PUBLIC HEALTH GENOMICS

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PUBLIC HEALTH GENOMICS

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The use of human genetic data has the potential to significantly improve healthcare, however a range of scientific, ethical and practical implementation barriers remain.

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EDITORIAL
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Editorial: Public Health Genomics

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Editorial on the Research Topic

Public Health Genomics

The term "Public Health Genomics" encompasses the many different areas where genomic information is used in public and population health. Primarily, this includes the use of human genotype in the prevention or treatment of disease. However, it also encompasses the use of pathogen genomics for outbreak monitoring, molecular profiling of tumor tissue for targeted therapies, and other areas.

Public Health Genomics (PHG) research also addresses regulatory and policy issues, related to the use of genetic information in society. In addition, it encompasses Ethical, Legal, and Social Issues (ELSI) raised by the growth and expansion of genomics. For example, newly emerging areas such as direct-to-consumer genetic testing via the internet and the use genetic information forensically for crime-solving purposes (1) are fast becoming PHG issues.

This research topic aims to provide an overview and introduction to the field of PHG. Articles have used language and addressed topics that we consider to be accessible for a general audience, including public health researchers not working in the field of genomics. Our intention is to introduce some of the key developments and challenges of the field, during a critical growth period.

Many articles focus on the Australian healthcare system and related policy, where progress has been made—including specific efforts underway to implement genomics into routine healthcare, address ELSI issues, and develop required PHG policy.

The series begins with Perspective articles on the history and evolution of PHG as a field. These provide an overview of some of the key issues and emerging trends, and how the field is currently poised. Molster et al. describe a range of activities that illustrate how genomics can be incorporated into public health practice. They present the evolution of public health genomics into the new era of "precision public health," which put simply is using the best available data to target more effectively and efficiently interventions of all kinds to those most in need (2, 3). Bilkey et al. discuss the potential impacts of precision medicine on public health policy and decision-making, with particular focus on patients living with rare diseases and rare cancers. They present precision public health as the bridge between precision medicine and public health. Burns et al. explore priority-setting for sustainable implementation of genomic testing into healthcare within the strategic priority areas of the Australian National Health Genomics Policy Framework. The priority areas include services, data, workforce, finances, and person-centered care. They argue that for full effectiveness resources should not be allocated genomic testing alone, but should cover all these priority areas.

The research topic then focuses on ELSI, including a review of issues across the lifespan of genomic testing—from newborn bloodspot screening, to adult predisposition testing, to reproductive carrier screening, to molecular autopsy (Bilkey et al.).

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Articles then focus on a particularly pressing and topical issue in PHG: the use of genetic test results in insurance underwriting. Tiller et al. provide a detailed account of the ethical and regulatory situation in Australia, amidst the ongoing use of genetic test results in life insurance underwriting. Concerns persist around industry self-regulation and lack of government oversight on this issue in Australia (4). In a separate study, Tiller et al. present original research, collecting quantitative survey data from genetic health professionals on workforce trends, practices, and knowledge around genetic testing and life insurance regulation in Australia. They report considerable variation amongst survey respondents (genetics professionals), genetic health services, and geographic locations regarding understanding and communication of current regulation. The evolving US regulatory landscape around employer use of genetic information is then considered by Bilkey et al., including implications for Australia and other jurisdictions.

Beyond the issue of insurance, Tiller and Lacaze also consider the difficulty of regulating internet-based genetic testing, in a rapidly evolving landscape. It is now estimated that over 26 million people have taken at-home ancestry tests—an unprecedented level of testing. This is mostly unregulated, raising several issues, including the practice of consumers imputing raw genotyping data from ancestry companies using third-party online tools to generate medical risk estimates of questionable quality (5). This can lead to confusion, unexpected findings, and an increased burden on local genetic health services (6).

Ryan et al. address the complex issue of dementia prevention for the aging population. Here, considerable biological and phenotypic heterogeneity in dementia make biomarker development challenging. Genomic and other 'omic approaches provide opportunities for novel biomarker classes (7), however far more research and development is still required.

Finally, Nunn et al. conduct a scoping review of public involvement in global genomics research. This is the first study of its kind to consider the degree of public involvement occurring in prominent human genomics projects around the world. The study suggests current levels of public involvement need to be improved, as the level of genomic research and testing in society approaches population scale (8).

Together, the Research Topic provides a broad and diverse overview of a field that is rapidly evolving. Articles are timely and address real-world issues. Genomics has the potential to improve the way we deliver healthcare and precision public health in the future. However, the many ethical, regulatory, and scientific challenges must be carefully addressed in coming years, if these benefits are to be realized.

AUTHOR CONTRIBUTIONS

PL and GB edited the Research Topic and wrote the manuscript.

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REVIEW
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The Evolution of Public Health Genomics: Exploring Its Past, Present, and Future

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Public health genomics has evolved to responsibly integrate advancements in genomics into the fields of personalized medicine and public health. Appropriate, effective and sustainable integration of genomics into healthcare requires an organized approach. This paper outlines the history that led to the emergence of public health genomics as a distinguishable field. In addition, a range of activities are described that illustrate how genomics can be incorporated into public health practice. Finally, it presents the evolution of public health genomics into the new era of "precision public health."

Keywords: public health genomics, precision public health, genomics, population genetics, population health

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PUBLIC HEALTH: THE PAST

The field of public health emerged as a means to "protect" the health of the individual and the community, and thereby minimize morbidity and mortality associated with disease (1, 2). Differentiating itself from the medical field, public health places an emphasis on improving the health of society as a whole through the use of organized, population-wide approaches. Instances of public health efforts have been documented throughout history. For example, by the eighteenth century, it was common practice to isolate and quarantine sick individuals, in order to contain the spread of contagious diseases such as leprosy and the plague (1, 3). Developing and delivering appropriate public health services requires an understanding about health and wellbeing, the presence and absence of disease, how health outcomes are distributed within populations and the factors that determine these outcomes.

Over the last two centuries, the essential activities of public health have evolved significantly. In the nineteenth century, the primary focus of public health was on managing the physical environment, such as the provision of safe drinking water and the development of effective sewerage systems. In the twentieth century, the scope of public health was increased to include social factors (such as housing, employment, income, educational level, and access to transportation and health care) and lifestyle behaviors (such as physical activity, diet, smoking, and alcohol consumption) that are now known to influence health outcomes. This led to the emergence of the "health promotion" era of public health, which stemmed from a movement aimed at providing evidence-based education that would enable people to increase control over and improve their health (4). The health promotion movement drove action in a range of areas of public health including: developing public policy, creating environments that support healthy behaviors, and empowering people to develop personal skills to make choices that lead to healthier lives.

At the heart of public health today is the recognition that health outcomes are influenced by a range of social, cultural, political, economic, environmental, behavioral, and biological (e.g., genetic) factors (5). Otherwise known as the "determinants of health," these factors may favor health or be harmful to it. Further, while some factors cannot be changed (such as age or ethnic background), others may be modifiable (for example, weight or smoking status). Understanding how these factors influence health outcomes is key to informing public health approaches for promoting health and wellbeing, through the implementation of practices that aim to "prevent" poor health. These prevention strategies can be categorized into three levels, being:

- **Primary:** where the aim is to prevent disease and injury from occurring, which will reduce their incidence in the population. This is done largely through interventions to eliminate risk factors. For example, seatbelts, sunscreen, tobacco-use cessation.
- **Secondary:** where the aim is to reduce the more immediate impact of disease and injury if it does occur. The focus of interventions is on early detection and treatment to alter or slow progress of the disease or injury, and thereby prevent the onset of long-term or permanent adverse consequences such as complications and disabilities. For example, population screening programs.
- **Tertiary:** where the aim is to help people manage the longer term impact of ongoing disease or injury. The focus of interventions is to improve, as much as possible, factors such as physical and mental functioning, quality of life, and life expectancy. For example, chemotherapy, rehabilitation.

A fourth category of prevention, known as quaternary prevention, has also been proposed (6, 7). This is defined as: "action taken to identify a patient or a population at risk of over-medicalization, to protect them from invasive medical interventions and provide for them care procedures which are ethically acceptable" [(6), p. 3]. In other words, the aim of quaternary prevention is to identify and protect those individuals for whom medical interventions are likely to cause more harm than good (7, 8).

CORE FUNCTIONS OF PUBLIC HEALTH

Following from the health promotion movement was a growing recognition that public health had changed significantly over the years, and that the governmental role in providing public health services needed to be clearly defined, adequately supported, and fully understood. This led the Institute of Medicine (IOM; now known as the Health and Medicine Division) of the United States of America's National Academies of Sciences, Engineering and Medicine in 1988 to identify and define the three core functions to be provided by all public health agencies (3), being:

- **Assessment:** to assess and monitor the health of communities and populations at risk, and to identify health problems and priorities. This requires the regular and systematic collection, assembly, analysis, and dissemination of information on the health of populations.
- **Policy development:** to formulate public policies, plans, standards, guidelines, and resources in collaboration and partnership with stakeholders, and to solve identified local and national health problems and priorities.
- **Assurance:** to assure that all populations have access to appropriate and cost effective care (including health promotion and disease prevention services), and to evaluate the effectiveness of healthcare and public health interventions.

Building on this work, in 1994 the three core functions of public health were further elaborated into 10 essential public health services, to support the application of the core functions in practice (9, 10). These 10 essential public health services are presented in **Box 1**.

Box 1 | The 10 essential public health services (9).

1. Monitor and evaluate health status to identify community health problems.
2. Diagnose and investigate health problems and health hazards in the community.
3. Inform, educate, and empower people about health issues.
4. Mobilize community partnerships to identify and solve health problems.
5. Develop policies and plans that support individual and community health efforts.
6. Enforce laws and regulations that protect health and ensure safety.
7. Link people to needed personal health services and assure the provision of health care when otherwise unavailable.
8. Assure a competent public and personal health care workforce.
9. Evaluate effectiveness, accessibility, and quality of personal and population-based health services.
10. Research for new insights and innovative solutions to health problems.

PUBLIC HEALTH GENOMICS: THE PRESENT

In the two decades since the core functions and essential services of public health were defined, rapid developments have occurred in the field of genomics (see **Box 2** to understand the distinction between the terms "genetics" and "genomics"). These developments have enhanced our knowledge of how human genes interact with each other and the environment to influence health. A notable example is the completion of the Human Genome Project in 2003, which led to the proliferation, in volume and complexity, of knowledge about the human genome. It also resulted in a significant reduction in the estimated number of genes expected to be found in the human genome, down from previous estimates of as many as 140,000 genes to a probable 20,500 (13). The impact that advancements in genomics have had on our understanding of disease is discussed in **Box 3**.

From these advancements comes the increasing recognition of the potential applications of genomic knowledge and related technologies to improve population health. For example,

BOX 2 | The difference between genetics and genomics.

Genetics is the science of inheritance and tends to look at the functioning and composition of a single gene at a time. Thus genetic studies into diseases tend to focus on those that are associated with variants in one gene only (11). These "single gene disorders" (or Mendelian disorders) are relatively rare in the population and examples include Fragile X syndrome, cystic fibrosis, muscular dystrophy, and Huntington's disease.

Most common diseases are multi-factorial, caused by variants in numerous genes that interact with each other and with a range of environmental factors (12). To gain more knowledge about these diseases, researchers work in the field of genomics. This field involves the study of the genome, that is, all the genes in the cells of an organism and how these genes interact with each other and with environmental factors to affect an organism's growth and development (11). Hence genomics researchers are able to explore the causes of diseases such as cancer, diabetes, and heart disease, which have multi-factorial determinants including genes, lifestyle behaviors, and other environmental influences.

BOX 3 | How genomics improved the understanding of diseases.

"Genomic knowledge" refers to the information that is obtained from studying the complete genetic makeup of a cell or organism. In recent years, scientific research in this area has contributed significantly to our knowledge about the human genome, improving our ability to understand disease etiology, risk, prevention, diagnosis, and treatment. The ways in which these areas can be enhanced by genomic knowledge are outlined below. Based on these improved understandings, genomic tools, and technologies are being developed to enable better health not just for the individual, but for populations as well.

Etiology

Increased genomic knowledge about a disease can provide insights into how the disease may develop. This can occur through a better understanding of the function of genes that make up the genome, how different genetic variants contribute to the phenotype of diseases, the role of gene expression, and the role of the interaction between genes (10, 14).

Risk

Genomic knowledge is expected to improve our understanding of why some individuals remain healthy while others are more susceptible to disease. For example, information on the genetic variants associated with an increased risk of common diseases, such as cardiovascular disease and diabetes, might at some point be used to make predictions about the likelihood a person will get these diseases (15). This knowledge could then be applied to develop new tools for risk prediction or predictive testing (5) in relation to the onset or recurrence of disease (16).

Prevention

Understanding how the genome influences the etiology and risk of diseases may lead to improved understanding of how diseases, or the symptoms of disease, can be prevented (5, 16). Genomic tools and technologies can also identify infectious diseases with greater speed and precision to enable rapid responses to disease outbreaks and more efficient surveillance (17–19).

Diagnosis

Historically, clinicians generally used a set of observable or measurable characteristics as the basis for diagnosing disease. Genomic knowledge takes this one step further, by enabling clinicians to look at a person's genes to provide a molecular diagnosis. In line with this, diagnostic technologies have been developed that include a plethora of clinical genetic tests (5, 14, 16).

Treatment

To date, genomic knowledge has mostly been used to inform disease treatments. Pharmacogenetics and pharmacogenomics are two fields where new and improved therapies and treatments have been developed, including hundreds of new drugs which are advancing disease management (16). The expectation is that genomic knowledge will further improve the ability to assess treatment responses, such as how different people metabolize drugs and which people are more likely to experience adverse drug reactions (11, 16, 20). Based on genetic profiles, tailored therapies may be developed for an individual and across individuals within specific patient populations to deliver the right drug in the right dose at the right time (12, 16, 21, 22).

genomic knowledge can offer new ways of differentiating individuals and sub-groups within populations, taking public health beyond the traditional correlates of disease risk such as gender, age, and socio-economic status (20). Specifically, it can enable the stratification and subsequent screening of individuals and sub-groups of populations based on their level of genetic risk for developing a disease. This can then lead to the development of more targeted prevention approaches to reduce the burden of disease (11).

It should be noted that advances in genomics have been dependent on, and facilitated by, progress in related fields such as informatics, and the development of novel technologies capable of evolving to meet the increasing demands of genomic medicine. Specifically, the huge volume of data generated by next generation sequencing has created significant challenges relating to data storage and analysis. These challenges are explored further in **Box 4**.

Many tools and technologies based on emerging genomic knowledge have been developed. However, for a range of complex reasons, only a small proportion of these tools and technologies have so far been fully translated into healthcare and public health practice from the discovery research phase, beyond the introduction of newborn screening for genetic conditions (20, 26). The literature refers to two key reasons why this may be so. Firstly, in genomic studies, most genetic variants that have been identified as contributing to common diseases are only associated with small increases in relative risk and explain only a little about the relationship between disease and genetic inheritance (10, 21, 27, 28). This is because most common diseases are the result of complex interactions between multiple genes and environmental factors. Furthermore, the genetic variants that contribute to a given disease, and how they are expressed, may vary among different people and sub-populations, as might the relative significance of genetic and non-genetic factors (12).

BOX 4 | The data informatics puzzle.

The concept of Moore's Law is useful to consider, when exploring the limitations of current computation and storage in genomics medicine. Moore's Law was proposed in 1965 to describe the long term trend whereby for every doubling of time of ∼18 months, there is an exponential increase in the capacity for disk storage and computation (23). Historically, this growth meant that data storage and computation were able to stay ahead of the demands of genomics. However, the advent of next generation sequencing in 2005 and the rapid decline in associated costs have resulted in demands on the informatics capacity outpacing developments in the informatics ecosystem (24). The 100,000 Genomes Project in the United Kingdom (UK) has highlighted the limitations of digital infrastructure in the progression of genomic medicine, and the UK government has committed to fund sufficient digital infrastructure in order achieve successful rollout of their Genomic Medicine Service (25). Future integration of genomics in population medicine must emphasize the development of sustainable computational analytics and storage infrastructure.

Consequently, attention has shifted toward rare and monogenic diseases where the gene and phenotype(s) may result in more clear causal pathologies. Nevertheless, obtaining a definitive association between a single-gene variant and a distinct disease phenotype remains a complex process.

Secondly, while tools and techniques based on genomic knowledge have been developed, there has often been limited evidence regarding their validity and utility (26). In part, this is due to a lack of investment in the infrastructure required to collect and evaluate tools and technologies in a systematic manner (10, 29) and also to the complexity of conducting evaluations (27). The recognition of this lack of evidence gave rise to the discipline of "public health genomics," defined in 2005 as "the responsible and effective translation of genome-based knowledge and technologies for the benefit of the population" (30).

While there are expectations that genomic knowledge, tools, and technologies benefit population health, it is essential that they are applied only when the benefits outweigh the potential harms. New tools and technologies that are prematurely introduced without the evidence demonstrating that they are valid and useful run the risk of posing harm to individuals, families, and the broader health system. Such issues might include the potential for over-, under-, or mis-diagnoses, or psychosocial harms. It is also critical to consider the ethical, legal, and social issues inherent in the field of genomics. These issues are particularly relevant in the context of genomic information relative to other medical information due to the fact that variants in genes, by nature, are shared within families. Uncovering genomic determinants of health therefore has implications not only for the individual but for genetic relatives as well. Moreover, genomic information can be obtained in the absence of clinical symptoms and therefore in isolation it may have a weaker predictive association with health outcomes compared to most other health information. In addition, determining who, what, and when to test is fraught with ramifications for service capacity and financial responsibility, and can also have implications for patient autonomy and privacy as evident in the case study presented in **Box 5**.

It is therefore essential to consider existing and emerging knowledge, tools, and technologies in order to determine which are actually beneficial to population health and how they could be appropriately implemented. This requires an objective evaluation of the potential benefits against the potential harms, and the resources required for implementing them (12). Public health genomics bridges this gap between new scientific discoveries and technologies, and the application of genomic knowledge to benefit population health (31, 32).

With genomics being increasingly integrated into population-level health initiatives, it has been internationally recognized that maintaining efficiency, effectiveness, ethics, and equity into the future requires a strategic approach. In line with this, there has been a call for the cooperative development and harmonization of policy on genomics in healthcare between 28 of the European Union member states and Norway (33). Of these nations, Italy has been a leader in the development of public health genomics policy, developing a National Plan for Public Health Genomics that includes consideration of translation of genomics into public health practice (34). An international working group on "Beyond Health Genomics" also recommended the improved facilitation of translation research through greater engagement between public health professionals, geneticists, and scientists (20).

Similarly, the Australian Government's Department of Health has released the *National Health Genomics Policy Framework 2018–2021* to harness the health benefits of genomic knowledge and technology into the Australian health system. This framework provides a shared direction and commitment between all governments in Australia to consistently and strategically integrate genomics into the Australian health system through five strategic priority areas: person-centered approach, workforce, financing, services, and data (35). The cohesive strategy is expected to ensure that the integration of genomics in healthcare is not only appropriate for the health of populations, but is also sustainable for the health system.

PUBLIC HEALTH GENOMICS IN PRACTICE

The ways in which genomics can contribute in public health practice are clear. However, capitalizing on genomic advances requires a coordinated approach in order to integrate the benefits of associated knowledge and technologies into each aspect of public health service delivery. Beskow et al. (31) were the first to link the 10 essential public health services—provided in **Box 1**—with genomics, in 2001. Integral to each essential service is the role of "system management" in ensuring the responsible, equitable, and sustainable integration of genomics into healthcare and public health practice.

Almost 20 years after the link between public health and genomics was established, **Table 1** furthers Beskow et al.'s. (31) work to provide examples from the literature of how genomics

BOX 5 | Case Study—Ethical, legal, and social implications to consider for applications of public health genomics.

Consider the hypothetical scenario in which a newborn screening program performs whole genome sequencing on every newborn within a population. The ethical, legal, and social implications to consider include:

- Which variants should be reported? Should they be limited to known pathogenic variants, or further limited to only those that have an available treatment? Should variants of unknown significance be reported?
- Who decides what information, such as variants of unknown significance or secondary findings, should be reported? Should this be a decision for parents, or for an independent governance body?
- Which conditions should be screened for? Would parents want to know their baby's risk of developing a late-onset disorder such as dementia, or an untreatable condition? Would a child want to know of their risk?
- How should genetic counseling be offered to all parents of newborns such that they can give informed consent for the tests?
- Does the population have sufficient genetic literacy to be able to fully understand the consent process, and implications of the results, for benign, pathogenic, and uncertain variants?
- Should the genomic data be kept, and if so, for how long?
- Should the data be re-interrogated, particularly with inevitable advances in technology? If so, at what time intervals?
- Should these genomic data be available to all healthcare providers?
- What are the implications on health and life insurance if disease risk can be stratified at birth?
- If a baby is shown to be stratified at higher risk for certain lifestyle diseases, what is their responsibility for mitigating that risk? What is the government's responsibility for mitigating that risk?

can be incorporated into public health practice. These examples reflect the rapid developments made in genomics and the significant impact the field has had to improve population health.

It should be noted that the ability of individuals to directly access health-related genetic and genomic tests, otherwise referred to as direct-to-consumer (DTC) or "personal genomic" tests, is one particular issue for public health that requires consideration. DTC tests may detect individuals at increased risk of certain diseases. However, the clinical utility and validity of DTC tests is largely uncertain (60–63). Furthermore, there are a range of ethical, legal, and social issues associated with such tests, such as challenges relating to the provision of information about the test and associated results, and obtaining informed consent (61, 64). Given that consumers are able to access some tests without clinical oversight, appropriate regulatory mechanisms need to be implemented to ensure public access to such tests is appropriate and that where possible, results are interpreted and communicated with caution (65). For those individuals with results of clinical significance, quaternary prevention principles should be applied to avoid their over-medicalization, particularly where results are uncertain or not based on evidence (63, 66, 67). Also for consideration is the possibility of under-medicalization of individuals if their genomic results are inappropriately interpreted or actioned.

PRECISION PUBLIC HEALTH: THE FUTURE

The integration of genomic knowledge and technologies into healthcare is revolutionizing the way we approach clinical and public health practice. In clinical practice, advances in genomics are allowing information about an individual's genetic and biochemical composition, as determined by the interactions between their genes, environment, and lifestyle, to be used in the delivery of targeted interventions; a field known as "precision medicine" (68). This then enables clinicians to tailor medical treatments better suited to the genetic composition of their patient.

An example of a current initiative that is anticipated to have significant implications for advancing precision medicine is the 100,000 Genomes Project in the United Kingdom, which is briefly discussed in **Box 4**. This project is sequencing genomes from people with a rare disease and their families, and patients with cancer, in order to improve diagnosis, treatment and care (69). Additionally, in the United States of America, the National Institutes of Health's "All of Us" research program aims to sequence at least 1 million Americans and analyse their health data (70). Launched as part of the US Precision Medicine Initiative, the program will gather environmental and biological information from participants to facilitate and advance research, technology, policies, and individualized medical care (71). The program presents a number of ethical, legal, and social challenges (72) and will serve as a guide for future precision medicine initiatives.

