471. doi:10.3390/curroncol28020138

McKay, S., Humphris, J., Johns, A., Gill, A., and Tucker, K. (2016). Inherited pancreatic cancer. *Cancer Forum* 40 (1).

Meisel, S. F., Rahman, B., Side, L., Fraser, L., Gessler, S., Lanceley, A., et al. (2016). Genetic testing and personalized ovarian cancer screening: A survey of public attitudes. *BMC Womens Health* 16, 46. doi:10.1186/s12905-016-0325-3 26

Menon, U., Gentry-Maharaj, A., Burnell, M., Singh, N., Ryan, A., Karpinskyj, C., et al. (2021). Ovarian cancer population screening and mortality after long-term follow-up in the UK collaborative trial of ovarian cancer screening (UKCTOCS): A randomised controlled trial. *Lancet* 397 (10290), 2182–2193. doi:10.1016/S0140-6736(21)00731-5

Menon, U., Gentry-Maharaj, A., Hallett, R., Ryan, A., Burnell, M., Sharma, A., et al. (2009). Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK collaborative trial of ovarian cancer screening (UKCTOCS). *Lancet. Oncol.* 10 (4), 327–340. doi:10.1016/S1470-2045(09)70026-9

Menzin, A. W., Anderson, B. L., Williams, S. B., and Schulkin, J. (2010). Education and experience with breast health maintenance and breast cancer care: A study of obstetricians and gynecologists. *J. Cancer Educ.* 25 (1), 87–91. doi:10.1007/s13187-009-0019-8

Mersch, J., Brown, N., Pirzadeh-Miller, S., Mundt, E., Cox, H. C., Brown, K., et al. (2018). Prevalence of variant reclassification following hereditary cancer genetic testing. *Jama* 320 (12), 1266–1274. doi:10.1001/jama.2018.13152

Meshkani, Z., Aboutorabi, A., Moradi, N., Langarizadeh, M., and Motlagh, A. G. (2021). Population or family history based BRCA gene tests of breast cancer? A systematic review of economic evaluations. *Hered. Cancer Clin. Pract.* 19 (1), 35. doi:10.1186/s13053-021-00191-0

Metcalfe, K. A., Mian, N., Enmore, M., Poll, A., Llacuachaqui, M., Nanda, S., et al. (2012). Long-term follow-up of Jewish women with a BRCA1 and BRCA2 mutation who underwent population genetic screening. *Breast Cancer Res. Treat.* 133 (2), 735–740. doi:10.1007/s10549-011-1941-0

Metcalfe, K. A., Poll, A., Llacuachaqui, M., TulmAn, A., MiaNN., et al. (2010). Patient satisfaction and cancer-related distress among unselected Jewish women undergoing genetic testing for BRCA1 and BRCA2. *Clin. Genet.* 78 (5), 411–417. doi:10.1111/j.1399-0004.2010.01499.x

Metcalfe, K. A., Poll, A., Royer, R., Llacuachaqui, M., Tulman, A., Sun, P., et al. (2010). Screening for founder mutations in BRCA1 and BRCA2 in unselected Jewish women. *J. Clin. Oncol.* 28 (3), 387–391. doi:10.1200/JCO.2009.25.0712

Metcalfe, K. A., Poll, A., Royer, R., LlacuachaquiM.Sun, P., et al. (2013). A comparison of the detection of BRCA mutation carriers through the provision of Jewish population-based genetic testing compared with clinic-based genetic testing. *Br. J. Cancer* 109 (3), 777–779. doi:10.1038/bjc.2013.309

Metcalfe, K. A., Price, M. A., Mansfield, C., Hallett, D. C., Lindeman, G. J., Fairchild, A., et al. (2020). Predictors of long-term cancer-related distress among female BRCA1 and BRCA2 mutation carriers without a cancer diagnosis: An international analysis. *Br. J. Cancer* 123 (2), 268–274. doi:10.1038/s41416-020-0861-3

Mighton, C., Charames, G., Wang, M., Zakoor, K. R., Wong, A., Shickh, S., et al. (2019). Variant classification changes over time in BRCA1 and BRCA2. *Genet. Med.* 21 (10), 2248–2254. doi:10.1038/s41436-019-0493-2