Parallel to the developments in precision medicine has been the advancement of technologies that enable the production, aggregation, analysis, and dissemination of extremely large volumes of individual- and population-level data on genes, environment, behavior, and other social and economic determinants of health. These data have proven useful in finding new correlations, patterns and trends, particularly those involving complex interactions, in relation to diseases, pathogens, exposures, behaviors, susceptibility (risk), and health outcomes in populations (73–75). These technologies and data, such as massively parallel sequencing and genomic reference databases, are now being further utilized to complement and extend the vision of precision medicine, to consider how they can be used to improve health outcomes at the population level (74, 76). This emerging field, of utilizing big data to guide the right intervention to the right people at the right time, has been termed "precision public health" (77). Another way precision public health has been defined is as "the application

TABLE 1 | Public health genomics activities in relation to the 10 essential public health services.

Essential public health services	Public health genomics activities
1. Monitor health status to identify and solve community problems	**Assess the distribution and impact of modifiable and genetic risk factors to determine their contribution to health status and the burden of disease** (31, 32). A better understanding of these risk factors could enable more precise decision-making about resource allocation and the prioritization and targeting of public health programs, and lead to new approaches to disease prevention and treatment (31).
	Promote the development of resources that enable monitoring of the genomic-related health status of populations. Key activities could include (5, 11, 36, 37): • assessing the inclusion of genomics information in the collection, management, and analysis of routine data • working with national surveys and large epidemiology groups to maximize potential from databases • exploring the potential for disease-specific, and population-based, registries to be used to conduct disease surveillance.
2. Diagnose and investigate health problems and hazards in the community	**Identify and track infectious disease outbreaks using genomic technology** This involves utilizing genomic technology to improve the speed and efficiency of infectious disease surveillance and response (17–19).
	Assist with the redesign of diagnostic and laboratory services to incorporate new genome-based technologies (38). Examples of these technologies include massively parallel sequencing such as whole exome and whole genome sequencing (39). There is potential for the incorporation of these technologies into diagnostic and laboratory services that can improve the diagnostic yield from genetic testing.
3. Inform, educate, and empower people about health issues	**Improve the genomic literacy of the public** (22, 31, 37). This involves providing education materials to communities that teaches them about genetics and genomics in understandable language (37, 39–43).
	Empower all stakeholders, including health professionals and the public, to make informed decisions about the uses of genetic information with realistic expectations about the risks and benefits (31). This includes the provision of relevant information on the uses of genomic information in disease prevention (22, 31), as well as on the associated ethical, legal and social issues.
	Facilitate the integration of genomics into health promotion and disease prevention programs (31). This will contribute to informing and educating people about genomics knowledge and technologies, as well as its limitations.
4. Mobilize community partnerships to identify and solve health problems	**Foster collaborations between stakeholders** (31). This encompasses capacity building, and developing networks and partnerships between diverse stakeholders including public policy makers, patients, the general public, academia, clinicians, researchers, and industry (16).
5. Develop policies and plans that support individual and community health efforts	Policies and plans that could be developed include those relating to: • the **appropriate use of genomic applications** (33, 37), through standards and guidelines that recognize the complexity of genomics and define when and how genome-based information and technologies should be used to promote health and prevent disease (31, 34, 44), including in the clinical setting (36, 45, 46) • **equity and accessibility**, to assure genomics knowledge and technologies are accessible across all segments of the population (20, 37) • the **use of family health history information** to inform people of the role of inheritance in the development of disease and identify people at risk of disease (26, 37) • **reproductive decision-making**, including prenatal screening, population-based carrier screening and pre-implantation genetic diagnosis (22).
6. Enforce laws and regulations that protect health and ensure safety	Contribute to: • **laws and regulations for genomic applications** (37). This could apply to genetic tests, including direct-to-consumer tests and related issues such as funding, data protection, insurance coverage for high-risk individuals and the prevention of genetic discrimination (22, 37, 42, 47). • **regulations for laboratories using genome-based technologies** (22). An example of these technologies is massively parallel sequencing.

(Continued)

TABLE 1 | Continued

Essential public health services	Public health genomics activities
7. Link people to needed health services and assure provision	**Support the appropriate integration of genomic knowledge and technologies into all aspects of healthcare and public health** (26, 41, 48). This may be operationalized in a number of ways, such as: • supporting the implementation of evidence-based genomic applications and discouraging the use of unvalidated applications (32), to prevent the premature use, misuse and overuse of genomic applications (11). • providing expert advice on the commissioning of services that use genome-based knowledge and technologies (38). This may relate to issues such as the appropriateness of the technologies for use; and the impact on, or requirements for, supporting functions such as counseling, education, and service coordination (45). • supporting the incorporation of genomic applications into existing public health practice, such as: using pathogen and human genomic technologies to control and manage communicable diseases (16); expanding population-based screening programs to include the use of genetic information (41); and targeting interventions for preventing diseases in population groups based on genetic information (11). • promoting the use of family health history to identify individuals at risk of disease (37, 40). Family history is the most consistent risk factor for all diseases and reflects the complex interactions between genes, behaviors, cultures and environments that family members share (49). It can be used to identify families at high risk for disease and could be incorporated into tailored chronic disease prevention and health promotion messages (40). • ensuring equity and accessibility to genomic applications and services (29, 36, 37, 42). This is especially important for population groups that traditionally face barriers to accessing health services, such as Indigenous and low socio-economic groups (31).
8. Assure a competent public and personal healthcare workforce	**Contribute to training and education in, and development of, genomic knowledge, skills and capacity for health professionals** (31, 43, 45, 50). This is so that: genomics is appropriately integrated into their work; they can effectively communicate genetic information; and they can support informed decision-making by patients (51). **Support the development of workforce capacity in genomics-related fields**. These fields include bioinformatics, genetic epidemiology, law and ethics, and health economics as applied to genetics and genomics (16, 38, 52, 53).
9. Evaluate the effectiveness, accessibility and quality of health services	**Evaluate new genome-based knowledge and technologies to determine their evidence base, quality, appropriateness and readiness for implementation in healthcare and public health practice.** The need for evaluation is based on concerns that the availability of genome-based tools and technologies, such as genetic tests, diagnostic equipment and therapies, are being driven more by technical feasibility and commercial potential than by evidence-based implementation. Such evaluations ensure that the benefits of genomic discoveries are realized efficiently, effectively and equitably, and are only implemented when it is in the public's best interest (2, 5, 27, 29, 31, 32, 42, 45, 54). **Evaluate the use of genome-based knowledge and technologies in healthcare and public health practice** (11, 55). Examples of evaluations include: the current use of genetic tests and services; the factors that influence utilization; cost-effectiveness; and the impact on service, intervention and patient outcomes (11, 20, 31, 36, 56).
10. Research for new insights and innovative solutions to health problems	**Monitor the results of human genome epidemiology studies** (45). This provides a population perspective on gene-disease associations, estimating the contribution of gene variants to the occurrence of disease in groups and the population overall (31, 37, 44, 46). Monitoring these studies can help identify gaps in knowledge at the population level (11) and could lead to changes in public health prevention interventions and disease management (14, 44). **Support the development of infrastructure for conducting genomic-related population research**. Patient registries, population data sets and linked biobanks are key resources enabling the conduct of large population studies to assess gene-environment interactions (14). However, steps must be taken to ensure that databases reflect genomic reference ranges for the whole population, inclusive of minority groups, to avoid inequity of the applications of genomic technology and knowledge (57). **Conduct and monitor translation research** (20, 37). The aim of translation research is to move appropriate genomic technologies from the discovery phase to application in healthcare and public health practice, and to evaluate its use in practice for improving health outcomes (11, 58, 59).

and combination of new and existing technologies, which more precisely describe and analyse individuals and their environment over the life course, in order to tailor preventive interventions for at-risk groups and improve the overall health of a population" (78).

Building upon the work of public health genomics from the last 20 years, precision public health enables the integration of genomics into public health strategies within the wider context of other determinants of health, such as socioeconomic, behavioral, and environmental factors. This can then lead to more precise individual and population-based interventions (74, 77, 79), and ultimately, improve population health outcomes (78).

The ways in which public health interventions and activities may become more "precise" as a result of technological innovations and the data they produce are evident in a number of areas including: epidemiology; knowledge of the determinants of health; targeting of healthcare disparities; screening and prevention; diagnosis; surveillance; and response to communicable diseases (10, 29, 73, 74, 76, 79–81). For example, genomic technologies could be applied using a precision public health approach to identify the impact of genomic variants in different population subgroups. Each subgroup could then be targeted with tailored interventions that are more relevant to their level of risk, resulting in more efficient and effective disease prevention, screening, and surveillance strategies. Such work is critical given current recognition that a lack of appropriate reference data for ancestral population subgroups could be contributing to disparities in access to effective health interventions (82). This is more likely to occur in minority or disadvantaged populations because they are commonly underrepresented in genomic research (82, 83). Consideration of genetic diversity helps to prevent the misclassification of benign genetic variants as pathogenic for these subgroups, and vice versa, which may otherwise lead to inappropriate care and management (84).

CONCLUSION

Public health genomics has been successfully integrated into existing paradigms for the provision of traditional public health services. The continued alignment of genomics with public health promises to deliver more precise, personalized health care to benefit the population. Governments and policy makers in this arena have a unique role to play in guiding this activity in such a way that ensures effective and equitable implementation of genomic knowledge and technologies into health systems. A national, coordinated approach to provide centralized governance of decision-making is required to ensure responsible delivery, universality, and equity of access. In addition, investment in important enabling infrastructure such as data informatics and a genomics-literate workforce will be critical to the sustainability of public health genomics and will prepare health systems to reap the valuable benefits of precision public health.

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Conflict of Interest Statement: 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.

GLOSSARY

Determinants of health	All the factors that determine health and wellbeing outcomes, including the presence or absence of disease.
DNA sequence	The linear order of the four bases of DNA, that is, the nucleotides called adenine, guanine, cytosine, and thymine.
Epidemiology	The study of the patterns, causes, and effects of health and disease in populations.
Gene	A defined unit of DNA (made up of a DNA sequence) that is inherited and provides instructions that determine characteristics of offspring.
Gene expression	The process by which information from a gene is converted into instructions that are used to create a functional gene product (e.g., a protein).
Genetic variant	A difference in the DNA sequence that makes up a gene. Genetic variations are what make each person unique.
Genetics	The science of inheritance, which generally focuses on one gene at a time.
Genome	All the genes within an organism.
Genome-based knowledge	Facts and information that are acquired through studies in "omics" fields such as genomics, proteomics, and metabolomics.
Genomics	The study of the genome, how all the genes in the genome function and are expressed, and how they interact with each other and the environment to affect an organism's growth and development.
Genomics knowledge	Facts and information that are acquired through the study of the genome.
Genomics technology	The collection of techniques, tools, methods, processes and tests that are developed based on knowledge of the genome.
Genotype	The full set of an organism's genetic variants that make up their unique personal genome.
Health disparities	Differences in the health status of different groups of people, including differences in the incidence and mortality of specific diseases.
Human genome epidemiology	The application of epidemiology approaches to understanding the impact of the human genome on patterns, causes and effects of health and disease in populations. This involves exploring the role of the genome and its interaction with environmental factors to contribute to health and disease.
Incidence	The number of new cases of a disease in a population within a given time period.
Interventions	Activities that aim to reduce risks or threats to health.
Massively parallel sequencing	An approach to DNA sequencing (the process of establishing the exact order of nucleotides within a sample of DNA), which is used to test for and diagnose genetic disorders.
Morbidity	The existence of a disease and the degree to which it affects a person, which can be measured by the incidence of ill health in the population.
Mortality	The number of deaths within a population.
Pharmacogenetics	The study of how variation in a single gene influences a person's response to a drug.
Pharmacogenomics	The study of how the full set of a person's genes (genome) affects their response to a drug.
Phenotype	The observable characteristics or traits of an organism, which is influenced by both genotype and the environment.
Precision public health	The application and combination of new and existing technologies, which more precisely describe and analyse individuals and their environment over the life course, in order to tailor preventive interventions for at-risk groups and improve the overall health of a population.
Prevalence	The number of people in a population who are alive with a disease during a period of time (period prevalence) or at a particular date in time (point prevalence).

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Optimizing Precision Medicine for Public Health

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Advances in precision medicine have presented challenges to traditional public health decision-making paradigms. Historical methods of allocating healthcare funds based on safety, efficacy, and efficiency, are challenged in a healthcare delivery model that focuses on individualized variations in pathology that form the core of precision medicine. Public health policy and decision-making must adapt to this new frontier of healthcare delivery to ensure that the broad public health goals of reducing healthcare disparities and improving the health of populations are achieved, through effective and equitable allocation of healthcare funds. This paper discusses contemporary applications of precision medicine, and the potential impacts of these on public health policy and decision-making, with particular focus on patients living with rare diseases and rare cancers. The authors then reconcile these, presenting precision public health as the bridge between these seemingly competing fields.

Keywords: genomics, public health, policy, precision medicine, genomic testing, molecular diagnostics, genetic disease, genetic therapies

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INTRODUCTION

Precision medicine has catalyzed strong debate over the merits and realities of a more personalized approach to healthcare. In one camp are the ideological, who believe that the utopia of medicine can exist in a world where patients' genomes, and -omics related information such as exposomics and metabolomics, can guide real-time, individualized prevention and therapeutics for improved outcomes to all (1, 2). In the other camp are those who tell a cautionary tale, citing current inability to reconcile the dream with the reality (3, 4). In particular, there is concern about the relevance and impact of individualized precision medicine approaches for public health, where populations are the traditional focus for intervention and decisions for which healthcare initiatives to fund must be rationalized within finite budgets.

Precision public health (PPH) is an emerging focus of public health that complements the development of precision medicine and utilizes advances in new technologies and knowledge unlocked through big data to better target public health efforts within populations (5). There has

been increasing global interest in this approach, with the White House and Bill and Melinda Gates Foundation sponsoring a 2016 conference entitled "Precision Public Health: The First 1,000 Days." Additionally, the Western Australian Department of Health and the Rockefeller Foundation hosted two separate international events on PPH in 2018 (6).

One of the many potential roles of PPH is to use population level data to better identify how individuals can be aggregated into larger groups. This could be achieved using the increased knowledge derived from precision medicine about the biological pathways involved in disease. Such an approach may be critical to ensuring that evidence-based research methodologies can still inform decision-making in the context of increasingly smaller target groups for therapies and diagnostics. In addition, a PPH approach, which is grounded in the public health values of whole population health improvement and equity, is seen as a safeguard against the potential "blind optimism" which can surround new technology (5). Herein, we provide an overview of key precision medicine initiatives, and consider how applying a PPH approach can ensure that precision medicine can be safely, effectively and equitably delivered for the benefit of the population. We illustrate this concept using examples from the fields of rare diseases and uncommon cancers, noting that the same approach could be applied in other areas of medicine.

Challenges will be faced in bringing precision medicine safely to the population. In particular, genomic technological advances and subsequent utilization of precision medicine within healthcare has given rise to unique ethical considerations (7–9). Such considerations present challenges to healthcare providers, governments and policymakers to provide assurance for patients and the population that privacy, testing, return of results and data storage are conducted in an ethical way. There are many papers that explore these considerations (7, 8, 10–12), and as such, these ethical issues will not be discussed in detail within this paper.

THE CONTRIBUTION OF GENETIC TESTS AND THERAPIES TO PRECISION MEDICINE

Advances in the development of genetic tests and therapies provide the potential to transform medicine and create unprecedented ability for detection, prevention, and treatment of diseases. Therapy approaches based on genetic variants and specific biomarkers have been increasing over the last few decades in association with the increasing availability and affordability of genomic sequencing technology. In this context, there has been growing interest in and advocacy for precision medicine approaches (13). This interest is highlighted by the World Economic Health Forum's Precision Medicine Programme, which "aims to support the development of policy frameworks and governance protocols to realize the societal benefits, and mitigate the risks from, precision medicine" (14).

Consideration of individual level variation, of both the person and/or their disease, is at the heart of precision therapies. For example, tumors have been eloquently described as "malignant snowflakes," which articulates that no two cancers will have the same molecular profile (15). Subsequently, therapeutic regimens must consider this inevitable variation in disease, with an individualized therapeutic approach likely to produce better health gains (15). Similarly, there are thought to be up to 6,000 rare diseases, many of which have underlying genetic causes and which may require different therapeutic approaches. Furthermore, genetic variants have been shown to influence metabolism of drugs and a range of drugs include information on their labels about adverse drug reactions or different dose recommendations based on a person's genomic profile (16, 17). It is possible that an individual's genomic information could be used to rationalize and guide therapeutic options and dosing at the point of prescribing. However, the approval and use of such precision therapies is often reliant on "companion" diagnostic tests that are able to identify who is likely to benefit from a particular medicine, requiring parallel mechanisms of assessment and regulation for diagnostic and therapeutic approaches. Some recent examples of precision therapies and interventions are explored below.

Biomarker Specific Therapies

In 2017, the Food and Drug Administration (FDA) of the United States of America (USA) approved more precision medicines and companion tests compared to any prior year (18). One example was the approval of pembrolizumab (Keytruda®), which marked the first solid cancer therapy approved for use based on the presence of a specific biomarker rather than a tumor's location (19). Similarly, trastuzumab-dskt (Ogivri™) was approved as the first biosimilar agent, targeting both stomach, and breast tumors overexpressing the *HER2* gene, possibly facilitating competition and aiding lower healthcare costs (20).

As these tests are dependent on the presence of specific biomarkers, they are therefore reliant on companion genetic tests. Two examples of companion tests are MSK-IMPACT™ (screens 468 genes) and FoundationOne CdX™ (screens 324 genes), both solid tumor tests and the first massively parallel sequencing *in vitro* diagnostic tests. Both tests screen multiple oncogenes to identify variants that might assist in the clinical management of patients, and identify patients with certain tumor types who may benefit from approved targeted treatment options (21, 22).

Genetic Therapies

Significantly, three of the 2017 FDA approvals were the first gene therapies ever approved by the FDA, including voretigene neparvovec (Luxturna™) for retinal dystrophy, the first to treat an inherited disease. Spark Therapeutics gave Luxturna™ a list price of US$425K per eye, making it the most expensive medicine in the USA per dose (23).

The FDA also gave fast track designation and priority review in 2016 for two orphan drugs for genetic neuromuscular diseases (both antisense oligonucleotides), representing significant advances in the treatment of rare diseases. In September 2016, the FDA provided accelerated approval for eteplirsen (Exondys 51™) for Duchenne muscular dystrophy (24), and nusinersen (Spinraza®) was approved in late December for early fatal spinal muscular atrophy (25). Both these treatments need to be

delivered for the remainder of a patient's life. Exondys 51™ costs around US$300K per patient per year, and in the second quarter of 2018 it generated Sarepta Therapeutics over US$73 million in net revenue (26). Spinraza® has a list price of US$125K per injection, translating to US$750,000 in the first year of treatment per patient, and US$375K for each subsequent year. In Australia, Spinraza® was listed on the Pharmaceuticals Benefits Scheme from 1 June 2018 (27), meaning patients pay less than AU$40 per script. However, in August 2018, Britain's healthcare cost agency (National Institute for Health and Care Excellence; NICE) deemed Spinraza® too expensive, and its long-term effectiveness too uncertain, for routine use within the National Health Service [NHS; (28)].

Genetic Editing

Presently, a strong focus for precision therapies is on genome editing or engineering, with greatest emphasis on three genome-modifying techniques all harnessing programmable nucleases, which can be considered "molecular tools." These are CRISPR-Cas9 (clustered, regularly interspaced, short palindromic repeats—CRISPR; CRISPR-associated protein 9—Cas9); zinc finger nucleases (ZFNs); and transcription activator-like effector nucleases (TALENs). All of these nucleases have been translated to patient care to some degree.

TALEN engineered cells were first applied to patients with B-cell acute lymphoblastic leukemia (B-ALL) (29). Extremely promising trial outcomes led to the drug tisagenlecleucel (Kymriah®) gaining FDA-approval in August 2017, with further approval in May 2018 for use with large B-cell lymphoma (30–32). In the European Union, tisagenlecleucel was approved for B-ALL in August 2018, and less than a fortnight after, the NHS England made a commercial arrangement with the drug's maker Novartis to provide the drug to children with advanced leukemia (33).

In November 2017 as part of a phase 1/2 trial, the first human had ZFN gene editing tools injected into their bloodstream, in an attempt to treat the patient's previously incurable, rare metabolic disease [Hunter syndrome; (34)]. Other trials harnessing ZFN technology are also underway [e.g., severe hemophilia B (35), mucopolysaccharidosis I (36) and transfusion-dependent beta-thalassemia (37)]. Multiple enticing reports have emerged of success from CRISPR-Cas9 application for disease treatment, prevention or reversal in preclinical models, e.g., with mouse [e.g., embryo (38) and postnatal (39) delivery], and dog (40) models of Duchenne muscular dystrophy. However, the first description of CRISPR-Cas9 gene technology used to correct human embryos (41) with genetic mutations causative of hypertrophic cardiomyopathy has been controversial (42). Yet current clinical trials harnessing CRISPR-Cas9 gene editing technology in adults include those for advanced esophageal cancer (43); leukemia and lymphoma (44); transfusion-dependent beta-thalassemia (45); and relapsed refractory multiple myeloma, synovial sarcoma, and myxoid/round cell liposarcoma (46).

New therapies such as these offer efficacious treatment options to patients with serious, rare conditions, when previously there were none. However, based on current prices, it is unlikely that these diagnostics and therapeutics present viable options to patients or their families, especially on an ongoing basis. Therefore, patients are reliant on governments and health insurers to cover the majority of the cost. Policymakers need to carefully evaluate the test or treatment's affordability, whilst appreciating the additional advantages it might bring to an affected person and the wider population. Additionally, balance is needed when deciding on the pricing of therapeutics to ensure access to excellent health care for patients, whilst also supporting biopharmaceutical innovation and investment into new therapeutics.

DECISION-MAKING APPROACHES FOR MAXIMIZING POPULATION HEALTH

In publically funded healthcare systems two broad priorities for decision-makers are "to do the most, for the most" (47), and to "reduce health inequity" across the population (48). Within the constraints of finite resources, the maximum number of people should receive the maximum benefit from the health programs and therapeutics that are publically funded. In other words, this is the "*n of many*" approach for optimizing population health outcomes. However, decision-making should not exacerbate existing health disparities and targeted investment is often required to address health inequities that emerge through societal mechanisms, including healthcare decision-making mechanisms. To assist with this, decision-makers rely on tools to allow for transparent, fair and reproducible decisions to determine which programs and therapeutics should receive public investment.

The economic evaluation of healthcare initiatives allows decision-makers to evaluate the cost of providing an intervention or therapy, and determine what the outcomes will be if that particular therapy or program is chosen over another (49). In short, it allows decision-makers to seek which outcomes can be "purchased" for the population and at what financial cost. Crucial to this paradigm is the need to evaluate which benefits to the population are foregone when one intervention is chosen at the expense of another (the "opportunity cost") (50). Ultimately, cost thresholds that determine which programs or therapeutics will be funded are somewhat flexible. However, in situations where interventions are costly or where there is a lack of available evidence for utility or cost-effectiveness, there is a greater reliance on other tools for decision-making, such as the determination of social values and the influence of the political agenda.

The incorporation of social values into decision-making is less defined than economic evaluations, given the inability to attribute a standardized weighted value to social concepts. However, research has occurred to quantify social preferences, although these methods are as yet not widely adopted (49). Examples of such social concepts include whether an intervention targets a population of unmet need; whether the intervention satisfies the "rule of rescue," i.e., patients for whom there is no other therapeutic option, or whether the program may target a population considered at higher risk such as lower socioeconomic groups. It is for such patients that standardized health care decision-making paradigms become challenged.

An additional consideration for decision-making in the event of unfavorable economic evaluations is the inability to attribute value to political goals for health care, which may catalyse innovation incentives and funding for conditions on the political agenda (51). Uncertainty of leadership, changing agendas and political factions can lead to the reliance on political will, which is arguably the most volatile tool for decision-making. While the window of political will is open, health systems could proceed with haste to sustainably integrate new methods into the delivery of healthcare to better the health of the population.

Therapeutic efficacy and outcomes used in economic evaluation and decision-making are traditionally determined through the results of large randomized controlled trials (RCTs) or systematic reviews of RCTs. Given the reliance of decision-making on large numbers of participants in RCTs, this presents a disadvantage for conditions and populations in which large numbers are difficult to achieve, such as has occurred for patients with rare diseases and uncommon cancers (52). In these situations it is difficult to generate enough data in support for the public funding of therapeutic agents, often leaving this subset of patients without the same therapeutic options as patients with more common conditions (53). This scenario fails the goal of equity of access to care, as a disparity will exist when only those who can privately afford these treatments are able to access them. In the oncology patient population, particularly for those with rare and uncommon cancers, or common advanced cancers where therapeutic options have been exhausted, the cost of an intervention may be high, the outcomes may be relatively poor, and the evidence base may be minimal (54, 55).

Although major challenges still exist with translating precision therapies and companion tests from bench to bedside, such as minimization of off-target effects, cytotoxicity, and immunogenicity, a new frontier in medicine is emerging. In theory it is possible that precision medicine approaches such as gene therapies and gene editing will eventually be capable of targeting most, if not every monogenetic disease. Whilst a suite of underlying technological platforms and their delivery routes could be a common base across most therapies, they could be made bespoke by using specific modifications dependent on the genetic variations, such as different guide RNAs in the case of CRISPR-Cas9 approaches. In such a scenario, not only may precision medicines be designed for small subsets of the population (such as those with a very rare disease), they may indeed be so precise that they are tailored to genetic variations unique to a single family or indeed only to one individual, e.g., an *n of 1*. In this context, traditional decision-making paradigms are challenged, because many population health decision–making approaches, as well as medical research funding models, rely on demonstrating the relevance of interventions to the broader population.

With potentially infinite combinations of therapies and interventions likely to arise from this precision approach, how can we continue to approach healthcare decision-making in a standardized way? In particular, how can this approach provide assurance that therapies are safe (e.g., safety data) when we are facing an infinite number of therapeutic combinations? Additionally, gene editing approaches are likely to be ineffective if applied to individuals without the targeted genetic variant/s, or indeed may create disease through their action. Consequently, efficacy within cells derived from affected patients, or preclinical models created with the same genetic variants, will be necessary yet labor- and cost-intensive. If we require data on safety, efficacy, and economic efficiency for every permutation of therapeutic agents available to precision medicine, how can we best integrate this emerging knowledge at a population level? A similar scenario to that seen for patients with rare diseases is likely to play out for precision medicines unless concerted effort is directed toward equitable and efficient processes.

Many of the lessons learned and approaches used to combat healthcare equity issues in the field of rare diseases and population health will become increasingly important in the move to precision medicine approaches. These lessons include aggregation of individuals or small population cohorts into larger cohorts with specific shared needs, international collaboration and sharing of expertise; appropriate disease coding; global data sharing and federated patient registries that facilitate global clinical trials and research projects; and targeted social policies and legislation to encourage investment in and access to therapies for small population groups. Moreover, there are additional challenges to be overcome that will require large-scale systemic change and will benefit all individuals, not just those with rare diseases. This will require a cohesive and collaborative population-based approach driven by ethical decision-making approaches.

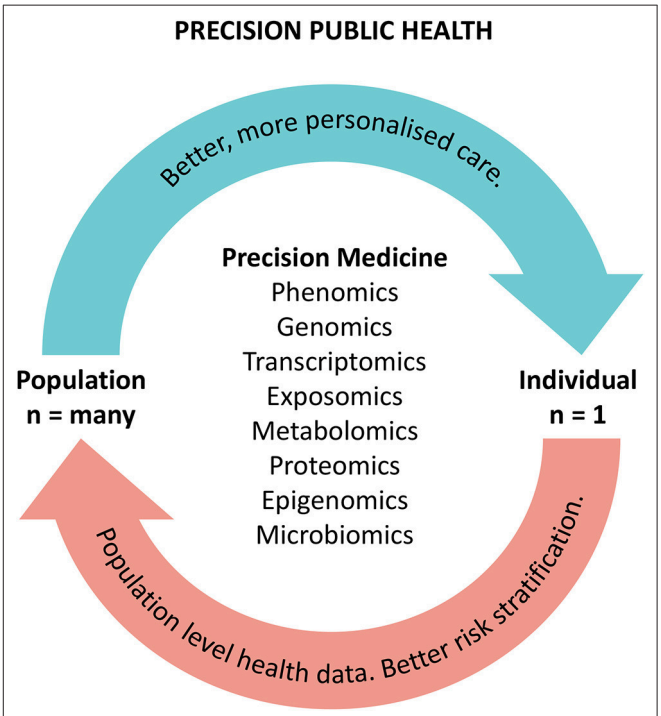

FIGURE 1 | The precision public health cycle. The cycle illustrates the benefits of precision approaches to improving patient care and population health.

LEVERAGING PRECISION MEDICINE FOR PRECISION PUBLIC HEALTH

These authors believe the solution in reconciling the *n of 1* with the *n of many* approach for precision medicine and public health respectively lies within using precision medicine technologies to more accurately identify and define population cohorts, through increased understanding of the underlying causes and biological pathways of disease and health. That is, improved molecular understanding of disease and the underlying biological pathways create new knowledge that unlocks opportunities for discovery and re-aggregation of patient cohorts. The benefits of this approach include drug repurposing, new therapies, and stratification into new clinical pathways. Aggregation of population cohorts based on commonalities in biological pathways could therefore unlock efficiencies in diagnostic and therapeutic approaches and improve equity of access to precision medicines. A highly functioning PPH system will deliver benefits from technologies such as better collective understanding of phenomics, genomics, and other "–omics" (such as proteomics, metabolomics, and exposomics) to enable more precise care for individuals. Crucially, our understanding of individual pathologies and biological pathways will also unlock data and knowledge for our population, allowing a PPH approach (5, 56) (see **Figure 1**).

There are a number of key enablers that will be important in applying a PPH approach to integrating precision medicine for populations. One of these enablers is precise, accurate and timely data with digitally-enabled health information systems. Big data drawing on all of the collective learnings from individual precision medicine applications can be utilized to inform decisions around how precision therapies can be delivered on a population level. This is a cyclical feedback loop where big data captured through PPH can then lead to better and more precise individual therapies, resulting in better health for both individuals and populations.

Globally, initiatives such as the "All of Us Research Program" in the USA that is collecting data from one million volunteers, are moving toward integrated data collection to better inform public health system initiatives and precision medicine (57). Such data include information about genomes, societies and behaviors to add insight into the prevention and treatment of disease, whilst also hoping to uncover new ways to reduce health disparities (58). Similarly in the United Kingdom, the 100,000 Genomes Project was established to develop the infrastructure and workflows to enable clinical whole genome sequencing on a grand scale. This project focuses on patients and their families with rare diseases, and patients with cancer, and not only links with research and provides longitudinal data, but also expedites molecular testing as part of NHS clinical care (59). These large-scale national collaborations are leaving a legacy of capability, with workflows and technology being established to enable precision medicine to occur on a scale that will inform better healthcare delivery for all. Importantly, embedding this kind of technology into public health information systems will ensure that the values of equity and access are upheld.

Decision-makers and government may tackle some of the more unique ethical issues surrounding precision medicine approaches through the use of expert forums or working groups. Such groups could develop guidelines and processes

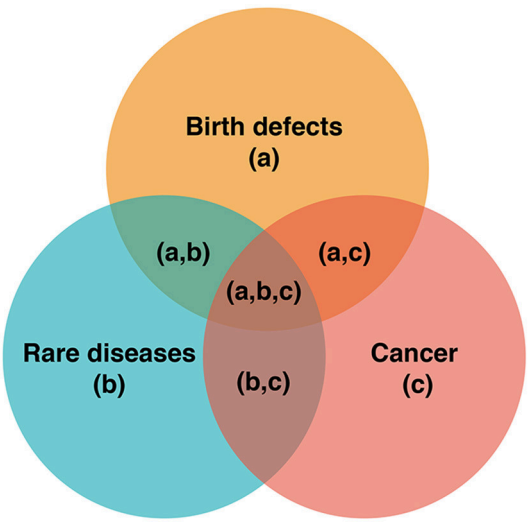

FIGURE 2 | Pathways, intersections and precision medicine. The intersections of (a), (b), and (c) represent opportunities for better risk stratification, surveillance, and therapeutics. For example, understanding the biological pathways resulting in the intersecting pathologies at (a,c), (a,b,c), and (b,c), can facilitate improved cancer surveillance (e.g., cancer screening).

BOX 1 | Case study 1. Biological intersections: insights from the *n of 1* unlocking knowledge for the *n of many.*

Collaborative international knowledge sharing helped discover the pathogenic gain-of-function variant in the mammalian target of rapamycin (*MTOR)* gene in multiple affected children presenting with birth defects from the same Aboriginal Australian family. This rare disease is now referred to as MINDS syndrome (macrocephaly intellectual disability neurodevelopmental disorder-small thorax syndrome), reflecting its multisystem nature and its associated components. MTOR is a critical component of the RAS-MAPK pathway and is also at the intersection of other biological pathways implicated in birth defects, rare diseases and cancer. Based on the phenotype of the affected Australian children, and the new and definitive knowledge of the underlying biological pathway, the children were anticipated to be at an increased risk of cancer and therefore placed on a new clinical pathway (tumor surveillance for intra-abdominal tumors of the solid viscera). Also, drug repurposing (MTOR inhibitors) became a possible treatment option for (pre)-cancerous lesions as well as neurocognitive endpoints. Subsequently, other families with the same syndrome were described, including one with early onset bowel polyps (73) that were managed by colonoscopic removal and surveillance; this has now become a risk management option for other families with this condition. The affected children have a characteristic facial phenotype and 3-dimensional facial analysis has been used to monitor MTOR inhibitor therapy (74), perhaps suggesting a new objective monitoring tool (75) for this and other families with MTOR-associated, and biologically related, conditions.

around the use of precision medicine that reflect societal values and the specific needs of the community. To truly unlock the potential for precision medicine approaches to transform the health of the population, participation and engagement of the community and the public is imperative (60, 61). The community voice must drive the PPH movement through understanding the community's priorities for action, as well as understanding and responding to barriers of engagement.

Even with favorable economic evaluations, supportive social values and an advantageous political agenda, the integration of precision medicine into the healthcare system will require foresight to ensure systems and processes are in place for sustainable and equitable delivery. Countries without the computational or data infrastructure to support the collection and analysis of large datasets will require investment in these areas. The additional workforce expertise and workflows created with new clinical pathways will require collaboration and global data sharing, mapping and monitoring to ensure longevity. Such workforce considerations include enhancing the understanding of precision medicine and genomic literacy of the healthcare and public health workforce (62, 63), and investment in laboratory technology and bioinformatics expertise (64). In addition, leveraging the expertise of data scientists and upskilling public health practitioners to utilize big data will be necessary to ensure that precision approaches are translated successfully into public health programs.

The examples of uncommon cancers and rare diseases exemplify some longstanding issues that will be faced increasingly as precision medicine is applied more broadly to population health through other fields, such as pharmacogenomics, precision psychiatry, or microbiomics. As with rare diseases, large, national and often international collaborations will be required to enable robust efficacy and economic evaluations to guide healthcare decision-making and investment in the precision era. In this era, multi-sectorial research perspectives, including health economics and health services research and approaches, must collaborate and evolve alongside therapeutics to ensure effective translation of research efforts into equitable public health initiatives (65).

Population-level data and knowledge will enable population-based public health programs that accurately identify and stratify population cohorts and will in turn enable greater benefits from precision medicine for all individuals. PPH acknowledges the possible inefficiencies in targeting whole populations in the same way for particular health outcomes, instead embracing the possibilities that advances in technology, genomic and other "-omics" knowledge and data capability may lead to more efficient allocation of healthcare resources to better target populations in need (66). A recent example where a new approach has improved outcomes for a patient population was demonstrated in an RCT of the use of pharmacogenomics testing to guide prescription of therapeutics in patients with major depressive disorder. In this patient population, response and remission outcomes were

BOX 2 | Case Study 2. Translating precision knowledge at the population level to better identify and stratify public health programs.

Cancer is amongst one of the leading causes of death globally, with a growing burden predicted to produce >18 million new cases of cancer and almost 10 million cancer deaths worldwide in 2018 (76). A significant proportion of mortality and morbidity from cancer is due to late diagnosis, when surgical and pharmacologic therapies are less effective (77). Therefore, timely identification of cancer can be crucial and highly beneficial, detecting cancers before they spread, and allowing precision medicines to be delivered as early as possible.

Due to this knowledge, cancer screening programs have as their aim the detection of cancer before it has developed or before symptoms arise. Current population-based cancer screening programs have target demographics based on age and/or sex [e.g., the national bowel, breast and cervical cancer screening programs in Australia (78)]; with the success of these programs recently described (79). Yet how might such screening programs be improved to better mitigate the growing cancer burden, and how might screening programs for other as yet unscreened cancers be developed? Is it possible to stratify populations beyond traditional groupings such as age and sex; are there emerging tools to detect the currently screened cancers earlier than the methods presently utilized; can emerging tools detect types of cancers that have previously not been effectively detected at an early stage; and once a person is identified with a cancer, how can the best therapy for them be known and then accessed? In other words, how can precision medicines be most effectively delivered to all those in the population who require them?

To address the great need to detect, diagnose, prognosticate and monitor cancers, accurate biomarkers have been extensively studied, with a focus on non- or low-invasiveness. Cell-free tumor DNA, created from apoptotic or necrotic tumor cells, or circulating tumor cells, has become a promising target for liquid biopsies (e.g., blood, urine, semen). Promising results have been achieved with the application of liquid biopsies for detection, therapy response and prognosis in clinical oncology [reviewed in (80)], for a range of cancers including pancreatic (81, 82), Ewing sarcoma and osteosarcoma (83), urothelial (84), lymphoma (85), and other hematological cancers (86). Some assays are able to detect multiple cancers, and prospective, multi-site observational clinical trials are ongoing (e.g., The Circulating Cell-free Genome Atlas Study; NCT0288978). CancerSEEK has a specificity >99% for eight different cancer types in asymptomatic individuals and a sensitivity range of 69–98% for five cancers with no existing screening tests for the general population (87). However, health economic evaluation of liquid biopsies is still in early stages (88).

Could liquid biopsies be integrated into current population-based cancer screening programs to provide even earlier detection of these cancers? Moreover, could there become a single, population-based cancer screening program able to detect a range of cancers with the same test, and indeed using a test that is easily and widely usable (e.g., even in remote regions with no specialized equipment)? Additionally, could it be possible to further stratify a target population to allow more tailored screening frequencies, so that those with a greater risk (e.g., those who have tested positive by oncogene panel testing; those with known high environmental exposure) are more frequently screened than those at less risk? A precision approach such as this is already being implemented for cervical cancer screening in Australia, with results from a human papillomavirus (HPV) test informing risk stratification of participants into different screening pathways.

Universal access to early diagnosis and subsequent accessibility to appropriate treatment for cancer is critical. A PPH approach to this problem would incorporate evidence-based technological advances, big data collection and analysis, and public health paradigms to ensure equity and effectiveness. The aim would be to facilitate everyone within a population (the *n of many*) receiving appropriate screening methodologies (both test type and test frequency) to detect the largest possible range of cancers at the earliest phase, and then offer all people with cancer the precision medicine most suited to them (the *n of 1*).

improved when pharmacogenomics testing assisted prescription of anti-depressants compared with standard care (67).

The aggregation of smaller datasets to demonstrate the efficacy of a precision medicine approach (such as molecular tumor sequencing for all oncology patients) rather than focusing on individual subtypes and novel agents, may mitigate the hurdle of small patient numbers preventing the individual demonstration of economic efficiency. New transformative trial designs have been developed to address the challenges of assessing the efficacy of precision therapies, which target the molecular profile of a disease. Basket trials are an innovative clinical trial design for evaluating targeted therapies across different tumor types through grouping patients based on molecular markers independently of their tumor histology (68). An alternative approach is the umbrella trial where patients with the same tumor type are assigned to different treatment arms based on molecular markers (69). Furthermore, adaptive trial designs provide more efficient mechanisms for assessing precision medicine therapies, through changing key components of the trial design during implementation, while retaining its scientific validity. This allows multiple research questions to potentially be answered at once, meaning that multiple precision therapies can be assessed at once (70). The design of an adaptive trial evolves dynamically based on the efficacy data collected during the trial; randomization ratios can be changed, treatment arms can be dropped and/or added and a biomarker selection strategy can be changed even when treatment assignment remains the same (71). Adaptive trials have the potential for decreased time to completion, reduced resource requirements and number of patients exposed to inferior treatments, and overall likelihood of trial success (72).

A broader example of the PPH approach, which bridges precision medicine and public health, is the discovery of overlap in understanding of birth defects, cancer, and rare diseases, such that previously distinct disciplines now intersect (see **Case Study 1**, **Figure 2**). While individuals with such conditions were previously categorized into three different disease groups, new knowledge from precision medicine allows better stratification of risk (e.g., the risk of an individual with a rare disease going on to develop cancer), new surveillance pathways, and new therapeutic options for identified patients. Better understanding of the pathogenesis of diseases within these three areas translates to better, more precise healthcare for patients with birth defects, cancer, and rare diseases. This new knowledge can be utilized to aggregate populations, better targeting health initiatives and fulfilling the PPH paradigm. Not only are there intersections for birth defects, rare diseases, and cancer, there is also an opportunity to identify more targeted prevention and surveillance based on more accurate knowledge of disease risk profiles (see **Case Study 2**).

CONCLUSION

Genomics and other-omics knowledge and technologies are transforming the way healthcare can be delivered through greater understanding of disease detection and therapeutics. Responsible decision-making in the climate of escalating healthcare costs is required to ensure that precision medicine can be properly tested on a scale to determine if this approach will lead to better patient outcomes. Additionally, traditional decision-making paradigms must be agile to the precision medicine approach to ensure knowledge and discovery can be translated effectively and efficiently for better patient care. Subsequently, decision-makers must determine if the goals of PPH can be met by equitably harnessing precision medicine approaches such that the right healthcare is delivered to the right population, at the right time, and in the right place.

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GAB conceived the paper concept. All authors drafted the manuscript, provided critical input and approved the final manuscript version for submission.

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REVIEW
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Healthcare System Priorities for Successful Integration of Genomics: An Australian Focus

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This paper examines key considerations for the successful integration of genomic technologies into healthcare systems. All healthcare systems strive to introduce new technologies that are effective and affordable, but genomics offers particular challenges, given the rapid evolution of the technology. In this context we frame internationally relevant discussion points relating to effective and sustainable implementation of genomic testing within the strategic priority areas of the recently endorsed Australian *National Health Genomics Policy Framework*. The priority areas are services, data, workforce, finances, and person-centred care. In addition, we outline recommendations from a government perspective through the lens of the Australian health system, and argue that resources should be allocated not to just genomic testing alone, but across the five strategic priority areas for full effectiveness.

Keywords: genomics, technology, genetic testing, Australia, healthcare, health system, policy framework, equity

INTRODUCTION

Genomic testing applications across the human life cycle are continually developing. Genomic testing in healthcare includes the testing of specific genes (technically "genetic testing") as well as the sequencing of entire genomes and the incorporation of genomic information into disease risk. The use of genomic information to inform healthcare is becoming increasingly common. Associated with these emerging technologies is the potential for growth of prognostic, predictive, diagnostic, and pharmacogenomic testing and screening, which can have relevance at multiple life stages (1). However, access to and governance of these potentially beneficial testing applications varies, with some already being embedded into national, publicly funded health systems while others are offered only in some jurisdictions, only in the private sector or directly to consumers.

Given the advent of genomic testing within these diverse health settings, leadership and coordination is required to ensure the safe and equitable delivery of genomic testing both within and across governmental borders. In the context of the decreasing cost of genomic technologies and their increasing relevance to healthcare, many countries have been restructuring their clinical genetics services to prepare for increasing demand (2–4). International collaboration and communication will be important in order to leverage the lessons learned around sustainable and equitable integration of genomic technology internationally (5). This is particularly true for some of the more universal issues in genomics, such as the availability and implementation of comprehensive and relevant genomic reference databases (5). The successful leveraging of genomic technology to improve healthcare will require a widespread, cohesive and collaborative approach.

Herein, we describe necessary aspects for countries to consider for enabling optimal harnessing of genomic technology for healthcare. We do this by framing discussion around the Australian healthcare system (described in **Box 1**). Australian governments recently developed the *National Health Genomics Policy Framework* (NHGPF) (10) in recognition of the need for a collaborative approach to the utilisation of genomic technology across the health system. The NHGPF was developed in consultation with the general public and various other stakeholders. The framework was endorsed in November 2017 by the Council of Australian Governments (COAG) Health Council, and delivers a strong and coherent structure from which to coordinate activities across jurisdictions. This framework also represents a shared commitment to implement genomic technology into health systems for the benefit of all Australians. The vision of the NHGPF is "helping people live longer and better through appropriate access to genomic knowledge and technology to prevent, diagnose, treat and monitor disease" (6, p. 5). The mission of the NHGPF is "to harness the health benefits of genomic knowledge and technology into the Australian health system in an efficient, effective, ethical and equitable way to improve individual and population health" (6, p. 5). The NHGPF represents the first national collaboration for health genomics at the whole-of-government level in Australia.