Mighton, C., Clausen, M., Sebastian, A., Muir, S. M., Shickh, S., Baxter, N. N., et al. (2021). Patient and public preferences for being recontacted with updated genomic results: A mixed methods study. *Hum. Genet.* 140, 1695–1708. doi:10.1007/s00439-021-02366-0

Mighton, C., Shickh, S., Uleryk, E., Pechlivanoglou, P., and Bombard, Y. (2021). Clinical and psychological outcomes of receiving a variant of uncertain significance from multigene panel testing or genomic sequencing: A systematic review and meta-analysis. *Genet. Med.* 23 (1), 22–33. doi:10.1038/s41436-020-00957-2

Mighton, C., Smith, A. C., Mayers, J., Tomaszewski, R., Taylor, S., Hume, S., et al. (2021). Data sharing to improve concordance in variant interpretation across

laboratories: Results from the Canadian open genetics repository. *J. Med. Genet.* 59, 571–578. doi:10.1136/jmedgenet-2021-107738

Miller, F. A., Hayeems, R. Z., Bombard, Y., Cressman, C., Barg, C. J., Carroll, J. C., et al. (2015). Public perceptions of the benefits and risks of newborn screening. *Pediatrics* 136 (2), e413–e423. doi:10.1542/peds.2015-0518

Moran, A., O'Hara, C., Khan, S., Woodward, E., Maher, E. R., et al. (2012). Risk of cancer other than breast or ovarian in individuals with BRCA1 and BRCA2 mutations. *Fam. Cancer* 11 (2), 235–242. doi:10.1007/s10689-011-9506-2

Morgan, K. M., Hamilton, J. G., Symecko, H., Kamara, D., Jenkins, C., Lester, J., et al. (2021). Targeted BRCA1/2 population screening among Ashkenazi Jewish individuals using a web-enabled medical model: An observational cohort study. *Genet. Med.* 24, 564–575. doi:10.1016/j.gim.2021.10.016

Muller, C., Lee, S. M., Barge, W., Siddique, S. M., Berera, S., Wideroff, G., et al. (2018). Low referral rate for genetic testing in racially and ethnically diverse patients despite universal colorectal cancer screening. *Clin. Gastroenterol. Hepatol.* 1216 (12), 1911–1918. e2. doi:10.1016/j.cgh.2018.08.038

Murray, M. F., Giovanni, M. A., Doyle, D. L., Harrison, S. M., Lyon, E., Manickam, K., et al. (2021). DNA-Based screening and population health: A points to consider statement for programs and sponsoring organizations from the American College of medical genetics and genomics (ACMG). *Genet. Med.* 23 (6), 989–995. doi:10.1038/s41436-020-01082-w

Murray, M. F. (2016). Your DNA is not your diagnosis: Getting diagnoses right following secondary genomic findings. *Genet. Med.* 18 (8), 765–767. doi:10.1038/gim.2015.134

Narod, S. A., Brunet, J. S., Ghadirian, P., RobsonM.Heimdal, K., Neuhausen, S. L., et al. (2000). Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: A case-control study. Hereditary breast cancer clinical study group. *Lancet* 356 (9245), 1876–1881. doi:10.1016/s0140-6736(00)03258-x

National Academies of Sciences Engineering and Medicine (2017). *Health and medicine Division, board on health care services, board on the health of Select populations, Committee on the evidence base for genetic testing. An evidence framework for genetic testing*. Washington, DC: National Academies Press (US).

National Comprehensive Cancer Network (NCCN) (2021). *NCCN clinical practice guidelines in Oncology. Genetic/familial high-risk Assessment: Breast, ovarian, and pancreatic*. National Comprehensive Cancer Network NCCN. Version 1.2022.

National Comprehensive Cancer Network (NCCN) (2021). *NCCN clinical practice guidelines in oncology. Genetic/familial high-risk assessment: Colorectal. Version 1.2021*. National Comprehensive Cancer Network NCCN.