The NHGPF reflects that for any country to achieve a health system that effectively integrates advances in medical technology such as genomic testing, consideration needs to be given to how to facilitate transparent decision-making, equitable access, provision of a suitable workforce, and effective services that can undergo expansion and redesign (11). This must occur with the support of rigorous assessment of evidence (12) and adequate infrastructure, and in a financially responsible and sustainable manner (10). Successful implementation of expanded genomic medicine services will also take into account the genomic literacy of the whole population, including the nuances of social and cultural norms around the acceptance of genomic information in healthcare (13). These requirements are outlined in the NHGPF's five strategic priority areas of services, data, workforce, financing, and person-centred care.

For countries to ensure universal access and equity of appropriate healthcare are met, an overarching national framework such as the NHGPF for genomics decision-making is necessary. However, governments, as well as local health service providers, must support such a framework to ensure effective, safe and equitable implementation of genomics into health services (3, 10). In this context, we outline some of the key activities for governments based on the five strategic priority areas outlined in the NHGPF, in relation to sustainable integration of genomic testing in healthcare.

GENOMIC SERVICES

Government health departments have a responsibility to ensure that genomic tests supplied in their health system are safe and effective for the target population. Genomic testing involves not only a laboratory testing component, but involves associated upstream and downstream services including information provisioning, counselling, interpretation of test results, and clinical decision-making. Implementation of genomic testing into a health system therefore requires consideration of these additional services in alignment with evidence-based best practice. In addition, implementation of genomic testing should be nationally consistent to ensure that all patients have access to the same high quality care. This will require appropriate governance and guidance around safety and quality of services, development of nationally consistent guidance, inter-jurisdictional and international coordination, rigorous processes for assessing the utility of genomic tests, transparent decision-making and timely monitoring and evaluation.

The importance of governance of genomic technology in Australia was recognised more than 15 years ago, when the Australian Government commissioned an inquiry into the use of genomic information. The inquiry was conducted by the Australian Law Reform Commission and the National Health and Medical Research Council (NHMRC). The initial outcome of the inquiry was a report entitled *Essentially Yours: The Protection of Human Genetic Information in Australia* (*Essentially Yours* inquiry) (14). Some of the most relevant recommendations from the inquiry related to the regulatory framework around access to genomic testing, and ensuring privacy and security of genomic information. Changes resulting from the inquiry included amendments to the *Therapeutic Goods Act 1989* to consider all genomic tests, including predictive tests, as *in vitro* diagnostic devices that are regulated by the Therapeutic Goods Administration. These legislative changes ensure that standards around the quality, safety and efficacy of genomic tests are met before supply by pathology laboratories.

Another key recommendation was the formation of a "Human Genetics Commission of Australia." The government response at the time was to create a principal committee of the NHMRC, namely the Human Genetics Advisory Committee, who were responsible for implementing the recommendations. The Committee developed national guidelines on genomic testing in medical practice (2010), direct to consumer genetic testing (2014) and translating complex "-omics" tests into healthcare, including genomic tests (2015) (15–17). However, the principal committee was ceased in 2015. Functions of the proposed Human Genetics Commission that remain highly

BOX 1 | The Australian health system and the funding of health-related genetic and genomic testing.

The Australian health system is unique. Six State and two Territory Governments, along with the Commonwealth Government are responsible for different aspects of healthcare delivery to citizens, coupled with both public and private healthcare arrangements (6). The Australian health insurance agency, Medicare, provides government funded universal access to healthcare for all Australians. Through this system, specific tests and treatments that have been approved for a Medicare Benefits Schedule (MBS) rebate are provided to patients at no direct cost.

In addition, people can augment their healthcare with privately paid health cover. However, through this private system there is no guarantee that any additional diagnostics and treatments are covered. Health insurance can allow for patients to choose their specialists and healthcare facility, and the agency covers many of these fees. However, insurance companies generally only subsidise genomic tests when a patient is admitted to a hospital, and only if these tests are already covered by the MBS. In 2016, the cost of Medicare-funded genetic and genomic tests was AU$43.5 million, with the value having increased by 24% since 2012 (7). This funding accounts for fewer than 30 genetic and genomic tests, in contrast to the approximately 1,700 such tests that are currently performed by laboratories in Australia (8) at a cost to State or Territory Governments, private healthcare providers, or consumers. Currently, there is no systematic data collection that identifies which tests are funded through these various sources. Perhaps it is due to the extensive process involved in applying for MBS funding for genomic tests and the rapid development of such tests that many are not funded through Commonwealth Government channels. Similar fragmented provision of genomic services occurs in Canada (9).

relevant for the governance of genomics in the healthcare sector, include (i) providing on-going advice on emerging issues; (ii) development of policy statements and national guidelines; (iii) identifying genetic tests that require special consideration; and (iv) developing practice guidelines for genetic counselling and genetic testing. These functions should be re-considered under the new NHGPF to guide implementation of genomic testing in healthcare, considering the changes in the regulatory landscape that have occurred since the inquiry.

Governance and Decision-Making Around Genomic Tests

There is a standardised process in Australia for assessing the safety and quality of tests when applying for public funding through the national health insurance scheme, Medicare. For a test to qualify for public funding through the Medicare Benefits Schedule (MBS) an application has to be made to the Medical Services Advisory Committee (MSAC) and the test included on the Australian Register of Therapeutic Goods. The MSAC evaluation process is robust and extensive and involves an assessment of the clinical validity, clinical utility and cost-effectiveness of the test (18). Although many of the safety and quality issues for genomic testing are similar to other types of medical tests, some issues are intensified in the case of genomic testing, and issues may differ depending on the target population or purpose of the test (1). For example, a genomic test may be less effective for population-based screening compared to use as a diagnostic test in a symptomatic individual (1, 19). Therefore, additional guidance and different kinds of evidence may be required around the appropriateness of genomic testing for these and future purposes (20, 21).

Specific evaluation models have been developed for assessing genomic tests, such as the ACCE model developed by the United States of America (USA) Centers for Disease Control and Prevention (CDC) (22). The ACCE model incorporates Analytical validity, Clinical validity, Clinical utility and Ethical, legal and social implications (23). A similar approach was adopted by the United Kingdom (UK) Genetic Testing Network. This concept has also been built on through the CDC's Evaluation of Genomic Applications in Practice and Prevention system for assessing genomic tests. Key learnings from these exercises include the difficulty associated with the heterogeneity of genomic tests, and the importance of defining the purpose of the test. MSAC is currently piloting Clinical Utility Cards to assess genomic tests for predisposition to disease (24). These are based on the Clinical Utility Gene Cards developed by EuroGentest, which in turn were based on the ACCE model.

However, only a small percentage of currently available genetic and genomic tests have been approved so far through the MSAC process, with the remainder funded directly by other parties (see **Box 1**). If tests are not approved through MSAC, there are a variety of ways that people can still access tests, including direct out of pocket payments, use of health insurance (at the discretion of the insurer), ordering of the tests by clinicians in public facilities with standalone budgets (such as major hospitals) and/or via research programs or clinical trials. The arrangements for these non-MSAC approved tests differ widely across Australian states and territories, are confusing for patients to navigate, and cannot be summarised simply. In **Box 1**, we provide examples of some existing insurance and payment options to highlight the fragmented nature of the system.

This complex approval process is not unique to Australia; internationally, genomic tests typically take a long time to be incorporated into clinical practice (25). This lag in or lack of approvals for genomic tests may be associated with several factors, including (i) the difficulty in gathering sufficient translational evidence, particularly for tests that only have clinical utility for a small number of patients (21, 26); (ii) the limitations of the indication-specific approval process in the context of rapidly expanding uses for genomic tests (21); (iii) the fact that sometimes a genomic test is not currently required for adequate clinical care; and (iv) the fact that some genomic tests have more personal utility than clinical utility (1, 20). This can be particularly problematic when genomic diagnostic tests are needed to inform novel treatment options for individuals with no existing treatment options or rapid progression of disease (1). Complementary governance frameworks, additional to existing assessment and approval processes, might be necessary to ensure that genomic tests can be evaluated and funded in a timely manner.

National and International Coordination and Standardisation

Given the large number of genomic tests that are funded outside of the MBS, coordination and standardisation across jurisdictions is critical for ensuring transparent and equitable decision-making around genomic testing, whilst accounting for local differences in infrastructure. Coordination across states and territories will enable pooling of expertise across jurisdictions, which is particularly important for providing services to people living with rare genetic conditions. Strategic investment into translational research to inform assessment of the benefits and harms of genomic tests for specific population cohorts is required (27–29). In particular, this will help to expand the benefits of genomic technology to different population groups, beyond rare genetic conditions to more common conditions. National networks that identify specific (e.g., gene-, disease-, and/or technology-specific) genomic testing hubs and facilitate coordination of evidence gathering could improve the speed of translation of new genomic tests into clinical practice. Many of these networks already exist in Australia, such as the Australian Genomics Health Alliance (AGHA) and the recently announced Australian Genomic Cancer Medicine Program (30–32). These research collaborations aim to bring together separate parties working toward the same goal, being equitable and effective genomic healthcare for all Australians.

International coordination of genomics policy, particularly in public health, was recognised recently at an international meeting of experts (33). A recent survey of European Union member states revealed that 63% had a policy on genomics in healthcare and 83% of those with a policy had developed specific guidelines (33). In 2018, 13 European countries declared that they will cooperate in cross-border sharing of genomic data, through sharing of infrastructure and expertise (34). A similar international model already exists to help find a diagnosis for people living with rare genetic conditions, the Matchmaker Exchange (35). These international models involve the alignment of policies, data sharing agreements and interoperability of data systems, through federated networks that preserve data governance arrangements for members.

Similar models could be developed across State and Territory Governments to achieve coordinated clinical implementation of genomic testing and ensure equity, sustainability and maximisation of benefits from genomic healthcare initiatives within the public health system. To date, although State and Territory Governments fund many genomic tests, there has been no formal mechanism for governments to strategically coordinate investment to support the implementation of genomic testing in health systems. This means there is an opportunity for further standardisation of decision-making around genomic testing under the NHGPF (36), that works with and complements the existing processes. Consistency in the implementation of genomic testing across the health system is important to ensure all patients receive access to the same high quality healthcare. In Australia this could be achieved through a mechanism to develop standardised policies and/or guidelines aligned with the NHGPF; however this will require further commitment at all levels of government and appropriate engagement with key stakeholders.

In Australia, some other pathology tests are funded by State and Territory Governments, such as the biochemical tests used for the Newborn Bloodspot Screening Programs. Australian jurisdictions have recently developed a *Newborn Bloodspot Screening National Policy Framework* [NBSNPF; (37)], which aligns with the *Australian Population Based Screening Framework* (38), and includes a decision-making framework for the addition or removal of conditions, including specific criteria relating to genetic tests. Similar national standards in relation to the development and implementation of other genomic services and population genetic screening programs may be required in those situations where tests are funded by State or Territory Governments or where different evaluation models are required. Such national guidance was one of the recommendations from the *Essentially Yours* inquiry, although this is yet to be realised. The development of these standards could benefit from learnings from the process undertaken to develop the NBSNPF and the ACCE model.

Classification of Genomic Tests to Inform Service Planning and Streamline Governance

A purpose-based classification of genomic tests may help to identify those test types that require specific evaluation approaches, specific expertise (e.g., genetic counselling) or specific upstream or downstream services. Identifying similarities among certain categories of genomic tests may help to streamline the governance and evaluation processes (26, 39). A classification process could also inform the development of national guidelines on what kinds of genomic tests should be provided in a health system and by whom (40). This may include the development of a register of approved uses for genomic tests that can be updated over time and inform guidance for healthcare providers (41). Information on such a register could be utilised to increase the awareness of non-geneticists about genetic testing options and communicate who can order specific tests. This kind of approach has been adopted in the UK through the UK Genetic Testing Network, which promotes equitable access to high quality genomic testing across the UK (42).

Horizon Scanning, Monitoring, and Evaluation

A key function of government health departments that could guide the development of genomic policy is the ability to monitor genomic testing usage within health systems. Together with appropriate horizon scanning, the ability to monitor genomic test usage will facilitate the provision of on-going advice on emerging issues. Such a process will help to identify which genomic testing applications are likely to change practice in the immediate and short term to inform key action areas for implementing system-wide change. Although there is a national process for assessing genomic tests for public funding in Australia through the MBS, this process does not involve on-going, routine monitoring to assess the usage and effectiveness of genomic tests. There is also limited evaluation of how genomic services are provided to ensure that healthcare providers comply with agreed

standards (16). Close monitoring and guidance around genomic testing is important for ensuring that the necessary infrastructure and workforce is available in the right areas, that genomic services are effective, and over-diagnosis and over-treatment are prevented (12, 43).

Evaluation of genomic testing should involve assessment of population health outcome measures including traditional measures such as reduction of morbidity and mortality, but also impacts on quality of life and reproductive decision-making (20). This function is currently limited in Australia due to a lack of national genomic testing reporting requirements. More robust and transparent data collection on genomic testing activity will allow governments and consumers to monitor and evaluate this part of the healthcare system, to ensure that the use of genomics is safe and equitable, as well as effective. Similar data could also increase our ability to assess the wider benefits of investing in genomic testing, through demonstrating the outcomes of knowledge translation from rare genetic diseases to more common, complex conditions (44). Evaluation is described as a cornerstone for the successful translation of genomics technology into healthcare practice, and is a key function of public health genomics (45–48).

Currently, governments are unable to measure or monitor direct-to-consumer testing usage and are limited in their ability to regulate this activity. Although consumers accessing personal genomic tests may be able to increase their health knowledge and take action to reduce their overall healthcare burden, there is evidence that some direct-to-consumer tests may be inaccurate or misleading and cause undue anxiety (49) or a false sense of complacency (50). There is a need to quantify how many consumers are accessing genomic tests directly through international channels, and determine the impact of this in the Australian regulatory and service planning context. This is likely to be a difficult task, and will require targeted research to survey the usage of direct-to-consumer testing by Australians.

GENOMIC DATA

Infrastructure to Support Data Storage and Sharing

The advent of new technologies has enabled rapid, massively parallel DNA sequencing and the production of enormous amounts of genomic data. This has occurred alongside reduced costs of sequencing, decreasing from US$3 billion for the first single genome, to around US$1,000 per genome in 2015 (51). Improved affordability of genomic sequencing enables more widespread accessibility (52), creating an urgent need for adjunct technologies for computation and storage to cope with the expanding demands (53). Until the early 2000s, advances in computation and storage were occurring faster than the ability to sequence DNA and store the respective data. However, with the introduction of massively parallel sequencing, for the first time the demands of genomic informatics out-paced existing models for computation and storage (54).

The cost of sequencing has also been halving every 5 months, much faster than the increases in informatics capacity, placing pressure on the existing genomic informatics ecosystem (54, 55). Genomic testing, particularly massively parallel sequencing, requires substantial computer processing infrastructure as well as bioinformatics expertise to both design the tests and translate raw genomic data into meaningful clinically relevant information (56).

Given the increasing use of massively parallel sequencing in clinical settings, it is likely that increased data storage capacity and developments in data sharing technology will be major enablers for the wider implementation of genomic testing in healthcare. In particular, data storage will be a key consideration for any proposed population-based genomic testing program, particularly any testing that produces a large amount of information (e.g., whole exome or whole genome sequencing). For example, even the data from the 1,000 genomes project in the UK has already reached 200 terabytes in size for just 1,700 genomes (57). Storage of genomic data in Australia is also governed by NPAAC standards, which require storage of certain data files such as interpreted or annotated variant files. Samples may also need to be re-analysed in the short term in order for testing laboratories to comply with the minimum regulatory standards. Recent developments in cloud computing technology are facilitating the collection, use and sharing of large datasets with reduced requirements for expensive data storage infrastructure (58, 59).

Anticipated data requirements will need to be considered for assessment of the minimum infrastructure needs for implementing a genomic test in the clinical setting. The growing application of genomic technology to all aspects of healthcare delivery suggests that the benefits of such technology in improving health are being increasingly recognised. Acknowledging the mismatch between current limitations for capacity of data storage and computation and our improving ability to create large volumes of genomic data, there is a necessity to address these limitations prior to implementation of any genomic testing, particularly at a population-wide level.

Governance and Privacy of Genomic Data

Apart from infrastructure requirements, the NHGPF also indicates a need for an appropriate level of governance around the collection, safe storage, and sharing of national genomic data (10). Privacy and security of genomic data are important issues, particularly since even a small amount of "de-identified" genomic information can become identifiable, due to the unique nature of an individual's DNA signature. In Australia, genomic information is considered to be sensitive and is protected for private health entities under the Commonwealth's *Privacy Act 1988* (Privacy Act), with each state and territory responsible for the privacy legislation and regulation for public health agencies. For genomic data obtained through research, compliance with the NHMRC *National Statement for Ethical Conduct in Human Research* is required to conduct research projects. Private health entities must adhere to the Australian Privacy Principles contained in Schedule 1 of the Privacy Act, which relates to transparent use, collection, disclosure, quality, security and access to personal information. Entities holding personal information must take reasonable steps to protect information from misuse,

unauthorised access, modification or disclosure. There are provisions in the Privacy Act allowing genetic information to be disclosed to family members in circumstances where this disclosure can prevent significant harm to the individual to whom the information relates.

While genetic information is defined as sensitive under the Privacy Act, Australia lacks adequate legislation to protect the privacy of genomic data and prevent genetic discrimination, compared to other countries. In the USA, the *Genetic Information Nondiscrimination Act of 2008* protects the genetic privacy of individuals by preventing insurers from requesting genetic information. Similarly, the European *Oviedo Convention on Human Rights and Biomedicine* (1997), the European Union *General Data Protection Regulation*, and the Canadian *Genetic Non-Discrimination Act* (2017) provide protections for the genetic information of citizens. In contrast, protection against genetic discrimination by life insurers in Australia is self-regulated by the life insurance industry (60). The absence of adequate protections for genomic information has implications for public trust in the collection, storage, and sharing of genomic data by government entities. This in turn may affect research opportunities and precision medicine initiatives enabled through national and international data collection and sharing.

The need for appropriate legislation and mechanisms to support the secure storage of genomic data was highlighted by the recent, controversial introduction of the My Health Record system in Australia. My Health Record is a national electronic health record for all Australians, except those who choose to opt out. This system is capable of storing genomic pathology reports; however, the decision to include genomic data on My Health Record was made without public consultation and seemingly without due consideration of the unique ethical issues pertaining to genomic information, given that this information is heritable in nature (61). Questions have arisen around the security of the system, as well as the ability of government agencies to access health records, and have raised concerns among health professionals and the public. A national, population-based electronic health record has enormous potential for furthering genomic research efforts. However, equally, a lack of transparency and appropriate consultation could permanently damage public trust and participation in the system. Therefore, further consideration is required around ethical issues and appropriate safeguards, as well as robust public consultation, before genomic data is uploaded onto the My Health Record system.

GENOMICS HEALTHCARE WORKFORCE

The current skillset required to deliver genomic healthcare is broad and varied depending on the application of testing. Generally, some or all of the following professionals may be involved: laboratory scientists, clinical pathologists, bioinformaticians, clinical geneticists, genetic counsellors, and non-genetics healthcare professionals. The genomics healthcare workforce must have adequate genomics literacy to know when to order genomic tests; how to interpret genomic tests to inform clinical decision-making; how to counsel patients on genetic conditions and genomic tests; how to obtain informed consent before a test or procedure; and how to ensure understanding and appropriate action following a test result or procedure (62). These aspects of genomic clinical expertise can be broadly categorised into two distinct domains: (i) clinical gatekeeping (ordering and interpreting genomic tests, including clinical utility), and (ii) counselling and consent.

Generally, genomic tests warrant a greater level of expertise than other medical tests and the provision of professional genetic counselling around medical decision-making, including reproductive options, due to the uncertain outcomes of testing and implications for genetic relatives. At the very least, the use of genomic tests requires a medical workforce that is confident undertaking appropriate genomic risk assessments and communicating this information to patients (62). However, the type of model for gatekeeping genomic testing, genetic counselling and seeking consent will depend on the characteristics of the condition/s being tested for and the test.

As was previously noted, the ability of Australian governments to predict demand for certain types of genomic tests is currently limited due to the lack of a national monitoring program. Nevertheless, there is evidence that the current model for ordering, interpreting and providing counselling around genomic tests is not feasible even if there was national agreement on their criteria (2, 63). This has been recognised for some time; for example, the *Essentially Yours* inquiry recommended that Australian governments "develop strategies to assess and respond to the need for increased and adequately resourced genetic counselling services" (14) and examine options for development of genetic counselling as a profession.

Training options are limited for potential counsellors in many Australian jurisdictions. Currently, genetic counselling is self-regulated, with counsellors choosing to become certified by the Human Genetics Society of Australasia (HGSA). In 2017, a working group of the HGSA was formed to explore the issue of regulation for this profession (64). A submission is being prepared to have genetic counselling professionally regulated through the National Alliance of Self Regulating Health Professions, which will facilitate consistency in practice and ensure quality in services.

Anecdotally, there is increasing demand internationally for complex genomic tests, particularly as part of population-wide screening programs (65, 66) and expansion beyond the diagnostic use of genomic testing to include screening and other uses (67). This is already putting pressure on expert genetic workforces (39, 68). In addition, with increasing use of somatic genomic testing in oncology, it is possible that more patients with germline mutations could be identified, requiring attention from clinical genetics centres (69, 70). In this context, how can we prepare the workforce for an inevitable increase in the use of genetic information in managing patient care? It may be necessary to reconsider current best practice approaches to delivering such care, by deconstructing the workforce requirements relating broadly to each type of genomic test. This may require a multi-pronged approach across the whole health system.

Clinical Gatekeeping

One approach to ensuring availability of an appropriate genomics workforce is to mainstream genomics education into the core of medical education (62). Online learning tools may help to increase access to genomic education and facilitate sharing of efforts nationally and internationally (5). Without appropriate education, there is a limited ability for non-geneticist specialists to know which patients could benefit from more complex genomic testing (12, 62, 71).

Alternative scenarios include general practitioners, specialist (non-geneticist) clinicians and even pharmacists directly ordering genomic tests from pathology providers to inform the clinical management of their patients (72–75). Nevertheless, genetic specialists have expressed concerns over the ability of non-genetic clinicians to order particular genomic tests, due to a potential lack of knowledge and understanding required for informed consent and reporting of results (75). Additionally, some genomic tests offered by international laboratories are available direct to consumers, often bypassing healthcare professionals as gatekeepers for decision-making (76). In certain cases, these companies require a referral or review of results by a doctor, but this may be a company employed doctor rather than an individual's personal doctor. A consolidated list of agreed uses for genomic testing in general practice or specialist settings could facilitate the mainstreaming of genomic tests, combined with the embedding of this guidance into workflows, such as the Health Pathways being developed by Australian primary health networks.

Certain uses for genomic testing may be more amenable to mainstreaming when compared to others. For example, once clinical utility can be agreed upon, it may be appropriate for non-genetics healthcare professionals to order certain tests, such as pre-conception, prenatal, and diagnostic tests and cascade screening tests for common conditions. This is already occurring with mainstreaming of hereditary ovarian and breast cancer testing (69, 77), and in Australia, tests for these conditions have recently been made available to be ordered by any healthcare practitioner under the MBS (78). Similar mainstreaming has occurred with many (non-genomic) medical tests, even to the point of direct consumer access (e.g., HIV testing) (79), although this remains controversial in many cases (80). However, mainstreaming of medical device use will take time, as adequate training of relevant members of the workforce will be required to ensure genomic testing occurs in a safe and appropriate way. For example, the Public Health Genomics Foundation in the UK has recommended the establishment of core competencies for ordering genomic testing (81).

In other instances, the involvement of genetic specialists may not be easily replaced. For example, clinical geneticists, clinical pathologists and bioinformaticians will continue to be required for testing associated with complex rare diseases and where whole exome or whole genome sequencing is being used with less targeted filtering applied for analysis. Given the dependence of implementing genomic technology on computer-based interpretation of sequence data, there is a need to ensure a suitably qualified bioinformatics workforce is in place to enable translation of this information into clinically meaningful results (47). Specific expertise is required to accurately interpret the information in a way that can inform clinical action to ensure the utility of genomic information in the clinical setting. Within Australia and internationally, there are examples of recognised super specialties and joint residencies and fellowships in genetics for paediatric, maternal-fetal and internal medicine specialties, and for cancer genetics and neurogenetics (62, 82). These all acknowledge the need for genomics expertise in particular settings.

Additional models for the gatekeeping of genomic testing exist, and these may need to be implemented into local programs (63). Examples include the increasing relevance of multi-disciplinary and interdisciplinary clinics, and coordination among health professionals in the diagnosis and management of patients with or at risk of genetic conditions (2, 4, 71). Multi-disciplinary teams have already been used as part of best practice for areas such as cancer genetics and rare genetic diseases (2), and are also being used in particular specialties such as cardiac, renal, liver, lung, and neurology clinics. However, particularly with gatekeeping around massively parallel sequencing technologies applied to whole exome or whole genome sequencing, and with increased demand for predictive and pre-symptomatic testing, multi-disciplinary teams may become increasingly necessary in other settings to facilitate reporting results back to individuals (3, 71, 75).

Counselling and Consent

Generally, genetic counselling is offered where individuals or their offspring are identified as being at higher risk than the general population of developing a genetic condition from a genetic or non-genetic (e.g., cholesterol) screening test, or due to family history. Traditionally the scope of practice has been focused on supporting people with certain Mendelian-inherited genetic conditions. According to the Australasian Society of Genetic Counsellors, genetic counselling is "a communication process, which aims to help individuals, couples and families understand and adapt to the medical, psychological, familial and reproductive implications of the genetic contribution to specific health conditions." Specific functions of a genetic counsellor include assessing risk, educating patients and families about a genetic condition, providing guidance around decision-making, and facilitating adjustment after a new diagnosis.

Depending on the condition, genetic counselling is usually offered close to the time that any complex decision-making is to occur, such as the decision to have children, undergo pre-implantation genetic diagnosis, undergo invasive diagnostic testing, or terminate a pregnancy when high risk for a condition is identified or following confirmation of a diagnosis. Many professional bodies consider the provisioning of professional genetic counselling with all genomic tests best practice. However, in reality if there is a substantial benefit to offering a genomic test to a larger population, this will not be feasible to implement and alternative models will be required where they are deemed appropriate based on a risk assessment. A key area for the need to find alternative models for delivery of genetic counselling is in any application of population-wide genomic testing. For

example, there is growing interest in introducing reproductive genetic carrier screening for certain rare inherited conditions where there may be no family history (e.g., recessive and X-linked conditions) (83–85).

Lessons could be learned from similar programs or practices such as cancer genetic counselling where demand for testing has begun to outstrip the available supply of genetic counsellors. For example, evidence from the USA has indicated that the majority of women tested for *BRCA1* and *BRCA2* variants are not receiving any genetic counselling (86). Alternative models could involve mainstreaming genetic counselling among non-genetics experts, such as genetic counselling provided by practice nurses with a special interest in genetics (4, 87, 88), counselling by the general practitioner or specialist, expanding the practice of genetic counsellors outside specialist genetics centres (4), or offering online counselling.

Preliminary evidence suggests that online delivery of information and counselling for carrier screening is equivalent to or non-inferior to in-person genetic counselling (89–91). Such alternative models are considered acceptable by some peak bodies in the USA (92). However, this approach has not been robustly tested among a pre-conception population or among populations with lower genomic literacy compared to research study participants. A further alternative model for providing pre-test genetic counselling and obtaining informed consent in the context of increasing demand involves group counselling. This model of service delivery has already been used in the prenatal and cancer genetics settings (86, 87, 93, 94). Finally, telehealth genetic counselling has been utilised extensively in cancer genetic counselling (95), and in other settings such as prenatal counselling (96). Recent developments in this space include the incorporation of chatbots (artificial intelligences with ability to converse via textual or auditory mediums) to help triage patients (97).

FINANCING GENOMICS

Like other countries globally, Australia's health expenditure is increasing faster than the inflation rate, and in a climate of budgetary constraints, there is a necessity for greater accountability in health expenditure to create truly sustainable public healthcare systems (98). For example, the present state of Australia's health systems is exemplified by Australia's 2015–2016 ratio of health expenditure to GDP at 10.30%, up from 8.68% in 2005–2006 (99). With fragmentation of healthcare across public, private, as well as state and commonwealth systems, the funding arrangements for genomic testing vary for different applications throughout the life cycle, as well as by jurisdiction.

In the context of the potential benefits of genomic technology, governments should be investing into the basic infrastructure and workforce required to support genomic healthcare and should invest in clinical DNA sequencing, data storage and computation infrastructure. Much of the investment in other countries so far has focused on funding large-scale research efforts, such as the 100,000 genomes project in the UK, the All of Us precision medicine research program in the USA, the Pilot Program for Personal Medicine in Estonia, Genome Canada's National Precision Medicine Initiative, and similar projects in China, Saudi Arabia, Dubai, and Turkey. Investments like these have involved the building of the capability for genomic sequencing (5).

The UK and USA are ahead of most other countries in beginning to translate the results of this research investment into the healthcare system. Both countries have had dedicated public health genomics centres since 1997. In June 2018, a United States Senate Appropriations Subcommittee approved an US$86 million increase for the All of Us precision medicine research program, which now operates with a budget of US$376 million from the National Institutes of Health. In the UK, part of the 100,000 genomes project included £20 million over 4 years for a Genomics Education Programme (3), and in 2018, the National Health Service in the UK started offering whole genome sequencing routinely for patients with rare diseases and certain cancers (100).

In Australia, there are a number of recent genomics research initiatives at a state, territory and national level. Several state-wide collaborative research entities have been developed aimed at harnessing healthcare, industry, and research expertise to determine how genomic testing can be incorporated into routine clinical practice (101). Similarly, the Australian Genomics Health Alliance, a research project funded by the NHMRC, aims to understand and address challenges associated with integrating genomic medicine into Australian health systems. Genomic testing is currently on the Commonwealth Government healthcare agenda, as evidenced by the allocation of AU$500 million in research funding to the Australian Genomics Health Futures Mission (102).

Along with these research efforts, health system implementation of genomic testing has also occurred in recent years in Australia. For example the Western Australian (WA) Government has a dedicated Office of Population Health Genomics. This Office has facilitated the alignment of existing resources within the WA health system and has developed policy to support a rare and undiagnosed diseases diagnostic service (103). An impact analysis of the service demonstrated a three-fold increase in confirmed diagnostic outcomes for the WA population. Similarly, the Victorian State Government provided AU$8.3M for the 2017/2018 financial year to enable publicly funded genomic sequencing for individuals with rare diseases, along with associated genetic counselling and multidisciplinary clinical care. Initial phases of the genomic test implementation were reported to be delivering six times the number of disease diagnoses compared to the previously available tests, at a quarter of the price (104).

Australia needs further investment in embedding genomics expertise into commonwealth and state health departments and health services to ensure appropriate oversight and strategic benefits realisation associated with genomic healthcare. Key priorities for government funding in the genomic healthcare space might include investing in a robust monitoring and evaluation system, ensuring that appropriate sequencing and data infrastructure is available to support increased

demand, improving reimbursement/funding streams for multi-disciplinary teams, and assessing cost-effectiveness of population based genomic screening programs.

Participation in multi-disciplinary and inter-disciplinary meetings is currently not adequately funded by the Commonwealth Government's activity-based funding for hospitals. Improving the funding pathway for this activity will be important for ensuring that genomic testing is utilised for those patients who need it most and that the appropriate clinical guidance is available. Processes are underway to improve this situation, such as reviewing current funding mechanisms to better reflect workloads (105). Similarly, ensuring that there is adequate reimbursement that recognises the necessary clinician time for interpretation of test results in preparation for appointments may be important (71).

Strategic Prioritisation of Investment Across Different Healthcare Settings

In a public healthcare system with finite resources, prioritisation of services is necessary (36). Agreed and consistent qualifiers to determine prioritisation can inform allocation of resources. One suggested approach for prioritising genomic tests is to favour those who are at high risk of imminent, serious, preventable conditions that are cost effective to treat (106). Other factors to consider are the severity of disease impact, the availability of prevention or a targeted treatment, and acceptance of the net cost for health gains achieved (36, 106).

Individual review of genomic tests, while necessary to establish analytical and clinical validity, clinical utility and cost-effectiveness, is onerous and resource intensive (36, 41). As a result, the individual assessment of tests contributes to the *ad hoc* approach to funding genomic tests in healthcare systems (9). This is particularly the case for applications used in the context of rare diseases and lethal conditions where limited baseline evidence is available to inform adequate review or where time is limited due to the progression and severity of the disease (27).

Part of the prioritisation process involves considering the opportunity costs of investing in one healthcare service over another, equally important service. Individual assessment methods based on medical need do not always take into account any comparison with investment into other services. Higher level considerations for prioritisation of healthcare services include maximising health gains for the population and addressing inequities in access (36). Considering the diverse criteria contributing to the need for genomic testing and the need for a more strategic approach, a potential area of interest is the development of a multi-criteria decision-making framework, such as that developed by the UK Genetic Testing Network (41). This framework involves ranking of genomic tests by a group of representative stakeholders, according to weighted criteria relating to reducing morbidity and mortality, enhancing reproductive choice, improving the process of care, deliverability of services and additional information (41). A similar model could be useful in Australia.

Cost Savings

In Australia, multiple funding arrangements exist for various genomic testing purposes creating issues for equitable access. Given the inevitable increasing use of genomic testing in the healthcare system, it is possible that a large proportion of the population will eventually have at least one genomic test during their lifetime. A cohesive approach to funding and access for genomic testing may ultimately provide cost savings to society. For example, for particular cohorts such as those with rare diseases, there is the potential for whole exome, whole genome, or targeted gene panel sequencing to produce cost savings by avoiding a long series of other genetic tests (3). A recent Australian study that investigated the health economic impact of whole exome sequencing for infants with a suspected monogenic disorder found a cost saving of AU$1,578 per quality-adjusted life year gained at 1 year, revealing an overall cost-benefit to the health system when genomic testing is incorporated into clinical care for this subset of patients (107). Learnings from rare diseases may also inform more targeted approaches to treatment for common, complex conditions, which could translate the benefits of reduced morbidity and mortality to the population at large, thereby increasing the cost savings of the initial investment (44).

In contrast, the use of genomic information may lead to increased need for healthcare services in the short term (108), such as genomic testing indicating an increased cancer susceptibility that encourages earlier and/or more frequent screening and heightened vigilance that would not have occurred in the absence of the genomic test. However, these costs may be offset by the savings from detecting cancer early, thereby avoiding deterioration in the patient's condition and possibly providing a better prognosis. This will of course depend on the availability and effectiveness of interventions and treatments, and if test results translate to behavioural change. Likewise, the application of genomic testing for complex polygenic diseases may be more cost effective if it is able to identify specific treatment options that are more likely to be efficacious (106) and be used. An outcomes-based approach to monitoring and evaluation will help to inform timely and strategic funding decisions.

PERSON-CENTRED CARE

As with any new medical technology, the successful integration of genomic medicine into healthcare delivery will rely not only on workforce engagement in the new technology, but also on the engagement of and acceptance by the greater population. Adequate understanding of genomic testing by the general public is required in order to obtain truly informed consent from patients. Future genomic medicine initiatives will need to be delivered in a way that is sensitive to the ethical, legal, and social issues associated with genomic information.

Genomic Literacy in Healthcare Consumers

Addressing public engagement and literacy in genomics is even more important in the context of the increasing availability of direct-to-consumer testing, although a recent study suggested

that Australian consumers' awareness of such tests is not as high as would be expected based on media reports (109). Similarly, recent surveys in the USA and UK on public opinion on personalised medicine and genomics found that most respondents were not familiar with these concepts (3, 110).

Successful engagement of the general public will require public health education and promotion programs that consider the nuances of public health behaviour change, such as the utilisation of behavioural economics (111). This approach acknowledges that new policies and technology alone are unlikely to catalyse changes in health behaviours. Significant learnings can also be drawn from the use of deliberative public engagement methods, which have been used to explore community opinions on similarly complex issues like biobanks (112, 113) and personalised medicine (114). Aspects to consider that ultimately affect an individual's choice to engage in a health service are strong fear of loss, considerations of the social norm, and emotional associations (111, 115).

There are also additional implications of obtaining greater genomic knowledge, such as the potential for perceived stigma associated with knowing carrier status (13), psychosocial impacts (116), negative effects on family dynamics (116), and privacy concerns such as fear of limitations on access to insurance (109, 116). The variable perspectives on the utility of genomic testing should also be deliberated when designing any public education and engagement interventions. Consideration should be given to providing educational interventions that are culturally appropriate, including language-appropriate communication materials (117).

Individuals in the community are likely to perceive information from governments and independent academic agencies to be legitimate (109). Consequently, appropriate information produced by these organisations, such as the NHMRC's resources for consumers, should be utilised to educate the general public and build acceptance in the community about genomics in healthcare. Strong leadership from governmental health departments will be critical to the success of raising public acceptance of genomic healthcare (48, 118).

Equity of Access to Genomic Tests and Their Health Benefits

The lack of existing national, state and territory policies and procedures in Australia surrounding access to genomic testing can lead to inequitable access. At the outset, effort should be made to ensure culturally appropriate genomic services are available for all. This includes minimising any disparity due to where people live, particularly those living in rural and remote areas, through informed service planning and telehealth solutions. The so called "post-code lottery" could currently result in differences in which genomic tests are offered to individuals, if indeed any are suggested or offered at all. Other possible areas of inequity include a lack of appropriate reference genomes (1, 119, 120); difficulty accessing international clinical trials for people with rare diseases; variation in access to publicly subsidised treatment options based on traditional cancer classifications; inequity of access to genomic tests based on ability to pay for tests that are only available in the private sector; and the potential for individuals with a higher education, genomic literacy and/or financial means to more readily access direct-to-consumer tests.

For example, currently in Australia pre-implantation genetic diagnosis (PGD) is not publicly funded. As such, this represents an inequity in enhanced reproductive choice for couples at higher than usual risk of having an offspring with a genetic condition who may wish to access such a technology to proactively prevent their future child having or developing that specific genetic disease/s. MSAC initially supported PGD to be publicly funded, however on further consideration advised that it was not appropriate for MBS listing, partly due to likely costs being largely speculative and complexities in implementation, and requested further information be gathered (121). Certainly providing PGD under a publicly funded scheme would achieve the NHGPF's goal of providing national consistency for equity.

Like PGD, private payment for non-invasive prenatal screening (NIPS) poses problems for equity of access when attempting to incorporate NIPS as part of widespread uptake into routine antenatal care. It has been estimated that with advances in technology, the cost per NIPS test will fall under AU$500 in the near future. However, as with PGD, any incorporation into routine antenatal care will require a stringent economic analysis for benefit (122) and cost utility such that efficient and transparent allocation of public resources can be achieved. NIPS is considered to have superior rates of detection compared to traditional prenatal screening methods for chromosomal abnormalities due to improved sensitivity and specificity. This means that fewer invasive diagnostic procedures are subsequently required, resulting in lower rates of procedure-related miscarriage (123). However, current prenatal screening programs that utilise ultrasound services are able to detect structural abnormalities of the foetus that would not be identified through NIPS, thus it is unlikely that NIPS alone will supersede all facets of the current prenatal screening program.

Serious consideration should be given to the infrastructure required to ensure that genomic testing is equitably accessible to all, and that there is culturally safe, timely and optimised outcomes and benefits. Focused effort is required to ensure that genomic tests are appropriate and accessible to disadvantaged groups and underserved populations (117). This will involve targeted research and significant stakeholder engagement to improve translation of genomic testing to benefit all members of the population. This effort extends to ensuring that genetic counsellors and other members of the healthcare workforce providing counselling to patients have the opportunity to engage in cultural sensitivity training. Other key priority areas for governments include public education campaigns, developing patient decision aids, integrating genomics into health promotion and disease prevention programs, empowering local community groups, and involving consumers in policy development. Moreover, incorporation of patient-facing interfaces in electronic medical records that contain genomic information and are accessible to patients will help to close

the loop and ensure that patients feel involved in their healthcare (124).

CONCLUSIONS

A strategic, holistic, and cooperative inter-governmental approach is needed to enable the successful integration of genomic testing into existing healthcare systems. Such an approach will help to prevent process duplication while also standardising genomic test implementation across jurisdictions, ensuring equity of access for a range of test applications, and identifying cost-savings through shared infrastructure and strategic planning.

The NHGPF in Australia serves as a guide, signposting areas for consideration prior to the implementation of a nationwide genomic testing strategy and directing key points for discussion for the purposes of this review. Successful implementation of the strategy is likely to require on-going leadership and coordination around genomic healthcare from governments and prioritisation of key healthcare settings for implementation.

The financial impact of expanding the use of genomic testing must be considered within the context of the NHGPF strategic goals for ensuring the sustainability of health service delivery, while simultaneously overcoming inequities of access, and delivering person-centred care. All stakeholders including the patient/individual and their family, clinicians, genomic technology companies, geneticists, molecular pathologists, laboratory scientists, bioinformaticians, and policymakers should be brought together as partners to help decide the future of genomic healthcare. However, a certain degree of genomic literacy is required by everyone who will be involved in such discussions, to facilitate significant engagement and shared decisions about the application of genomic tests and interpretation of results.

AUTHOR CONTRIBUTIONS

KN, BB, GAB, and HD conceived the paper concept. BB, GAB, EC, and KN drafted the manuscript. All authors provided critical input and approved the final manuscript version for submission.

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REVIEW
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Genomic Testing for Human Health and Disease Across the Life Cycle: Applications and Ethical, Legal, and Social Challenges

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The expanding use of genomic technologies encompasses all phases of life, from the embryo to the elderly, and even the posthumous phase. In this paper, we present the spectrum of genomic healthcare applications, and describe their scope and challenges at different stages of the life cycle. The integration of genomic technology into healthcare presents unique ethical issues that challenge traditional aspects of healthcare delivery. These challenges include the different definitions of utility as applied to genomic information; the particular characteristics of genetic data that influence how it might be protected, used and shared; and the difficulties applying existing models of informed consent, and how new consent models might be needed.

Keywords: genomics, public health, healthcare, genomic testing, molecular diagnostics, genetic disease, clinical utility, genomic data

INTRODUCTION

Genomic testing is used to diagnose, monitor, treat, predict and prevent disease, as well as promote good health in individuals, across communities and whole populations. Technological advances have allowed for greater integration of genomics into healthcare delivery, from screening and molecular diagnostics, to the accurate detection of microbes, and the ability to prescribe and monitor the efficacy of more precise therapeutics (1). The potential for increased use of genomic testing in the health setting is available throughout the life cycle, including in preimplantation, prenatal, neonatal, pediatric, adult, preconception, and posthumous settings (2). The person (who is often, but not always, also the "patient") should be firmly at the center of the genomics revolution

in healthcare. We begin this review by discussing a variety of current and emerging situations in which genomic testing is being utilized in health settings, focusing on the ethical, legal and social issues that apply at each point in the cycle-of-life and at particular decision points relevant to specific healthcare situations.

Subsequently, we focus on three main areas in which genomic technology, which is considered to be both disruptive and transformative to healthcare delivery (3), creates unique ethical issues that can challenge traditional aspects of healthcare. We summarize some of the key challenges and considerations surrounding the increasing application of this technology, highlighting issues that may arise when genomic tests are used at different life cycle stages. Within this section, we firstly outline the juxtaposition between clinical utility of a genomic test with personal and other utility, particularly where genomic testing is utilized in non-clinical settings (4). Related to questions around the utility of testing are issues surrounding the limited ability to interpret incidental findings and variants of unknown significance, which presents ethical challenges for the responsibility to return such results to patients (5).

Secondly, we consider how the personal nature of genomic data is such that it can never be truly de-identified. This creates potential issues around data storage and sharing; however, integral to this is the necessity to share genomic information to allow for advancement of knowledge of the etiology of disease (6). Furthermore, appropriate reference genomes are critically important for capturing the genomic diversity of the population being tested (7) so as to deliver equitable healthcare.

Finally, we discuss how genomic testing can challenge traditional models of informed consent in an environment where online DNA tests are available, where genomic testing is being increasingly utilized for individuals who are unable to consent, and where re-interrogation of stored genomic data is possible (8). For the purposes of this review, the term "genomics" is used to encompass both genetics (individual genes) and genomics (all genes in a genome).

CURRENT AND EMERGING APPLICATIONS OF GENOMIC TESTING ACROSS THE LIFE CYCLE

Genomic testing in the healthcare context can be applied in a multitude of ways throughout the human lifespan (**Table 1**). The application of massively parallel sequencing is expanding across different healthcare domains. This technique allows for the concurrent sequencing of numerous DNA fragments, enabling multiple loci to be investigated at one time and consequently, more efficient and cost-effective genomic analysis. Most of the current and emerging uses of genomic healthcare technology involve analyses for screening, diagnostic or prognostic purposes; testing to guide and evaluate treatment options; and identification and tracking of human disease-causing pathogens. Furthermore, genomic technology is increasingly available outside of healthcare settings through personal genomics tests that may be accessed directly by consumers, also known as direct-to-consumer or personal DNA tests (13, 22). Genomic sequencing technology has provided numerous benefits, particularly the significant improvement in the provision rate of molecular diagnoses (22). Continued developments with massively parallel sequencing include greater sensitivity of detecting previously difficult disease-causing deletions (23) and growing ability to detect copy number variants (24).

Genomic technology has increasing potential to contribute transformative new treatments in the form of genetic therapy. Recently this was demonstrated in a research setting with the treatment *in utero* of 3 fetuses affected with X-linked hypohydrotic ectodermal dysplasia. In this study, prenatal intervention occurred in the successful delivery of a recombinant version of the previously absent protein (25). Also on the horizon is the potential to use circulating tumor DNA in the blood or urine to assist in the clinical diagnosis of cancer, potentially alleviating the current reliance on invasive tissue sampling of solid tumors (26, 27).