Ndugga-Kabuye, M. K., and Issaka, R. B. (2019). Inequities in multi-gene hereditary cancer testing: Lower diagnostic yield and higher VUS rate in individuals who identify as hispanic, african or asian and pacific islander as compared to European. *Fam. Cancer* 18 (4), 465–469. doi:10.1007/s10689-019-00144-6

Nelson, H. D., Pappas, M., Cantor, A., Griffin, J., Daeges, M., and Humphrey, L. (2016). Harms of breast cancer screening: Systematic review to update the 2009 U.S. Preventive services task force recommendation. *Ann. Intern. Med.* 164 (4), 256–267. doi:10.7326/M15-0970

Nguyen-Pham, S., Leung, J., and McLaughlin, D. (2014). Disparities in breast cancer stage at diagnosis in urban and rural adult women: A systematic review and meta-analysis. *Ann. Epidemiol.* 24 (3), 228–235. doi:10.1016/j.annepidem.2013.12.002

Nherera, L., Marks, D., Minhas, R., Thorogood, M., and Humphries, S. E. (2011). Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. *Heart* 97 (14), 1175–1181. doi:10.1136/hrt.2010.213975

O'Shea, R., Taylor, N., Crook, A., Jacobs, C., Jung Kang, Y., Lewis, S., et al. (2021). Health system interventions to integrate genetic testing in routine oncology services: A systematic review. *PLoS One* 16 (5), e0250379. doi:10.1371/journal.pone.0250379

Office of the Auditor General (2017). *Annual report: Section 3.07 laboratory services in the health sector*. Toronto, ON: Ontario Ministry of Health and Long-term Care.

Oleske, D. M. (2010). *Epidemiology and the delivery of health care services*. 3 ed. Springer.

Oliva, J., López-Bastida, J., Moreno, S. G., Mata, P., and Alonso, R. (2009). Cost-effectiveness analysis of a genetic screening program in the close relatives of Spanish patients with familial hypercholesterolemia. *Rev. Espanola Cardiol.* 62 (1), 57–65. doi:10.1016/s1885-5857(09)71514-2

Ontario Ministry of Health and Long-Term Care (2018). *The Ontario public health standards: Requirements for programs, services, and accountability are published as the public health standards for the provision of mandatory health programs and services by the minister of health and long-term care, pursuant to section 7 of the health protection and promotion act.*. Toronto, ON: Ontario Ministry of Health and Long-Term Care.

Otten, E., Plantinga, M., Birnie, E., Verkerk, M. A., Lucassen, A. M., Ranchor, A. V., et al. (2015). Is there a duty to recontact in light of new genetic technologies? A systematic review of the literature. *Genet. Med.* 17 (8), 668–678. doi:10.1038/gim.2014.173

Pande, M., Peterson, S., and Lynch, P. M. (2022). Development and evaluation of an online, patient-driven, family outreach intervention to facilitate sharing of genetic risk information in families with Lynch syndrome. *J. Med. Genet.* 59 (6), 589–596. doi:10.1136/jmedgenet-2020-107615

Pang, J., Sullivan, D. R., Brett, T., Kostner, K. M., Hare, D. L., and Watts, G. F. (2020). Familial hypercholesterolaemia in 2020: A leading tier 1 genomic application. *Heart Lung Circ.* 29 (4), 619–633. doi:10.1016/j.hlc.2019.12.002

Pelczarska, A., Jakubczyk, M., Jakubiak-Lasocka, J., Banach, M., Mysliwiec, M., Gruchala, M., et al. (2018). The cost-effectiveness of screening strategies for familial hypercholesterolaemia in Poland. *Atherosclerosis* 270, 132–138. doi:10.1016/j.atherosclerosis.2018.01.036

Peterson, J. M., Pepin, A., Thomas, R., Biagi, T., Stark, E., Sparks, A. D., et al. (2020). Racial disparities in breast cancer hereditary risk assessment referrals. *J. Genet. Couns.* 29 (4), 587–593. doi:10.1002/jgc4.1250

Petrucelli, N., Daly, M. B., and Pal, T. (1998). "BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer," in *GeneReviews® [Internet]*. Editors M. P. Adam, D. B. Everman, and G. M. Mirzaa (Seattle, WA: University of Washington, Seattle), 1993–2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1247/

Petrucelli, N., Daly, M., and Pal, T. (2022). *Chap BRCA1- and BRCA2-associated hereditary breast and ovarian cancer*. GeneReviews.