The potential for genomic technology to continually improve the health and wellbeing of the population across the life cycle is anticipated. Further genomic and associated phenotypic data are integral for the advancement of knowledge and interpretation of genomic variants, and in turn the understanding of disease risk and disease etiology to inform better healthcare (6, 28, 29). The benefits of genomic technology in healthcare go beyond the immediate improvements in diagnosis and treatment, where a diagnosis is the portal to best care, to contributions to general understanding about disease and health and informing appropriately targeted public health initiatives.

The future ability to utilize "big data," not only for the incorporation of genomic information but also other "-omic" information (e.g., metabolomics, proteomics), epigenetic, phenotypic, environmental and personal data, will depend on data collection and sharing. Big data will allow more precise healthcare, specifically healthcare that is tailored to individuals (i.e., precision medicine), and will facilitate precision public health interventions tailored to genetically identified population subgroups (30, 31). Additionally, large, shared datasets are likely to become even more important to further knowledge about disease mechanisms for common and complex polygenic diseases (29).

CHALLENGES AND CONSIDERATIONS FOR GENOMIC APPLICATIONS ACROSS THE LIFE CYCLE

As described above, application of genomic technology and new genomic knowledge is being applied across the life cycle in both clinical and wider healthcare settings. Importantly, although the genomic technology itself may remain fairly consistent across different applications, the scope of the test can differ in terms of who is tested, for whom healthcare decisions are made about, the types of tests available, the potential conditions that can be identified, the clinical information available and the potential consequences of false positives or false negatives (see **Table 2**). Moreover, the issues surrounding utility, incidental findings and

TABLE 1 | Current and emerging applications of genomic tests across the life cycle.

Type of test	Description
Diagnostic	Used to investigate the cause of an observed phenotype. Testing follows onset of patient symptomatology, a clinical discovery or a positive screening test. Can be performed any time from *in utero* through to old age, and can be applied postmortem or posthumously. May detect germline or somatic variants.
Microorganism genomics	Involves testing the genomes of organisms that interact with and influence human health. Enables understanding and tracing of infections, outbreaks and identification of genomic changes behind antimicrobial resistance. Emerging applications include investigation of human microbiomes [e.g., lung, gut (9, 10)] and their influence on immunity, drug interactions, and disease expression (11).
Newborn bloodspot screening	Screening of newborns using blood collected by the Guthrie (heel prick) test. It typically detects the increased likelihood of the newborn having one of a number of rare and serious genetic conditions for which clinical interventions are available. Screening assays are typically biochemical, with a second line genomic test subsequently applied (possibly in conjunction with a clinical assay) to confirm the disease diagnosis for some conditions. The number and types of conditions included in newborn bloodspot screening programs varies around the world (12).
Personal/online DNA tests/direct-to-consumer	Genomic tests available direct to consumers through companies, with services ranging from having little or no clinical oversight through to comprehensive genetic counseling and clinician sign-off options (13). e.g., Ancestry.com, 23andMe, Genome.One, Counsyl, Helix, and Color. Options include gene panels for carrier, newborn, and inherited cancers testing. Availability of these services varies internationally.
Pharmacogenomics	Screening for genetic variants that alter drug-response with the aim of informing drug dosages and regimens to improve drug efficacy and patient compliance, whilst reducing side effects and avoiding life-threatening reactions.
Predictive/presymptomatic	Performed to establish an at-risk individual's predisposition to the development of a condition prior to symptoms onset. Traditionally this type of predictive testing involves both pre- and post-test genetic counseling. Huntington's disease provides a prototypical model.
Preimplantation genetic diagnosis (PGD)	Screening embryos created via *in vitro* fertilization (IVF) procedures to select those without a particular genomic variant/s for subsequent implantation. This follows identification of increased risk of the embryo having a genetic condition via molecular diagnosis or carrier screening of the parent/s.
Preimplantation genetic screening (PGS)	Screening embryos created via IVF procedures to select those without an identified chromosomal anomaly. This technique arose as an embryo selection tool in combination with IVF for women of advanced maternal age or with a history of failed implantation in IVF, to attempt to improve implantation rates for IVF cycles (14).
Prenatal/antenatal screening	*In utero* screening of a fetus can guide reproductive choice, preparedness and early interventions. An expanding approach for prenatal screening of genetic conditions is non-invasive prenatal screening (NIPS). From 10 weeks gestation, NIPS can be used to screen for the same chromosomal conditions as the combined first trimester screening test, as well as additional chromosomal disorders, by direct analysis of cell-free fetal DNA circulating in maternal blood. Although NIPS is non-invasive and is more accurate screening tool for these genetic conditions (15, 16), it is currently greater in cost than the combined first trimester screening test. Women who opt for NIPS over combined first trimester screening are still recommended to have an ultrasound (17), as these may detect pregnancy/fetal abnormalities not screened for by NIPS.
Prognostic	Utilizes gene variant/s or expression information to predict disease progression, severity and outcomes, as well as optimize and monitor therapeutic interventions. May also predict adverse responses to treatments.
Reproductive carrier screening	Traditionally used to determine the carrier status of couples suspected to be at a higher risk of having a child with a recessive or X-linked genetic condition. This has included individuals with an ethnic background known to have a greater prevalence of certain genetic conditions (e.g., Tay-Sachs disease in the Ashkenazi Jewish population) (18), or based on family history (e.g., a family member, including a previous child, with cystic fibrosis) (19). Simultaneous "expanded" carrier screening for more than one recessive or X-linked condition has been facilitated through the use of gene panels (20). In many countries it is possible for individuals or couples, including those with only average risk, to access these tests through a user pays scenario. When a couple is determined to be at greater risk of their future children having a genetic condition/s, their options include averting the birth of an affected child by refraining from having children, PGD, prenatal diagnosis and subsequent termination of an affected fetus, adoption or the use of donor gametes; preparation for the arrival of a child with a given condition; and the early commencement of treatments or preventions to alleviate disease in an affected fetus/child.
Posthumous	Molecular autopsies can occur on post-mortem tissue for sudden unexplained death (SUD), including *in utero* death. For example, inherited arrhythmia syndromes identified through molecular diagnosis may be identified as the cause of death for some autopsy-negative sudden unexpected death patients (21). For *in utero* deaths where other clinical signs were evident, or even those that might have been predicted, posthumous testing can confirm a suspected diagnosis. Increasingly this is also being applied for fetuses, stillbirths, and neonatal deaths with multiple congenital anomalies.

informed consent may differ depending on the life cycle stage and purpose of the test (**Table 2**).

For example, the ethical issues surrounding diagnostic testing are undoubtedly less contentious than those involved with predictive testing of a living individual. In the first scenario a patient has usually already presented to a healthcare professional with symptomology, therefore the choice of the genomic diagnostic test and subsequent data interpretation is simplified and clinical utility usually aligns well with an individual's expectation of personal utility. This is true even if a treatment or intervention is not available, as a molecular diagnosis can end the diagnostic odyssey and potentially facilitate access to applicable health and social services (32). Comparatively, it can prove more complicated to predict the likelihood of a person

TABLE 2 | The scope and challenges associated with genomic testing across different life cycle stages.

Considerations across the life cycle	Life cycle stage					
	Reproductive age	**Preimplantation**	**Prenatal**	**Pediatric**	**Adult**	**Posthumous**
SCOPE OF TEST						
Who is primarily tested?	Prospective parents	Embryo	Fetus/mother	Child	Adult	Deceased
Who does the healthcare decision primarily concern?	Prospective parents/potential embryos	Embryo	Fetus/mother	Child	Adult	Family members
Is a phenotype available at time of testing?	No	No	Possibly	Possibly	Possibly	Possibly
TYPE OF TESTS AVAILABLE						
Screening	✓	✓	✓	✓	✓	
Diagnostic		✓	✓	✓	✓	✓
Personal/direct-to-consumer (non-clinical)/pharmacogenomics				✓	✓	
Microorganism			✓	✓	✓	
Prognostic/Predictive/Presymptomatic		✓	✓	✓	✓	
CONDITIONS IDENTIFIED						
Inherited germline	✓	✓	✓	✓	✓	✓
Acquired germline		✓	✓	✓	✓	✓
Somatic				✓	✓	✓
PERSONAL AND CLINICAL UTILITY OF GENOMIC INFORMATION FOR TESTED INDIVIDUALS AND/OR FAMILY MEMBERS VIA CASCADE SCREENING						
Reproductive choice (e.g., not having children, assisted reproduction, termination)	✓	✓	✓	✓	✓	✓
Preparation for future	✓	✓	✓	✓	✓	✓
Prevention or intervention			✓	✓	✓	
Providing a molecular diagnosis (new or suspected)		✓	✓	✓	✓	✓
Inform treatment and/or management options			✓	✓	✓	
POTENTIAL HEALTH CONSEQUENCES OF FALSE POSITIVES						
Decision not to implant an unaffected embryo		✓				
Termination of an unaffected fetus			✓			
Unnecessary use of assisted reproductive technology	✓					
Over diagnosis, over treatment, or wrong treatment			✓	✓	✓	
Unnecessary cascade testing or cascade testing for a wrongly attributed variant	✓		✓	✓	✓	✓
POTENTIAL HEALTH CONSEQUENCES OF FALSE NEGATIVES						
Missed opportunity for prior preparation, prevention, or intervention	✓	✓	✓	✓	✓	✓
No or wrong treatment			✓	✓	✓	✓
Missed opportunity for cascade testing for a wrongly attributed variant	✓		✓	✓	✓	✓
INFORMED CONSENT						
Tested individual unable to consent		✓	✓	✓		✓
ASPECTS RELEVANT ACROSS THE LIFE CYCLE						
Implications, considerations, and uses of test results	Research translation, incidental or secondary findings, non-actionable findings, non-health related traits, forensic investigation, ancestry, insurance, variants of unknown significance, sensitivity of data, longevity of data, versatility of data, reference data, genomic literacy.					

potentially developing a disease at some point in the future. This is especially true for a person who has not yet been born, such as when predicting risk of a disease for a current (preimplantation or prenatal diagnosis) or future (preconception carrier screening) embryo or fetus. The absence of familial information such as in the case of adoption or gamete donation can add more complexity. The potential implications of the action/s taken based on genomic information in these situations are also greater, due to the possibility of an embryo not being selected for implantation, or the choice to terminate an affected fetus (**Table 2**).

Despite the potential benefits associated with increasing use of genomic testing, our knowledge of the relationship between genomic variants and health is still evolving and

is limited by the complex interactions between the genome and other biological and environmental influences. Three key considerations relating to this potential include the utility of genomic testing for clinicians and the person, or patient; issues around genomic data such as the sensitivity and potential longevity of the data, data sharing and appropriateness of the reference genome; and issues around informed consent in the context of the complexity and expanding usage of genomic testing. The issues that are explored below, while not exhaustive, provide a broad overview of some of the challenges and considerations of genomic testing across the life cycle. Additional ethical, legal and social issues associated with genomic testing, including challenges associated with direct-to-consumer testing, are beyond the scope of this paper and are discussed elsewhere (33, 34).

Utility

Personal and Clinical Uses for Genomic Information

Clinical utility for genomic testing is generally limited to situations where genomic information directs and improves patient care. Therefore, genomic testing may not be recommended clinically if the results are unlikely to impact care. However, genomic information has multiple applications beyond the healthcare setting. For example, individuals may wish to have their genome sequenced to learn about their ancestry or non-health related traits; a genomic diagnosis can inform eligibility for special education and employment services; and genomic information is of interest to insurance companies and can be used in forensic settings. The manifold nature of genomic information could allow for more efficient healthcare due to the potential ability to reinterrogate data for multiple healthcare purposes. However, the value of such data to individuals and organizations beyond healthcare raises issues around consumer expectations when clinical utility and other kinds of utility diverge.

The utility of testing varies across the lifespan, potentially in relation to when the testing is performed and for which conditions the testing may relate (**Table 2**). In some settings genomic information is used to make healthcare decisions about an individual who may not have been able to provide consent (e.g., prenatal screening or diagnosis; patients with cognitive impairment). Furthermore, in particular settings the test not only informs treatment and management, but influences reproductive decisions which can be inherently more personal (as opposed to clinically led), compared to other healthcare decisions.

There are also limitations to the clinical utility of testing. For example in the preconception setting, the genomic test can only inform parents about risk of inherited conditions, and cannot provide information about *de novo* or acquired genetic conditions (**Table 2**). A particular consideration for the utility of testing across the life cycle is the presence (or absence) of a phenotype to aid clinical, as well as personal, decision-making. Genomic data has the potential to identify disease risk earlier than is possible through the use of clinical or physiological symptoms alone, meaning that interventions can be enacted more promptly. However, there is a conundrum presented whereby presence of a genetic variant may not necessarily mean that the disease will manifest (i.e., there is incomplete penetrance) (35), or where a variant is variably expressed among individuals and it is not possible to predict the severity based on genomic information alone.

In such situations, clinicians would ideally draw upon the presence of phenotype to aid in decision-making, and this is absent in the preconception and preimplantation stages, and often absent, or markedly limited, in the *in utero* setting (**Table 2**). Likewise, the use of genomic testing for screening includes the testing of asymptomatic individuals by definition, and this can occur at any life stage (**Table 2**). Assurance of the natural progression of genetic variants and the likelihood of resulting disease is required for individuals to make reproductive and healthcare choices. Similarly this information is needed for clinicians to make clinical decisions, yet currently this knowledge is limited. As a consequence, the clinical utility of genomic testing for many conditions currently remains relatively low.

In some circumstances, genomic information may have greater personal utility to patients compared to other medical test results. Therefore, there may be times where personal utility and clinical or healthcare utility are non-congruent. Available evidence indicates that many consumers would only seek genomic testing for actionable health information, particularly in situations where there is a perceived need for that information (4). However, certain subsets of the population may be more receptive to receiving non-actionable genomic results, in which case personal utility may override a lack of overt clinical utility. Common situations where these benefits arise include for parents of children with rare undiagnosed genetic diseases (36), testing for the risk of late-onset conditions at a point in the lifecycle where there is no clinical utility for such information (37), and testing for risk of conditions with no current treatments, such as Alzheimer's disease predisposition (38). Additional benefits cited for wanting to access testing in these situations include ending the diagnostic odyssey, a clearer understanding of the cause of a condition, greater understanding of future needs, the ability to connect with others in the same situation, and helping to gain access to social and healthcare services (32, 38, 39). Personal utility of a genomic test may also vary depending on a person's cultural background (40, 41).

In the era of personalized medicine and given that the degree of personal utility is likely to vary between persons, the utility of a genomic test is ultimately best estimated on an individual basis (42). Empowering patients and families to be involved in decisions will help to facilitate this (32). However, individuals and healthcare providers should recognize the inherent differences in value placed on genomic testing by different stakeholders. Variation in perceptions of the utility of genomic testing highlights the importance of accessible and appropriate education and genetic counseling for anyone considering a genomic test (43) (see **Box 1**). To enable this, sufficient genomic literacy is required across the health workforce to ensure health professionals are able to competently counsel individuals and families (46, 47). This could be

BOX 1 | Genetic counseling.

Genetic counseling has traditionally focused on the education and support for patients and family members who have, or are at risk of, Mendelian disorders (44). With the increased integration of genomic testing in the healthcare system across the life cycle, the ability to provide adequate counseling to patients with the current workforce and services model will be tested. The current workforce will be challenged to provide optimal counseling with increased demand, and new models for delivering genetic counseling services may be required to fill this gap. New models could include bolstering the skills of the primary healthcare workforce (45), increasing the use of evidence-based online delivery, and utilization of technology such as telehealth to mitigate hurdles such as geography for the rural and remote population. Issues around genetic counseling for genomic tests are outlined in Burns et al. 2019 (46).

enabled through increased education and training of health professionals (48).

Research and Translational Uses of Genomic Testing

Genomic testing may be used in situations where the primary utility is to inform basic research or to identify eligibility for treatments or services. For genetic conditions without well-defined natural histories, for which there are few or no treatments available (e.g., rare diseases, including rare cancers), or where disease progression is rapid (e.g., advanced cancers), research and translational uses of genomic testing may be crucial. There could be a lack of knowledge or clinical consensus of the clinical utility of genomic testing in such contexts (49), but there might still be real or perceived utility for patients, clinicians, and researchers. Due to the rarity of genetic conditions and the increasing utility for genomic testing in treating cancer, management of these particular patient cohorts relies heavily on basic research.

Consideration of these additional uses for genomic testing in healthcare is important, particularly through the lens of providing equitable healthcare to those who need it. Only 14% of new scientific discoveries enter daily clinical practice, after an average lag of 17 years (50). This lag is especially problematic for (i) cancer patients, where disease prognosis can often be poor, but for whom tailored treatment is showing promise, and (ii) for patients with rare diseases for whom no, or limited pre-existing treatment is available. In this context, translating the benefits of genomic technology into the healthcare setting in a timely manner is challenging (51). Multiple agencies at both the national and international levels may be working on similar, smaller-scale research projects. This could lead to inconsistent findings due to sample size limitations, thereby becoming one of the rate-limiting steps in the integration of genomic advances into daily practice, and then into population-level programs. National and international collaboration between researchers has the potential to streamline this approach so that collective goals are expedited, and translation into practice is accelerated (51–53).

An additional consideration around the lag in translation of testing into the public healthcare setting is the potential for individuals to have their genome sequenced in a non-clinical setting (e.g., personal genomics) or a private healthcare setting, which may create expectations for increased access in public health systems. Genomic tests may be introduced first into private (user pays) settings due to the initially high cost and the lag in translation into public health systems, which must balance investment into multiple different aspects of healthcare (54), and as a result, often have a high evidence threshold for integrating new tests into practice. This can increase demand for, and produce inequity of access to, testing that may be beneficial for improving healthcare, but which health systems are not yet prepared to offer at a population-wide level (55).

Incidental or Secondary Findings

Genomic data can be interrogated in different ways, including broad approaches designed to capture as much information as possible and targeted approaches focused on a few variants of interest. Incidental or secondary findings are classified as gene variants that are not the primary focus of a specific genomic test and are not necessarily related to the condition/s being investigated [e.g., (56)]. These variants can be obtained when performing whole genome and exome sequencing, as well as with certain gene panels, and if scrutinized, may reveal the need to consider medical action. There have been efforts to identify a minimum list of variants that are considered medically actionable. The American College of Medical Genetics and Genomics has developed a widely used list of 59 genes to be reported in clinical settings as incidental or secondary findings (57). Incidental findings relating to germline variants and familial relationships are relevant across the life cycle (**Table 2**). A particular point of difference is the use of non-invasive prenatal testing, in which fetal DNA and maternal DNA can be identified in the same sample, which may reveal incidental findings relating to somatic changes present in the mother.

There is variation among consumers, pathologists, specialists, researchers and professional societies regarding the need to return incidental findings to patients, with the definition of incidental often being dependent on the medical specialty or setting (58, 59). Consumers may consider that raw data or medically significant incidental findings should be accessible to them even when their genome is sequenced for a non-clinical purpose (60, 61). This raises important legal issues surrounding the right to access personal information (43, 60), particularly when incidental findings relate to potentially actionable variants (62). However, there may be issues in the clinical utility of such information given the different requirements for sequencing quality in non-clinical settings (60, 63). Managing consumer/patient expectations is therefore of critical importance.

A dialogue involving all stakeholders, including the patient or consumer, may be required to agree on a set of criteria that could indicate when incidental findings should or should not be returned to individuals (64). A relevant question is whether researchers and genomics laboratories should be returning raw data or incidental findings given that many patients access genomic testing through research projects or directly from laboratories. Recent changes to the National Health and Medical Research Council's *National Statement for Ethical Conduct in Human Research*, with which researchers must comply,

require a system to be in place to return findings that have health significance to participants (65). Other relevant questions include, will guidelines and regulations around incidental findings influence clinicians in ordering gene-specific analyses rather than clinical genomes or exomes? What is the likely effect of this on the utility of the test?

Variants of Uncertain Significance

By definition, variants of uncertain significance (VUS) have unknown clinical utility (66). It is understood that as knowledge of genomic variants and the relationship between variants and disease pathology advances, variants that have previously been identified as uncertain may be recognized as pathogenic, or alternatively benign. Internationally, guidelines surrounding the responsibility to report VUS are a work in progress. Variant interpretation, even in the setting of a clear phenotype, can be challenging at both the individual and health system levels. The medico-legal implications of variants at one point in time being identified as uncertain, and then with advances in knowledge being later identified as pathogenic, are highlighted in the law case of Williams vs. Athena (see **Box 2**). Significant questions include where do we draw the line on requirements to report based on knowledge of pathogenicity? How frequently should reference databases be updated and consulted to inform contemporary interpretation of results? Do patients wish to know about VUS if they are found? Is there an obligation to follow up VUS after the test has been taken, in accordance with changes in classification as knowledge develops? If so, who is responsible for doing this?

Genomic Data

Genomic data are becoming increasingly useful not only for understanding the causes of ill health, but also the genomic determinants of good health. However, there are ethical, legal, and social issues that need to be considered to ensure appropriate use of genomic data in healthcare. These include that genomic information is not only personal, but also familial (i.e., it can reveal familial relationships and personal information about relatives); that the longevity, particularly of germline genomic data, exceeds that of typical health information; that the broad utility of genomic data increases the demand for data sharing; and that equitable genomic testing relies on appropriate reference data.

Sensitivity of Genomic Data

The collection and generation of genomic information comes with some unique ethical issues. The security and privacy of genomic information challenges traditional paradigms of confidentiality for sensitive information, given that a person's genomic information can be compared to a fingerprint, such that it can never be truly de-identified. Genomic information may therefore require additional regulation, such as the addition of noise to the data to ensure protection of privacy (67, 68).

Genomic data can impact biologically related family members even if they have not accessed genomic testing themselves. With the possibility for on-sharing of genomic information for future uses other than the intended purpose of the initial test, concerns over the privacy of genomic data and issues of informed consent for the disclosure and use of genomic information become paramount. Recently this was illustrated in California, where police used genomic information from an open source database from genealogy company GED match to facilitate the arrest of a serial rapist and murderer known as "The Golden State Killer" (69). The suspect, who is accused of committing crimes more than 3 decades ago, did not himself have genomic information in the database, but rather one of his relatives had participated.

Longevity of Genomic Data

Germline genomic data is somewhat unique in its unchanging nature, meaning that the same data could be reinterrogated over the life cycle for different health and non-health related purposes. The potential of genomic information is therefore longer lasting in contrast to many other types of health test results, which may provide more of a health snapshot. This makes genomic information more similar to stored biological samples collected in biobanks. Future innovations will allow for improved interrogation of historical genomic data (3, 70). In the inevitable advent of improved interrogation ability, is it ethical to analyse existing, historical datasets with improved technologies, and contrastingly, is it ethical to omit reinterrogation of existing datasets with new technologies (71)? Future tools for analysis and enhanced genomic knowledge may alter an individual's risk profile with reinterrogation of existing data (72). With increasing applications in precision medicine and precision public health, disease risk could become dynamically updated depending on current knowledge and data. The potential for rapid change in technology should be considered when determining how long to store genomic data. Careful management of consumer or patient expectations should also be considered.