Piedimonte, S., Power, J., Foulkes, W. D., Weber, E., Palma, L., Schiavi, A., et al. (2020). BRCA testing in women with high-grade serous ovarian cancer: Gynecologic oncologist-initiated testing compared with genetics referral. *Int. J. Gynecol. Cancer* 1130 (11), 1757–1761. doi:10.1136/ijgc-2020-001261

Pijpe, A., Andrieu, N., Easton, D. F., Kesminiene, A., Cardis, E., Nogues, C., et al. (2012). Exposure to diagnostic radiation and risk of breast cancer among carriers of BRCA1/2 mutations: Retrospective cohort study (GENE-RAD-RISK). *BMJ* 345, e5660. doi:10.1136/bmj.e5660

Pitini, E., D'Andrea, E., De Vito, C., Rosso, A., Unim, B., Marzuillo, C., et al. (2019). A proposal of a new evaluation framework towards implementation of genetic tests. *PLoS One* 14 (8), e0219755. doi:10.1371/journal.pone.0219755

Ponti, G., Castellsagué, E., Ruini, C., Percesepe, A., and Tomasi, A. (2015). Mismatch repair genes founder mutations and cancer susceptibility in Lynch syndrome. *Clin. Genet.* 87 (6), 507–516. doi:10.1111/cge.12529

Popejoy, A. B., Crooks, K. R., Fullerton, S. M., Hindorff, L. A., Hooker, G. W., Koenig, B. A., et al. (2020). Clinical genetics lacks standard definitions and protocols for the collection and use of diversity measures. *Am. J. Hum. Genet.* 107 (1), 72–82. doi:10.1016/j.ajhg.2020.05.005

Popejoy, A. B., and Fullerton, S. M. (2016). Genomics is failing on diversity. *Nature* 538 (7624), 161–164. doi:10.1038/538161a

Purificacion, S. J., French, J. G., and d'Agincourt-Canning, L. (2015). Inequities in access to cancer care in Canada: An ethical perspective. *Healthc. Manage. Forum* 28 (6), 265–269. doi:10.1177/0840470415599136

Ramsey, M. L., Tomlinson, J., Pearlman, R., Abushahin, L., Aeilts, A., Chen, H. Z., et al. (2022). Mainstreaming germline genetic testing for patients with pancreatic cancer increases uptake. *Fam. Cancer*. doi:10.1007/s10689-022-00300-5

Reed Johnson, F., Lancsar, E., Marshall, D., Kilambi, V., Muhlbacher, A., Regier, D. A., et al. (20132013). Constructing experimental designs for discrete-choice experiments: Report of the ISPOR conjoint analysis experimental design good research practices task force. *Value Health* 16 (1), 3–13. doi:10.1016/j.jval.2012.08.2223

Reisel, D., Burnell, M., Side, L., Loggenberg, K., Gessler, S., Desai, R., et al. (2022). Jewish cultural and religious factors and uptake of population-based BRCA testing across denominations: A cohort study. *BJOG.* 129 (6), 959–968. doi:10.1111/1471-0528.16994

Rew, L., Kaur, M., McMillan, A., Mackert, M., and Bonevac, D. (2010). Systematic review of psychosocial benefits and harms of genetic testing. *Issues Ment. Health Nurs.* 31 (10), 631–645. doi:10.3109/01612840.2010.510618

Richards, S., Aziz, N., Bale, S., Bick, D., Das, S., Gastier-Foster, J., et al. (2015). Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet. Med.* 17 (5), 405–424. doi:10.1038/gim.2015.30

Ridic, G., Gleason, S., and Ridic, O. (2012). Comparisons of health care systems in the United States, Germany and Canada. *Mater. Sociomed.* 24 (2), 112–120. doi:10.5455/msm.2012.24.112-120

Riedl, C. C., Ponhold, L., Flöry, D., Weber, M., Kroiss, R., Wagner, T., et al. (2007). Magnetic resonance imaging of the breast improves detection of invasive cancer, preinvasive cancer, and premalignant lesions during surveillance of women at high

risk for breast cancer. *Clin. Cancer Res.* 13 (20), 6144–6152. doi:10.1158/1078-0432.CCR-07-1270