The integration of genomic testing that is currently occurring separately across the life cycle may facilitate greater efficiencies in healthcare, but would require coordination and communication among previously isolated healthcare settings. With the increasing application of genomic testing across the life cycle, the potential to use one test for multiple purposes is increasing (73). For example, if genomic testing is introduced at a population level in more than one setting, the possible number of individual tests taken over the lifespan for a single individual is likely to increase. Assuming there is agreed utility for each type of testing at a population level, would broad sequencing such as whole genome or whole exome sequencing and long-term storage of genomic test results ultimately become more cost effective than repeat testing?

What if every baby's exome or genome was sequenced and reanalyzed as needed for different purposes throughout their life, would the cost savings from a reduced need to re-test outweigh the cost of storing the relevant data? A single genomic test could provide the answer to a patient's symptomatology that would have otherwise required multiple tests (74), and may also provide information relevant for different healthcare decisions in that person's life (**Table 2**). However, it may also lead to a short-term increase in healthcare demand from different healthcare professionals. For example, an actionable secondary finding may mobilize cascade screening in family members that would

BOX 2 | Case study-Legal issues in variant interpretation.

A case study which highlights potential legal issues surrounding variant interpretation is the current USA lawsuit, *Williams* vs. *Athena*, where a 2 year old boy, Christian Jacob Millare, died of a fatal seizure from Dravet syndrome in January 2008. In 2007, Christian was tested for Dravet syndrome, and the report concluded that he had a "variant of unknown significance," and as such Christian continued to be treated as if he had a mitochondrial disorder rather than Dravet syndrome. In 2015, the laboratory responsible for the test, Athena, updated its report to reclassify the mutation as pathogenic for Dravet syndrome, as Christian was found to have a pathogenic variant in the *SCN1A* gene. Interestingly at the time of the initial report, there were two publications (published in 2006 and 2007) each based on another single case reporting the same variant that Christian had as being pathogenic. Inherent to this case were the issues of whether a laboratory classifies as a health service provider, and relatedly the communication and responsibilities of laboratories and physicians. The case also emphasized the need for stricter governance around how variant databases report and interpret their data (6).

otherwise not have occurred (53), or may indicate consideration of alternative reproductive choices for individuals in the family. In addition, such long term storage and reinterrogation of genomic data would require processes for obtaining consent for each subsequent analysis over a long time period. The implications of broad sequencing methods and use of genomic data should be carefully examined prior to any large-scale implementation (75).

The potential for integration of genomic testing across the life cycle will not be without challenges. In such a context it is important to determine who is responsible for reporting results; which results should be reported and when; and whether to store and reanalyse results at a later time. The complexities of healthcare systems and governance arrangements across responsible organizations create the need for a harmonized approach at the local, national and international levels.

Data Sharing and Regulation

The benefits to be obtained from the use of genomic technology in healthcare are reliant on global cooperation and data sharing (2, 76). This is particularly the case for rare genetic conditions, where sharing of patient data can be critical to achieving a diagnosis or conducting research to improve healthcare. Adequate governance and regulation is required to ensure that genomic data are used responsibly by those who are permitted access. In 1997, the United Nations Educational, Scientific and Cultural Organization developed a Universal Declaration on the Human Genome and Human Rights, and, in 2003, adopted an International Declaration on Human Genetic Data to guide the use of such data at an international level (77).

Internationally, the regulatory space continues to evolve. The United States of America (USA) has developed regulations and legislation governing the protection and use of genetic information. The *Genetic Information Nondiscrimination Act of 2008* protects the genetic privacy of individuals by preventing insurers or employers from requesting genetic information. However, a bill for the *Preserving Employee Wellness Programs Act* has been introduced to the USA Senate, and has the potential to jeopardize present legislation protecting individuals from their employers requesting disclosure of genetic information and imposing penalties for non-disclosure (35). In Canada, the *Genetic Non-Discrimination Act* prohibits a person from requiring an individual to disclose their genetic information as a condition of providing goods or services to that individual, with exceptions for healthcare practitioners and researchers.

The requirements for responsible use of genomic information are similar to those for other health-related and personal information. The European Union (EU) has developed a General Data Protection Regulation that applies to businesses that process or control data from within the EU. Discrimination against individuals on the basis of their genetic information is also banned in Europe in accordance with the Council of Europe's Oviedo Convention. These regulations are important to ensure that data can be shared responsibly and ethically, which will encourage individuals to continue to participate in health research.

Reference Data

The importance of reference genomes in utilizing genomic testing is reliant on large-scale data sharing and collaboration. Reference genomes are used for comparison purposes, as a representative example of a typical human's genome sequence. These genomes are developed using a mosaic of genetic information sourced from different individuals and combined to form a template sequence. The use of reference genomes in utilizing genomic technology raises concerns around offering genomic testing that is less effective in some ethnicities compared to others, since genetic disease risk varies among ethnicities (78, 79). However, the use of an appropriate reference genome is made more difficult by the increasing multiculturalism within countries.

For equitable understanding of genomic variants, reference databases must be capable of reflecting the ethnic diversity of the relevant population/s, such as minority groups and/or Indigenous populations (80). It has been highlighted that most genomic reference databases do not adequately reflect the diversity of human populations (7). As an example, the cultural makeup of Australia's population is highly diverse, including Aboriginal and Torres Strait Islander peoples, and having a higher proportion of people born overseas compared to the USA, New Zealand, and Canada (81). However, there is a paucity of genetic data available for Aboriginal and Torres Strait Islander peoples, such that interpretation of genetic variants currently needs to be addressed with caution (82). For multicultural societies, it is vital to ensure that minority ethnic populations are not disadvantaged in accessing the benefits of genomic technology.

Informed Consent

Informed consent for genomic testing in healthcare is complex when we try to consider all of the issues outlined above,

including the variety of different testing methods and potential to test for multiple conditions at once; the testing of non-consenting individuals; potential for reinterrogation or sharing of data; the lack of diagnostic certainty in particular test settings; the complexities surrounding interpretation of tests, VUS and incidental findings; implications for insurance and other services; and the potential impact of testing on family members. Some of these issues are more pertinent in particular test settings across the life cycle (**Table 2**).

For example, the current guidelines on prenatal testing from the Royal Australian and New Zealand College of Obstetricians and Gynaecologists state that information provided to women should include descriptions of conditions to be tested, as well as information about both the variance in phenotype and ability to predict the conditions tested (83). In the context of increasing lists of conditions to be screened for through the use of expanded genetic testing panels or whole exome/genome sequencing, how can healthcare providers ensure that the decision to undergo such testing is adequately informed?

The complexity of ethical, legal, and social issues surrounding consent for genomic testing indicate that substantial effort is required to ensure adequate understanding of the test by consumers. Depending on how many of these issues apply, professional genetic counseling may be critical for obtaining truly informed consent for genomic tests. Informed consent should be obtained based on the individual's circumstances to the extent that this is possible. Patient decision aids may be helpful for achieving this approach, particularly for applications where for some people the personal benefits outweigh the lack of clinical utility (84, 85). Such tools have been developed to help parents decide whether to undergo screening for Down syndrome (86), and to support reproductive decision-making for individuals with a genetic predisposition to heritable cancer (87). Decision aids may need to be tailored to the level of health literacy of users (88).

Consideration must also be given to a model where informed consent to personal genomic data analysis and storage can allow for the possibility that data may be reviewed, and thus for the possibility that an individual or their family might be contacted in relation to the updated outcomes in the future if this occurs (89). In the context of including late-onset conditions in tests performed on fetuses or children, is there a moral obligation to ensure this information can be communicated to individuals once they reach the age of informed consent? Dynamic consent models in this instance are one such example of a flexible, digitally-enabled consent model that may cater more broadly to the needs of healthcare consumers (8). Evidence so far shows that healthcare consumers want ownership and control over their health data (90, 91). Several companies are developing applications to allow greater access to, and control of, genomic information by consumers (e.g., Helix online genomics marketplace; Seqster platform). Much of this development is currently occurring in the personal genomics space, but similar efforts are being made in public health systems in association with moves to electronic health records. This patient-centered approach will be increasingly important with the rise in personalized medicine and precision public health, but will need to be implemented in a considered and ethical manner.

CONCLUSIONS

Genomic technologies challenge aspects of traditional healthcare delivery, with new ethical issues arising from these unchartered waters. The increasing utilization of genomic testing across different healthcare settings over the life cycle necessitates increased clarity of purpose and raises important ethical, legal, and social issues. Healthcare providers will be required to adopt an approach to genomic technology that will allow for the advancement of genomic knowledge and the responsible application of technology to benefit the population across the life cycle. In the context of the complexity and versatility of genomic information and its inherently personal and familial nature, adequate governance and informed consent are critical considerations for implementing genomic testing for healthcare.

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TW, HD, and GAB conceived the paper concept. BB, GAB, EC, and KN drafted the manuscript. All authors provided critical input and approved submission of the final manuscript.

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Should Australia Ban the Use of Genetic Test Results in Life Insurance?

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Under current Australian regulation, life insurance companies can require applicants to disclose all genetic test results, including results from research or direct-to-consumer tests. Life insurers can then use this genetic information in underwriting and policy decisions for mutually rated products, including life, permanent disability, and total income protection insurance. Over the past decade, many countries have implemented moratoria or legislative bans on the use of genetic information by life insurers. The Australian government, by contrast, has not reviewed regulation since 2005 when it failed to ensure implementation of recommendations made by the Australian Law Reform Commission. In that time, the Australian life insurance industry has been left to self-regulate its use of genetic information. As a result, insurance fears in Australia now are leading to deterred uptake of genetic testing by at-risk individuals and deterred participation in medical research, both of which have been documented. As the potential for genomic medicine grows, public trust and engagement are critical for successful implementation. Concerns around life insurance may become a barrier to the development of genomic health care, research, and public health initiatives in Australia, and the issue should be publicly addressed. We argue a moratorium on the use of genetic information by life insurers should be enacted while appropriate longer term policy is determined and implemented.

Keywords: genetics, insurance, genetic discrimination, regulation, legislation, moratorium

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Australia has a concerning lack of regulation around the use of genetic test results by the life insurance industry. Many other countries have passed legislation or moratoria banning use of genetic data in life insurance (1). However, in Australia, life insurance applicants must still disclose results of any genetic test if requested. These include findings from research or direct-to-consumer genetic testing, if known to the applicant. Genetic results can be used for underwriting life insurance, permanent disability and total income protection insurance in Australia, with minimal consumer transparency or Government oversight into the process.

Genetic test results cannot affect private health insurance premiums in Australia, which are community-rated under the *Private Health Insurance Act 2007* (Cth). This means private health insurance companies in Australia must offer the same premiums to all consumers for equivalent policies and cannot discriminate on the basis of health or other information.

Section 46 of the *Disability Discrimination Act 1992* (Cth) permits life insurers to discriminate on the basis of genetic test results, only where actuarially sound or otherwise reasonable. Yet cases of life insurance policies being declined or premiums loaded without adequate supporting data or justification have been documented in Australia over a number of years (2–4), despite the known difficulties in documenting such cases of discrimination (5, 6).

In one case, a woman with an identified BRCA gene change indicating elevated risk of breast cancer, elected to have a bilateral prophylactic mastectomy to reduce her risk. However, the risk reduction surgery was not taken into account by her life insurer and in her application for death and critical illness cover, the insurer excluded any cancer cover and imposed a 50% premium loading for death cover (7).

In another case, a man with a family history of colorectal cancer had an identified gene change confirming his increased risk. He actively sought increased surveillance through colonoscopies to reduce his risk back down to population average, yet was still refused cancer cover. The man eventually obtained cover, but only after taking a complaint to the Human Rights Commission (8).

These examples of genetic discrimination can occur because of the current lack of enforced regulation of the Australian life insurance industry. The issue is of increasing public health concern, with evidence of insurance fears now deterring the uptake of genetic testing and participation in medical research at a critical time for genomics in Australia.

The strongest evidence for deterred uptake of genetic testing due to insurance fears in Australia comes from within the context of Lynch syndrome (increased risk of hereditary colorectal cancer), whereby predictive gene testing can identify risk and prompt surveillance to prevent cancer. A Victorian study related to Lynch syndrome saw the number of individuals declining predictive gene testing more than double after insurance was mentioned on consent forms, compared with a similar time period without mention of insurance (9). Predictive genetic testing for Lynch syndrome can identify risk and prompt surveillance to prevent cancer, and so the deterrence of at-risk individuals is a significant public health concern. A qualitative study from the same group found insurance fears quoted as a leading reason for refusal of testing in Lynch syndrome families (10). Documented cases of deterrence from medical research participation by healthy volunteers are more difficult to identify, yet do exist in Australia (11).

We argue that this mounting evidence, in conjunction with the ethical and social imperatives, justifies a moratorium on the use of genetic data in life insurance in Australia, with the exception of negative (mutation-absent) test results, until appropriate long-term policy is implemented.

INTERNATIONAL ACTION, AUSTRALIAN INACTION

Currently in Australia, genetics professionals commonly recommend clients organize life insurance policies before undertaking genetic testing. This practice, which is designed to protect clients from insurers refusing cover based on the results of future genetic tests, can also result in some individuals declining genetic testing altogether due to insurance fears (9, 10). For some individuals, declining predictive genetic testing can mean missing out on information that could prompt life-saving measures, such as surveillance and early intervention for serious but treatable conditions such as cancer.

Internationally, many countries have instituted bans on the use of genetic test results by life insurers (1). Two noteworthy examples are Canada and the UK. Canada passed the *Genetic Non-Discrimination Act* (previously Bill S-201) in May 2017, prohibiting insurers from requesting or requiring disclosure of any previous or future genetic test results. There is some controversy over whether the Act is a legitimate exercise of Federal power (12) and it has been referred to the Court of Appeal of Quebec for determination of a challenge of its Constitutionality (13). This challenge is unique to the division of power under Canada's Constitution and would not apply in Australia.

Since 2001, a moratorium and concordat between the UK Government and the Association of British Insurers has been in place on the use of predictive genetic test results by life insurers (other than negative test results and results for Huntington's Disease for policies above £500,000). This moratorium has been extended until 2019 (14).

Furthermore, the European Convention on Human Rights and Biomedicine and Recommendation CM/Rec(2016)8 direct Member States to take steps to prevent discrimination, including on grounds of genetic characteristics, in insurance contracts. A mix of legislative reforms and moratoria have been enacted as a result in many European countries (1).

By contrast, Australia has left its life insurance industry to self-regulate the use of genetic information, without independent regulatory oversight. The Australian Government has not reviewed regulation since 2005 when it made non-binding recommendations following the Australian Law Reform Commission report "Essentially Yours" (15, 16). Many of these recommendations, although commendable, unfortunately have not been implemented or adhered to by the Australian life insurance industry.

The Financial Services Council, the peak industry body in Australia for life insurers, writes the Industry Standard on Genetic Testing (17) which binds its members. The Standard now contains several clauses that could be considered to conflict with the 2005 Government recommendations, including a recently added clause requiring applicants to disclose to insurers even a *consideration* of genetic testing, if requested. It is uncertain how insurers will use an affirmative response, but we consider even the inclusion of this request to be evidence of an erosion in consumer rights made possible by lack of regulatory oversight (18). Any model of industry self-regulation for the use of genetic information by life insurers, who are inherently motivated by commercial gain, represents a conflict of interest. Independent government oversight is needed.

AUSTRALIAN PARLIAMENTARY INQUIRY INTO THE LIFE INSURANCE INDUSTRY

In 2016, the Australian life insurance industry came under scrutiny by an Inquiry of the Parliamentary Joint Committee on Corporations and Financial Services in relation to a range of practices. Authors of this article, with input from others, presented our concerns regarding genetics and life insurance to the Committee

in May 2017 making recommendations for an immediate moratorium on the use of genetic test results and a flexible legislative instrument for long-term regulation. The written submission and transcripts of the public hearings can be found online (19) (see Supplementary Material).

Any moratorium or ban on use of genetic test results for life insurance in Australia should consider the use of negative (mutation-absent) test results to counter family history. That is, individuals who undertake predictive gene testing for a known family variant but are found *not* to carry the family variant, thereby having their risk reduced compared with gene-positive family members, should have this information taken into account by insurers to counter increased risk indicated by family history of disease. Without introducing such measures, any regulation aimed at regulating insurer conduct and protecting consumers from insurance discrimination is likely to have unintended consequences. These include excluding individuals from being able to prove that family history does not lead to an increased individual risk, which would put them in a worse position than currently. This would benefit some consumers to the detriment of others, which is a poor public health outcome. For this reason, an exception for negative test results has been incorporated into the UK Moratorium and Concordat (14).

POSSIBLE IMPLICATIONS OF A BAN

The insurance industry claims that if genetic test results cannot be used in life insurance, adverse selection by gene-positive applicants will lead to significantly increased premiums for consumers and incapacitate the operation of insurance markets (17). However, there is little evidence produced in Australia to support this claim. A report prepared for the Actuaries Institute 2017 Summit (20) asserts that a ban on genetic test results will result in adverse selection, but its claims are arguably based on a set of worst-case assumptions that are unlikely to be met (18). Independent modeling undertaken elsewhere, including in Canada prior to legislation being passed, indicates that a ban on the use of genetic test results would not have a significant effect on the operation of a reasonably sized life insurance market (21–23).

Another argument is that genetic data should not be treated differently from other medical risk information. However, we argue that given the lack of underlying actuarial data currently available for genetics, the family implications of genetic test results, and other attendant ethical, legal and privacy issues, genetic data is different than and should be treated differently to other types of medical risk information.

We acknowledge the insurance industry must be commercially viable. However, the use of individuals' genetic information has wide-ranging ethical and social implications which warrant curtailment of the industry's use of this information. Over time, the self-regulating industry in Australia has changed its policy on genetic testing with relative freedom, meaning current requirements for disclosure of genetic test results could be further changed, without necessary government involvement or independent regulatory oversight. This poses a growing concern for consumers.

Our understanding of human genetic variation is still evolving, and the classification of most genetic variants is not yet supported by robust population data, certainly not to the level of being sufficient for insurance underwriting. Some of the first large-scale surveys of human genetic variation are only now underway (24), and we are still largely unaware of the true population frequency of most genetic risk variants. Social policy considerations, which include factors such as privacy, fairness, equality of access to insurance, non-deterrence and non-maleficence should also be carefully considered.

FUTURE FOR AUSTRALIA

More than ever, now is a critical time for genomics and genomic research in Australia. The Commonwealth, Queensland, Victorian, and New South Wales Governments have each recently committed $25 million toward the implementation of genomics into health care, with new genomic technologies and whole-genome sequencing showing much promise. Consultation has been undertaken for a National Health Genomics Policy Framework, which aims to integrate genomics further into national health care. However, these steps are being taken without adequately addressing the issue of life insurance. As the lines between research and clinical care for genomics are blurred, Australia needs more education, consumer protection and building of public trust in genetics, not an environment of uncertainty, consumer fears and inadequate regulation. The Government must be more proactive, and take ownership of the issue within a specific department for closer oversight.

Insurance fears now represent a growing threat to public trust in genetics in Australia at a time when it is needed most. A failure to address this key issue will remain an ongoing barrier if action is not taken. The threat of genetic discrimination in Australia has been voiced for well over a decade without a satisfactory Government response. The Human Genetics Society of Australasia has for years called for both a moratorium and legislation banning use of predictive genetic test results by the insurance industry (25). We urge Australia to follow most developed nations and enact a moratorium, then pass legislation to safeguard its population. There is still time for Australia to proactively address this issue; however, the time to take action is now.

AUTHOR CONTRIBUTIONS

JT, MO, and PL conceived and wrote the manuscript jointly.

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The Supplementary Material for this article can be found online at http://www.frontiersin.org/articles/10.3389/fpubh.2017.00330/full#supplementary-material.

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Genetics, Insurance and Professional Practice: Survey of the Australasian Clinical Genetics Workforce

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In Australia and New Zealand, by contrast with much of the developed world, insurance companies can use genetic test results to refuse cover or increase premiums for mutually-rated insurance products, including life, income protection and disability insurance. Genetics professionals regularly discuss insurance implications with clients and report the issue as a clinical challenge, yet no studies have examined clinical practices or opinions. This study surveyed genetic counsellors and clinical geneticists from Australia and New Zealand to (i) investigate variability in professional practice across the Australasian clinical genetic workforce relating to the insurance implications of genetic testing, and (ii) ascertain views regarding current regulation of the issue. There was considerable variability in training and clinical policies, especially around the communication of insurance implications. Almost half of participants reported receiving no training on the insurance implications of genetic testing, and almost 40% were unsure whether they could adequately advise clients. A number of deficits in professional knowledge and understanding of the issue were identified. Widespread concerns regarding regulation of this area were reported, with <10% of Australian participants considering current Australian regulations as adequate to protect clients from genetic discrimination. The findings from this study highlight scope for greater education, consistency and professional training on the issue of genetics and insurance in Australasia, and strong agreement about the need for regulatory reform.

Keywords: insurance, life insurance, genetics, genetic discrimination, genetic counselling, regulation, Australia

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INTRODUCTION

In Australia and New Zealand, insurance companies can use genetic test results to refuse cover, increase premiums or exclude aspects of cover for mutually-rated life insurance products, including life, income protection and total disability insurance. Genetic test results cannot be used for health insurance in Australia, which is community rated (1), but can be used in New Zealand for this purpose.

Many countries, including Canada, the UK and much of Europe, have banned or restricted the use of genetic information by life insurance companies (2, 3). In Australasia[1] however, life insurance companies can require applicants to disclose any results of genetic testing known to the applicant. This includes genetic results from clinical testing as well as research and online, direct-to-consumer genetic tests (4). Insurers can then use that information, with other health and lifestyle information, in making underwriting decisions.

The use of genetic test results by life insurers is particularly relevant for individuals who are unaffected by disease and undergoing clinical predictive genetic testing (e.g., for neurogenetic conditions, such as Huntington disease or cancer predisposition, such as Lynch syndrome). Emerging research demonstrates that some at-risk individuals are deterred from having predictive genetic testing (5, 6) and choosing not to participate in genomic research (7) because of insurance fears.

Life insurers in Australia and New Zealand are currently self-regulated [managed by the peak industry body in each country, both named the Financial Services Council (FSC)], without government oversight (8). It can be argued that this creates uncertainty for consumers and genetics professionals regarding how insurers will use genetic information and raises numerous other concerns which have been discussed elsewhere (8). It is argued that the Australian FSC's recent policy changes are only likely to increase this uncertainty, as the new policy recommends insurers ask whether applicants are "considering" a genetic test. Given the applicant at this stage has no knowledge of genetic test information that the insurer does not have, there would appear to be no imbalance of information if consideration of a genetic test is not revealed to the insurer (8).