Roa, B. B., Boyd, A. A., Volcik, K., and Richards, C. S. (1996). Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat. Genet.* 14 (2), 185–187. doi:10.1038/ng1096-185

Rolle, L., Zayhowski, K., Koeller, D., Chiluiza, D., and Carmichael, N. (2021). Transgender patients' perspectives on their cancer genetic counseling experiences. *J. Genet. Couns.* 31, 781–791. doi:10.1002/jgc4.1544

Rosenthal, E., Moyes, K., Arnell, C., Evans, B., and Wenstrup, R. J. (2015). Incidence of BRCA1 and BRCA2 non-founder mutations in patients of Ashkenazi Jewish ancestry. *Breast Cancer Res. Treat.* 149 (1), 223–227. doi:10.1007/s10549-014-3218-x

Rowley, S. M., Mascarenhas, L., Devereux, L., Li, N., Amarasinghe, K. C., Zethoven, M., et al. (2019). Population-based genetic testing of asymptomatic women for breast and ovarian cancer susceptibility. *Genet. Med.* 21 (4), 913–922. doi:10.1038/s41436-018-0277-0

Rubenstein, J. H., Enns, R., Heidelbaugh, J., Barkun, A., and Committee, C. G. (2015). American Gastroenterological association Institute guideline on the diagnosis and management of lynch syndrome. *Gastroenterology. Gastroenterology* 149 (3), 777–782. quiz e16-7. doi:10.1053/j.gastro.2015.07.036

Rubinsak, L. A., Kleinman, A., Quillin, J., Gordon, S. W., Sullivan, S. A., Sutton, A. L., et al. (2019). Awareness and acceptability of population-based screening for pathogenic BRCA variants: Do race and ethnicity matter? *Gynecol. Oncol.* 154 (2), 383–387. doi:10.1016/j.ygyno.2019.06.009

Sanderson, S., Zimmern, R., Kroese, M., Higgins, J., Patch, C., and Emery, J. (2005). How can the evaluation of genetic tests be enhanced? Lessons learned from the ACCE framework and evaluating genetic tests in the United Kingdom. *Genet. Med.* 7 (7), 495–500. doi:10.1097/01.gim.0000179941.44494.73

Sardanelli, F., Podo, F., D'Agnolo, G., Verdecchia, A., Santaquilani, M., Musumeci, R., et al. (2007). Multicenter comparative multimodality surveillance of women at genetic-familial high risk for breast cancer (HIBCRIT study): Interim results. *Radiology* 242 (3), 698–715. doi:10.1148/radiol.2423051965

Savatt, J. M., Ortiz, N. M., Thone, G. M., McDonald, W. S., Kelly, M. A., Berry, A. S. F., et al. (2022). Observational study of population genomic screening for variants associated with endocrine tumor syndromes in a large, healthcare-based cohort. *BMC Med.* 20 (1), 205. doi:10.1186/s12916-022-02375-4

Scheinberg, T., Young, A., Woo, H., Goodwin, A., Mahon, K. L., and Horvath, L. G. (2021). Mainstream consent programs for genetic counseling in cancer patients: A systematic review. *Asia. Pac. J. Clin. Oncol.* 17 (3), 163–177. doi:10.1111/ajco.13334

Schmeler, K. M., Lynch, H. T., Chen, L. M., Munsell, M. F., Soliman, P. T., Clark, M. B., et al. (2006). Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. *N. Engl. J. Med.* 354 (3), 261–269. doi:10.1056/NEJMoa052627

Schofield, L., Grieu, F., Amanuel, B., Carrello, A., Spagnolo, D., Kiraly, C., et al. (2014). Population-based screening for lynch syndrome in Western Australia. *Int. J. Cancer* 135 (5), 1085–1091. doi:10.1002/ijc.28744

Schwartz, M. L. B., McCormick, C. Z., Lazzeri, A. L., Lindbuchler, D. M., Hallquist, M. L. G., Manickam, K., et al. (2018). A model for genome-first care: Returning secondary genomic findings to participants and their healthcare providers in a large research cohort. *Am. J. Hum. Genet.* 103 (3), 328–337. doi:10.1016/j.ajhg.2018.07.009

Screening programmes: a short guide (2020). *Increase effectiveness, maximize benefits and minimize harm*. Copenhagen: WHO Regional Office for Europe.

Senter, L., Clendenning, M., Sotamaa, K., Hampel, H., Green, J., Potter, J. D., et al. (2008). The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology* 135 (2), 419–428. doi:10.1053/j.gastro.2008.04.026

Shickh, S., Rafferty, S. A., Clausen, M., Kodida, R., Mighton, C., Panchal, S., et al. (2021). The role of digital tools in the delivery of genomic medicine: Enhancing patient-centered care. *Genet. Med.* 23 (6), 1086–1094. doi:10.1038/s41436-021-01112-1

Shkedi-Rafid, S., Ofer-Bialer, G., Meiner, V., and Calderon-Margalit, R. (2013). Clinicians' attitudes toward general screening of the Ashkenazi-Jewish population for prevalent founder BRCA1/2 and LRRK2 mutations. *Public Health Genomics* 16 (4), 174–183. doi:10.1159/000351592

Siegel, J. E., Heeringa, J. W., and Carman, K. L. (2013). Public deliberation in decisions about health research. *Virtual Mentor* 15 (1), 56–64. doi:10.1001/virtualmentor.2013.15.1.pfor2-1301

Sirchia, F., Carrieri, D., Dheensa, S., Benjamin, C., Kayserili, H., Cordier, C., et al. (2018). Recontacting or not recontacting? A survey of current practices in clinical genetics centres in Europe. *Eur. J. Hum. Genet.* 26 (7), 946–954. doi:10.1038/s41431-018-0131-5

Slavin, T. P., Manjarrez, S., Pritchard, C. C., Gray, S., and Weitzel, J. N. (2019). The effects of genomic germline variant reclassification on clinical cancer care. *Oncotarget* 10 (4), 417–423. doi:10.18632/oncotarget.26501

Slavin, T. P., Van Tongeren, L. R., Behrendt, C. E., Solomon, I., Rybak, C., Nehoray, B., et al. (2018). Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. *J. Natl. Cancer Inst.* 110, 1059–1066. doi:10.1093/jnci/djy027

Smith, A. J., Turner, E. L., and Kinra, S. (20162016). Universal cholesterol screening in childhood: A systematic review. *Acad. Pediatr.* 16 (8), 716–725. doi:10.1016/j.acap.2016.06.005

Solano, A. R., Liria, N. C., Jalil, F. S., Faggionato, D. M., Mele, P. G., Mampel, A., et al. (2018). BRCA1 and BRCA2 mutations other than the founder alleles among Ashkenazi jewish in the population of Argentina. *Front. Oncol.* 8, 323. doi:10.3389/fonc.2018.00323

Solomon, I. B., McGraw, S., Shen, J., Albayrak, A., Alterovitz, G., Davies, M., et al. (2020). Engaging patients in precision oncology: Development and usability of a web-based patient-facing genomic sequencing report. *JCO Precis. Oncol.* 4doi, 307–318. doi:10.1200/PO.19.00195

Soper, E. R., Suckiel, S. A., Braganza, G. T., Kontorovich, A. R., Kenny, E. E., and Abul-Husn, N. S. (2021). Genomic screening identifies individuals at high risk for hereditary transthyretin amyloidosis. *J. Pers. Med.* 11 (1), 49. doi:10.3390/jpm11010049

Stjepanovic, N., Moreira, L., Carneiro, F., BalaguerF.CervAntes, A., Balmana, J., et al. (2019). Hereditary gastrointestinal cancers: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 30 (10), 1558–1571. doi:10.1093/annonc/mdz233

Stoll, K., Kubendran, S., and Cohen, S. A. (2018). The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. *Am. J. Med. Genet. C Semin. Med. Genet.* 178 (1), 24–37. doi:10.1002/ajmg.c.31602

Suther, S., and Kiros, G. E. (2009). Barriers to the use of genetic testing: A study of racial and ethnic disparities. *Genet. Med.* 11 (9), 655–662. doi:10.1097/GIM.0b013e3181ab22aa

Ten Haaf, K., Jeon, J., Tammemägi, M. C., Han, S. S., Kong, C. Y., Plevritis, S. K., et al. (2017). Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. *PLoS Med.* 14 (4), e1002277. doi:10.1371/journal.pmed.1002277

Terris-Prestholt, F., Neke, N., Grund, J. M., Plotkin, M., Kuringe, E., Osaki, H., et al. (2019). Using discrete choice experiments to inform the design of complex interventions. *Trials* 20 (1), 157. doi:10.1186/s13063-019-3186-x

Teutsch, S. M., Bradley, L. A., Palomaki, G. E., Haddow, J. E., Piper, M., Calonge, N., et al. (2009). The evaluation of genomic applications in practice and prevention (EGAPP) initiative: Methods of the EGAPP working group. *Genet. Med.* 11 (1), 3–14. doi:10.1097/GIM.0b013e318184137c

The Breast Cancer Linkage Consortium (1999). Cancer risks in BRCA2 mutation carriers. *J. Natl. Cancer Inst.* 91 (15), 1310–1316. doi:10.1093/jnci/91.15.1310

Tischkowitz, M., Balmaña, J., Foulkes, W. D., James, P., Ngeow, J., Schmutzler, R., et al. (2021). Management of individuals with germline variants in PALB2: A clinical practice resource of the American college of medical genetics and genomics (ACMG). *Genet. Med.* 23 (8), 1416–1423. doi:10.1038/s41436-021-01151-8

Tognetto, A., Michelazzo, M. B., Calabró, G. E., Unim, B., Di Marco, M., Ricciardi, W., et al. (2017). A systematic review on the existing screening pathways for lynch syndrome identification. *Front. Public Health* 5, 243. doi:10.3389/fpubh.2017.00243

Toland, A. E., Forman, A., Couch, F. J., Culver, J. O., Eccles, D. M., Foulkes, W. D., et al. (2018). Clinical testing of BRCA1 and BRCA2: A worldwide snapshot of technological practices. *NPJ Genom. Med.* 3, 7. doi:10.1038/s41525-018-0046-7

Turner, S. A., Rao, S. K., Morgan, R. H., Vnencak-Jones, C. L., and Wiesner, G. L. (2018). The impact of variant classification on the clinical management of hereditary cancer syndromes. *Genet. Med.* 21, 426–430. doi:10.1038/s41436-018-0063-z

Villegas, C., and Haga, S. B. (2019). Access to genetic counselors in the Southern United States. *J. Pers. Med.* 9 (3), E33. doi:10.3390/jpm9030033

Vohnout, B., Gabcova, D., Huckova, M., Klimes, I., Gasperikova, D., and Raslova, K. (2016). Genetic testing of familial hypercholesterolemia in a real clinical setting. *Wien. Klin. Wochenschr.* 128 (23-24), 916–921. doi:10.1007/s00508-016-1053-2

Wade, C. H. (2019). What is the psychosocial impact of providing genetic and genomic health information to individuals? An overview of systematic reviews. *Hastings Cent. Rep.* 49 (1), S88–S96. doi:10.1002/hast.1021

Wade, C. H., Wilfond, B. S., and McBride, C. M. (2010). Effects of genetic risk information on children's psychosocial wellbeing: A systematic review of the literature. *Genet. Med.* 12 (6), 317–326. doi:10.1097/GIM.0b013e3181de695c

Wald, D. S., Bestwick, J. P., Morris, J. K., Whyte, K., Jenkins, L., and Wald, N. J. (2016). Child-parent familial hypercholesterolemia screening in primary care. *N. Engl. J. Med.* 10375 (17), 1628–1637. doi:10.1056/NEJMoa1602777 27

Walsh, R., Bezzina, C., and Wilde, A. A. M. (2022). First steps of population genomic medicine in the arrhythmia world: Pros and Cons. *Circulation* 145 (12), 892–895. doi:10.1161/CIRCULATIONAHA.122.058738

Walsh, T., Mandell, J. B., Norquist, B. M., Casadei, S., Gulsuner, S., Lee, M. K., et al. (2017). Genetic predisposition to breast cancer due to mutations other than BRCA1 and BRCA2 founder alleles among Ashkenazi jewish women. *JAMA Oncol.* 3 (12), 1647–1653. doi:10.1001/jamaoncol.2017.1996

Warner, E., Messersmith, H., Causer, P., Eisen, A., Shumak, R., and Plewes, D. (2008). Systematic review: Using magnetic resonance imaging to screen women at high risk for breast cancer. *Ann. Intern. Med.* 148 (9), 671–679. doi:10.7326/0003-4819-148-9-200805060-00007

Warner, E., Plewes, D. B., Hill, K. A., Causer, P. A., Zubovits, J. T., Jong, R. A., et al. (2004). Surveillance of BRCA1 and BRCA2 mutation carriers with magnetic resonance imaging, ultrasound, mammography, and clinical breast examination. *JAMA*. 292 (11), 1317–1325. doi:10.1001/jama.292.11.1317

Warner, E., Zhu, S., Plewes, D. B., Hill, K., Ramsay, E. A., Causer, P. A., et al. (2020). Breast cancer mortality among women with a BRCA1 or BRCA2 mutation in a magnetic resonance imaging Plus mammography screening program. *Cancers* 23 (11), E3479. doi:10.3390/cancers12113479

Watkins, K. E., Way, C. Y., Fiander, J. J., Meadus, R. J., Esplen, M. J., Green, J. S., et al. (2011). Lynch syndrome: Barriers to and facilitators of screening and disease management. *Hered. Cancer Clin. Pract.* 9, 8. doi:10.1186/1897-4287-9-8

Watts, G. F., Sullivan, D. R., Hare, D. L., Kostner, K. M., Horton, A. E., Bell, D. A., et al. (2021). Essentials of a new clinical practice guidance on familial hypercholesterolaemia for physicians. *Intern. Med. J.* 51 (5), 769–779. doi:10.1111/imj.15327

Wauters, A., and Van Hoyweghen, I. (2016). Global trends on fears and concerns of genetic discrimination: A systematic literature review. *J. Hum. Genet.* 61 (4), 275–282. doi:10.1038/jhg.2015.151

Wilson, J. M., and Jungner, Y. G. (1968). Principles and practice of mass screening for disease. *Bol. Oficina Sanit. Panam.* 65 (4), 281–393.

Wonderling, D., Umans-Eckenhausen, M. A., Marks, D., Defesche, J. C., Kastelein, J. J., and Thorogood, M. (2004). Cost-effectiveness analysis of the genetic screening program for familial hypercholesterolemia in The Netherlands. *Semin. Vasc. Med.* 4 (1), 97–104. doi:10.1055/s-2004-822992

Yoon, S. Y., Wong, S. W., Lim, J., Ahmad, S., Mariapun, S., Padmanabhan, H., et al. (2021). Oncologist-led *BRCA* counselling improves access to cancer genetic testing in middle-income Asian country, with no significant impact on psychosocial outcomes. *J. Med. Genet.* 59, 220–229. doi:10.1136/jmedgenet-2020-107416

Yorkshire Cancer Research (2022). *Yorkshire Cancer Research announces £7.3 million in funding for new research*. Harrogate, United Kingdom: Yorkshire Cancer Research. Availlable at: https://yorkshirecancerresearch.org.uk/news/7-3-million-in-funding-for-new-research.

Youngblom, E., Pariani, M., and Knowles, J. W. (2016). *Familial hypercholesterolemia*. GeneReviews.

Yurgelun, M. B., Hiller, E., and Garber, J. E. (2015). Population-Wide screening for germline BRCA1 and BRCA2 mutations: Too much of a good thing? *J. Clin. Oncol.* 33 (28), 3092–3095. doi:10.1200/JCO.2015.60.8596

Zhang, L., Bao, Y., Riaz, M., Tiller, J., Liew, D., Zhuang, X., et al. (2019). Population genomic screening of all young adults in a health-care system: A cost-effectiveness analysis. *Genet. Med.* 21 (9), 1958–1968. doi:10.1038/s41436-019-0457-6

Zuurbier, L. C., Defesche, J. C., and Wiegman, A. (2021). Successful genetic screening and creating awareness of familial hypercholesterolemia and other heritable dyslipidemias in The Netherlands. *Genes (Basel)* 12 (8), 1168. doi:10.3390/genes12081168

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