Clinical genetics professionals are in a unique position to inform clients about insurance implications of genetic testing before testing takes place (9). Guidance from the Human Genetics Society of Australasia (HGSA), the representative body for human genetics professionals in Australia and New Zealand, indicates genetics professionals should include a discussion of relevant insurance issues during consultations (10, 11). Two published Australian studies have shown that genetics professionals routinely discuss life insurance implications with clients during pre-test counselling sessions (12, 13). This takes time in sessions that cover a significant amount of information; however, to our knowledge there are no Australasian studies exploring professional practice in this area.

This study was designed to determine if variability exists in workplace trends, training policies and opinions related to the issue of genetic testing and insurance, and its current regulation.

METHODS

Participants

Genetics professionals were recruited through the HGSA by email to members of the Australasian Society of Genetic Counsellors and the Australasian Association of Clinical Geneticists, the HGSA newsletter, and the 2017 HGSA Annual Scientific Meeting. Although the focus of the project was on Australian practice, the HGSA includes Australian and New Zealand practitioners and any interested participants were encouraged to participate. A screening question was used to include only genetics professionals who see clients considering genetic testing.

Data Collection and Analysis

The study utilised an online survey (**Appendix 1** in Supplementary Material), which was developed and refined through consultation with statistical and subject matter experts, including genetic counsellors, geneticists, and law and ethics experts. The survey aimed to measure (1) presence and adequacy of training and policies held by genetics services regarding communication of insurance issues with clients; (2) knowledge and practice of genetics professionals; and (3) attitudes regarding regulation of the area. The published literature was reviewed and relevant validated scales were considered, however, no scales were suitable for the topics in the survey.

The survey was open for data collection from 7 June 2017 until 18 August 2017. Data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Murdoch Children's Research Institute (14). Online survey data were de-identified and exported for analysis using STATA 14 (StataCorp, Texas). No calculations related to power or statistical significance were performed for this exploratory study. Qualitative data were collected from selected participants through telephone interviews, but these data are not reported in this paper.

Ethics Committee Approval

This study was completed in partial fulfilment of the requirements for the Master of Genetic Counselling, University of Melbourne, Victoria, Australia, and was supported by the Victorian Government's Operational Infrastructure Support Program. Approval for the project was granted by the Human Ethics Advisory Committee, Department of Paediatrics, University of Melbourne on 12 May 2017.

RESULTS

Participant Response

Eighty-seven genetics professionals participated in the online survey. The number of participants who completed each question (n value) is reported. The demographics of the survey participants are set out in **Table 1**.

Figure 1 summarises results about training, policy, knowledge, professional practice and views on regulation presented below.

Training, Policy, Knowledge

Forty-nine percent ($n = 43/87$) of participants reported the genetics service where they work had not provided training about the insurance implications of genetic testing (**Figure 1**, box 1), and 20% of participants who had received training ($n = 9/44$) felt this training was inadequate. Sixty-one percent ($n = 53/87$) of participants stated that either their genetics service did not

[1]Used here to refer to Australia and New Zealand.

TABLE 1 | Participant demographics.

Demographic	Category	Number of online survey participants ($n = 87$)
Gender	Male	8 (9%)
	Female	79 (91%)
Profession	Medically trained genetics professionals	15 (17%)
	Genetic counsellors	72 (83%)
Years of experience	0–5 years	34 (39%)
	6–10 years	17 (20%)
	11–15 years	14 (16%)
	15–20 years	15 (17%)
	>20 years	7 (8%)
Appointments per fortnight	0–5	13 (15%)
	6–10	37 (42%)
	11–20	31 (36%)
	>20	6 (7%)
Location	Australian Capital Territory	1 (1%)
	New South Wales	23 (27%)
	New Zealand	6 (7%)
	Queensland	7 (8%)
	Tasmania	2 (2%)
	South Australia	6 (7%)
	Victoria	27 (31%)
	Western Australia	15 (17%)

have a policy (44%, $n = 38/87$) or they were unsure whether there was a policy (17%, $n = 15/87$) regarding communicating with clients about the insurance implications of genetic testing (**Figure 1**, box 2).

Forty-six percent of participants ($n = 36/79$) indicated their genetics service has one standard consent form for all types of genetic testing, and 53% ($n = 19/36$) of these do not include a statement about insurance implications (**Figure 1**, box 3).

Thirty-nine percent ($n = 34/87$) of participants did not have (25%, $n = 22/87$) or were unsure of having (14%, $n = 12/87$) sufficient knowledge about the insurance implications of genetic testing to properly advise clients (**Figure 1**, box 4). Of these, 71% ($n = 24/34$) had <10 years' professional experience. Of participants with more than 10 years' experience, 27% ($n = 10/36$) did not have or were unsure of having sufficient knowledge. Fifteen percent of Australian participants ($n = 11/74$) believe that genetic information could be used for health insurance policies in Australia,[2] which is incorrect (1). Ninety-three percent ($n = 74/79$) of participants stated it could be used for life insurance, 68% ($n = 54/79$) for disability insurance, 91% ($n = 72/79$) for income protection insurance and 42% ($n = 33/79$) for travel insurance, indicating variability in knowledge of current regulation. Travel insurance is a mutually rated insurance product,[3] meaning providers can use genetic test results to assess risk, though their decisions, in theory, must have a reasonable basis. Three participants of 79 (4%) did not know which insurance policies genetic information could be used for.

Eighty-five percent ($n = 68/80$) of participants had read the Centre for Genetics Education (CGE)'s Fact Sheet 20 titled, "Life insurance products and genetic testing in Australia" (15). This document, to the authors' knowledge, is the most comprehensive resource currently available to professionals and the public on this issue. Eleven of the 12 participants who had not read the Fact Sheet were not made aware of its existence by their workplace.

Professional Practice

All participants stated that communicating information about insurance implications of predictive genetic testing in adults is very important ($n = 60/79$) or somewhat important ($n = 19/79$), and 99% ($n = 78/79$) consider that this communication is their responsibility (**Figure 1**, box 5).

Ninety-four percent ($n = 74/79$) of participants always discuss insurance implications with unaffected adults considering predictive genetic testing. Practice differed for other kinds of testing (diagnostic testing in children/adults, predictive testing in children, and prenatal testing). Participants were next most likely to discuss insurance implications in predictive testing in unaffected children (75% always discussed, $n = 59/79$) and least likely in prenatal testing (3% always discussed, $n = 2/79$).

Use of Genetic Results by Insurers and Regulation

Twenty-two percent ($n = 16/73$) of participants have had direct experience with a client/s who had an adverse policy outcome on the basis of genetic test results (**Figure 1**, box 6). Ninety-five percent of participants ($n = 70/74$) sometimes ($n = 19/74$), often ($n = 24/74$) or always ($n = 27/74$) discuss with clients the option to go away and organise their insurance before having genetic testing (**Figure 1**, box 7). Only three percent of participants ($n = 2/74$) agreed with the suggestion that this practice may amount to fraud (**Figure 1**, box 8).

Fifty-nine percent ($n = 43/73$) of survey participants considered insurers should not be allowed to ask whether applicants are considering having a genetic test, while 21% ($n = 15/43$) thought it should be allowed. Twenty percent ($n = 15/73$) were unsure (**Figure 1**, box 9).

Of the Australian participants surveyed, 9% ($n = 6/69$) considered current Australian regulations adequate to protect clients from genetic discrimination. Fifty-two percent ($n = 36/69$) felt they were inadequate and 39% ($n = 27/69$) were unsure (**Figure 1**, box 10). When asked about types of regulation that could be implemented, 62% ($n = 43/69$) considered Australia should have separate legislation regulating the use of genetic information by insurers. Two percent ($n = 1/69$) of participants answered no to this question, and 36% ($n = 25/69$) were

[2]Health insurance is specifically protected from risk rating in Australia. This specific protection does not apply in New Zealand and so data from New Zealand participants was excluded from this question.

[3]It should be noted that FSC policies do not relate to travel insurance.

FIGURE 1 | Results about training, policy, knowledge, professional practice, and views on regulation.

TABLE 2 | Recommendations.

No	Issue	Recommendation
1	Some genetics professionals are inadequately equipped to advise client	Genetics services work with the HGSANHMRC, and the Centre for Genetics Education to develop training modules, resources and national guidelines regarding insurance issues, and maintain a regularly-updated resource page for access by genetics professionals.
2	Variability of professional practice	
3	Lack of consistency in consent forms	Genetics services work with the HGSA, state and territory Health Departments (with reference to the work already undertaken in NSW), the NHMRC and other interested bodies, such as the Australian Genomics Health Alliance (AGHA), to build on existing national precedents and develop national consent forms regarding genetic testing that include information about the insurance implications of genetic testing.
4	Regulation inadequate to protect clients from genetic discrimination	The Australian federal government must consider reforms regulating the use of genetic test results by insurers.

unsure (**Figure 1**, box 11). Thirty-nine percent ($n = 27/69$) of participants considered Australia should ban the use of genetic information by insurers, while 23% ($n = 16/69$) did not agree with a ban and 38% ($n = 26/69$) were unsure (**Figure 1**, box 12).

DISCUSSION

Results of this study suggest many Australasian genetics professionals, while acknowledging it as a major issue in clinical practice, do not feel adequately equipped to advise clients regarding the insurance implications of genetic testing.

Practice Implications

Genetic professionals have a fundamental obligation to promote informed consent and ensure clients understand the implications of genetic testing (16). Where genetics professionals have either self-declared, or demonstrated through incorrect survey responses, a lack of knowledge, the implications are significant for their practice. Although the majority of professionals self-reporting inadequate knowledge in this area had <10 years' experience, almost 30% had >10 years' experience, and more than a quarter of the participants with >10 years' experience reported inadequate knowledge. Although, as acknowledged in the Limitations section, these numbers are reasonably small, which limits the generalisability of this study, the results indicate that this lack of knowledge may be persistent even in more experienced professionals. Further, as the genetics workforce is growing, with a large number of junior professionals, this data represents a proportion of the workforce whose training and knowledge needs must be addressed. The current HGSA guidelines on genetic counselling practice place responsibility on genetics professionals to discuss insurance issues with clients (11), but do not allocate responsibility for appropriate training and resourcing of professionals in this area. While the results suggest that that CGE's Fact Sheet 20 has been widely disseminated and most professionals are familiar with it, gaps in knowledge persist.

Almost all participants always discuss insurance implications of predictive testing with unaffected adult clients, despite evidence of professional knowledge limitations and a number self-reporting insufficient knowledge to adequately advise clients. This suggests that genetics professionals may not always provide correct information to clients on this issue. A Canadian study (9) has shown that genetic counsellors are comfortable discussing matters about which they are uncertain because discussions of uncertainty are routine in genetic counselling. In these circumstances, there is a risk that the legal implications could be poorly understood and incorrectly communicated to clients (9).

One mechanism to ensure consistent practice in Australasia is to include insurance implications on clinical consent forms signed by a client before genetic testing takes place, although this will not necessarily ensure informed consent. The findings showed variation across genetics services in this regard, indicating further inconsistency in client experience and mirroring international findings (17). The New South Wales Ministry of Health has recently implemented a new suite of consent forms for genetic and/or genomic testing in that state (18). It may be timely for genetics services to review their consent forms and ensure that the information on insurance issues are correct and consistent across sites. This will also assist with ensuring fully informed consent is obtained prior to testing, but would not negate the need for an explanation or discussion for many patients.

In addition, genetics services and state Health Departments, as well as interested bodies, such as the National Health and Medical Research Council (NHMRC) and the Australian Genomics Health Alliance (AGHA) could collaborate to build on existing precedents and develop nationally consistent training modules and resources, and model consent clauses that could be adapted to each clinic's needs. However, while a collaborative approach to the insurance implications of genetic testing will assist with national consistency, each genetics service must ultimately take final responsibility for maintaining appropriate policies, communicating them to staff and ensuring knowledge and practice are up-to-date. Given the potential financial implications of misinformation in this area for clients, action is needed

to address this situation. Encouragingly, the findings of this study have already led to the implementation of some training initiatives in Victoria, and prompted the development of a patient brochure in conjunction with the Centre for Genetics Education.

A major finding of the study is the considerable professional concern regarding Australian regulation. Very few participants considered Australian regulations adequate, consistent with the HGSA's position statement regarding genetic testing and personal insurance products (10), which urges the implementation of a moratorium on the use of genetic test results.

There was no clear consensus among participants regarding what type of regulation should be implemented, though more participants agreed with the implementation of legislation than a moratorium (ban) on the use of genetic test results by insurers. It is argued elsewhere that a ban should be implemented (with the exception of mutation-negative results used to counter a family history of disease), along with longer term regulatory reform (19).

Regulatory Reform

The model of a self-regulated life insurance industry does not compel a rigorous standard of evidence regarding which genetic test results have a sufficient evidence base for use in underwriting (8). A key recommendation of the Australian Law Reform Commission's 2003 inquiry into the protection of genetic information (20) was the establishment of a body for this purpose. The Human Genetics Advisory Committee (HGAC) was established in November 2005 in response to this recommendation (21). Unfortunately, the HGAC has since been disbanded (22) and has not been replaced, meaning this recommendation has not been implemented. Any longer-term regulatory reform in this area should include a mechanism for oversight of the level of evidence that must be satisfied before genetic test results can be used for underwriting.

Regulatory reform on the use of genetic test results in life insurance underwriting must be considered by the Australian government to allow individuals to access genetic testing without fear of insurance implications. An inquiry into the life insurance industry has been conducted by the Joint Parliamentary Committee on Corporations and Financial Services. The Committee report, tabled in March 2018 (23), highlights the issues with industry self-regulation and the need for a moratorium on the use of genetic test results by insurers. At the time of writing, a moratorium has not been implemented. Unless the need for regulation is satisfactorily addressed, the potential for genetic testing to improve health outcomes for Australians will continue to be limited by insurance fears.

Our recommendations for addressing the issues identified in this paper are summarised in **Table 2**.

Study Limitations

The study has a number of limitations. Its relatively small sample size of 87 limits its generalisability, providing an indication of the issues that could be found in the broader professional workforce with further investigation. Participant demographics were skewed towards inexperienced professionals, with 59% having 0–10 years' experience and senior professionals (>20 years' experience), constituting only 8% of the sample. It is difficult to determine whether these percentages accurately represent the current workforce distribution, given the lack of publicly available data on this. All participants' experiences and attitudes were given equal weight, where participants with many years of experience and knowledge may have a more informed view. The survey questions could have better encompassed the New Zealand regulatory system to allow for more meaningful comparison.

The findings indicate an emerging clinical issue, highlighted by a lack of knowledge and/or training by a considerable proportion of genetics professionals. Individuals and health service organisations could better address the inconsistency of training provision and knowledge limitations in this area. Genetics services are responsible for developing appropriate policies and ensuring staff are adequately equipped in this regard. However, collaboration with other genetics services, the HGSA, and other relevant bodies, such as state governments, the National Health and Medical Research Council (NHMRC) and the Centre for Genetics Education (CGE), to develop a nationally consistent training programme, should be encouraged.

Research Recommendations

Future research could focus on exploring these issues in a larger cohort, as well as considering the content of genetic counselling sessions by direct transcript analysis, further investigation of the differences between clinical services in various Australasian locations, and consumer views and experiences regarding genetic testing and insurance issues.

AUTHOR CONTRIBUTIONS

JT wrote the initial draft of the manuscript. PL substantially revised the manuscript. SW and LK provided research input to the development of the project and reviewed the manuscript and suggested revisions. MO and MD reviewed the manuscript and suggested 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/fpubh.2018.00333/full#supplementary-material

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Changes to the Employers' Use of Genetic Information and Non-discrimination for Health Insurance in the USA: Implications for Australians

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In the USA, a bill has been introduced to the senate that may jeopardize an individual's rights to privacy and non-discrimination. This piece examines the proposed Preserving Employee Wellness Programs Act (PEWPA), and implications this will have on the use of genetic information. The Act allows for employers to apply financial penalties for health insurance based on genetic information, which raises concerns as the capacity to interpret genetic results is limited by knowledge of the significance of both benign and pathogenic variants. In Australia, genetic information can only be used to determine life insurance, not to stratify health insurance, and any precedent set internationally should raise concerns of the potential for change on the horizon.

Keywords: genetic testing, medicolegal, ethics, gene expression, privacy, indigenous health, confidentiality, politics

The year 2017 saw the introduction of the proposed "Preserving Employee Wellness Programs Act" (PEWPA) to Congress in the United States of America (USA). At its core, PEWPA allows for employers to bypass the employee's rights for privacy of genetic information when requested under a loosely defined guise of a "wellness program." Such programs are purported to inform and empower employees for health lifestyle choices, and implement targeted health promotion and prevention programs. However, PEWPA enables employers to impose both rewards and penalties for its employees to participate in such wellness programs, such as the ability to increase health premiums as a financial penalty based on a person's genetic data, or more worryingly, a person's non-disclosure of their genetic information. The ability to apply such penalties represents a significant encroachment on an individual's rights under the Genetic Information Non-discrimination Act (GINA), and the Americans with Disabilities Act (ADA). PEWPA provides a loophole to undermine the privacy and nondiscrimination provisions that GINA and the ADA attempt to protect. With access to healthcare tied with employment for most citizens of the USA, the

decision for the employee to participate in any employer initiated requests for genetic information and disclosure are complex (1, 2).

Fraught with ramifications for health information privacy and discrimination, the international precedent that may be set in the USA has potentially global implications. At present, genetic testing technology has outrun our ability to interpret the results, culminating in the identification of gene variants of unknown clinical significance. Robust interpretation of genetic information requires extensive knowledge of benign and pathogenic variants. While technology has allowed us to "read" the genome, our genomic literacy is lagging behind, challenging our ability to understand and interpret the many variations of uncertain clinical significance (3). This is particularly, and inequitably, so for Aboriginal and Torres Strait Islander Australians as there is a paucity of reference genomic data for this population (4).

The interplay between genetics and nurture for many of these variants, and how this impacts on penetrance of disease processes is poorly understood. PEWPA seemingly ignores the conundrum that presence of a variant (existence of a genetic mutation) does not necessarily lead to penetrance (realization of a disease). That an employer could apply a financial penalty for simply having the presence of a genetic variant, over realization of the disease is of grave concern. Similarly for an employer to request genetic information, questions both informed consent of genetic testing, and autonomy of health care decision-making for the employee (5).

Furthering understanding of both benign and pathogenic variants relies on the impartation and sharing of genetic data, without fear of discrimination. For potential research participants in the USA, significant consideration would need to be given to the future use of their genetic information, knowing that an employer may request disclosure of such data, and penalties applied for non-compliance. PEWPA therefore significantly risks slowing the rapid progress made toward our understanding of disease and precision medicine, with uncertain global implications for research and innovation in genomics (2).

In Australia, two key pieces of Commonwealth legislation provide protection to the public against discrimination based on genetic information from insurance agencies and employers. These are the *Disability Discrimination Act (DDA) 1992,* and the *Human Rights and Equal Opportunity Commission Act (HREOC) 1984*. More specifically for health insurance in Australia, the *Private Health Insurance Act (PHIA) 2007,* prohibits the stratification of individuals' premiums based on health status (6). Furthermore, the *Workplace Relations Act (WRA)* prohibits discrimination on a range of grounds in terminating employment. These Acts currently prohibit discrimination on the basis of genetic information, however this assumption holds true only as long as these Acts are in force in their present form (7). Currently, in accordance with the *DDA* (s.46), the insurance industry in Australia allows for genetic information to be used for determination of life insurance, but not for health insurance, provided compliance with the terms of the *PHIA* (s.55.5) (6, 8). The ability for life insurance companies to ascertain genetic information in Australia has been documented to deter uptake of genomic services in at-risk individuals, and it is noted that there has been no review of legislation since 2005 (9). In recognition of the complexities in genomic medicine, the Commonwealth Department of Health recently published the National Health Genomics Policy Framework, which prioritizes the responsible collection, storage, use, and management of genomic data, as well as recognizing the need for a coordinated approach to the ethical, legal, and social issues inherent in this space (10).

With the landscape in the USA providing new uncertainty in the protection of genetic information, the future implications for public policy and comparable legislation in Australia, as well as other countries, must be considered. The propensity for global policy transfer has been demonstrated through the adoption of the "work for welfare" programs, which commenced in the United States, subsequently catalyzing uptake in other industrialized countries such as Britain, Australia, and Sweden (11, 12). Similarly, the addition of medicinal cannabis to the political agenda in Australia and around the world can also be aligned with social pressure arising from legalization in other jurisdictions (13). If PEWPA is realized, the overarching implications for research, development, discrimination, and privacy are portentous and are likely to reverberate beyond our northern hemisphere neighbors.

AUTHOR CONTRIBUTIONS

GAB and GB have made a substantial, direct and intellectual contribution to the work. CM assisted in the concept development and initial stages. All authors have approved it for publication.

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Regulation of Internet-based Genetic Testing: Challenges for Australia and Other Jurisdictions

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The Internet currently enables unprecedented ease of access for direct-to-consumer (DTC) genetic testing, with saliva collection kits posted directly to consumer homes from anywhere in the world. This poses new challenges for local jurisdictions in regulating genetic testing, traditionally a tightly-regulated industry. Some Internet-based genetic tests have the capacity to cause significant confusion or harm to consumers who are unaware of the risks or potential variability in quality. The emergence of some online products of questionable content, unsupported by adequate scientific evidence, is a cause for concern. Proliferation of such products in the absence of regulation has the potential to damage public trust in accredited and established clinical genetic testing during a critical period of evidence generation for genomics. Here, we explore the challenges arising from the emergence of Internet-based DTC genetic testing. In particular, there are challenges in regulating unaccredited or potentially harmful Internet-based DTC genetic testing products. In Australia, challenges exist for the Therapeutic Goods Administration, which oversees regulation of the genetic testing sector. Concerns and challenges faced in Australia are likely to reflect those of other comparable non-US jurisdictions. Here, we summarize current Australian regulation, highlight concerns, and offer recommendations on how Australia and other comparable jurisdictions might be more proactive in addressing this emerging public health issue.

Keywords: direct-to-consumer genetic testing, regulation, public health genomics, Australia, Therapeutic Goods Administration

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INTRODUCTION

A direct-to-consumer (DTC) genetic test is any DNA test for a medical or non-medical trait that provides interpretation or communication of test results directly to a consumer, rather than via a health professional. DTC genetic tests are often accessed *via* the Internet without the need for a medical referral, outside of the health system. Sample collection kits can be posted directly to the consumer without involvement from any health professional. Internet-based DTC genetic tests vary in price, quality, and genetic content measured, ranging from "recreational" testing (1) to return of medical disease risk information (2). Online DTC genetic tests are growing in popularity due to various consumer motivations, many of which are not necessarily medical in nature (2, 3). There are several potential harms and consequences of poorly regulated Internet-based DTC testing, which have been well documented (4–6) and are summarized in **Figure 1**.

Online DTC genetic tests are generally delivered in the absence of genetic counseling or medical oversight. Some consumers with DTC test results are now looking to general practitioners or clinical

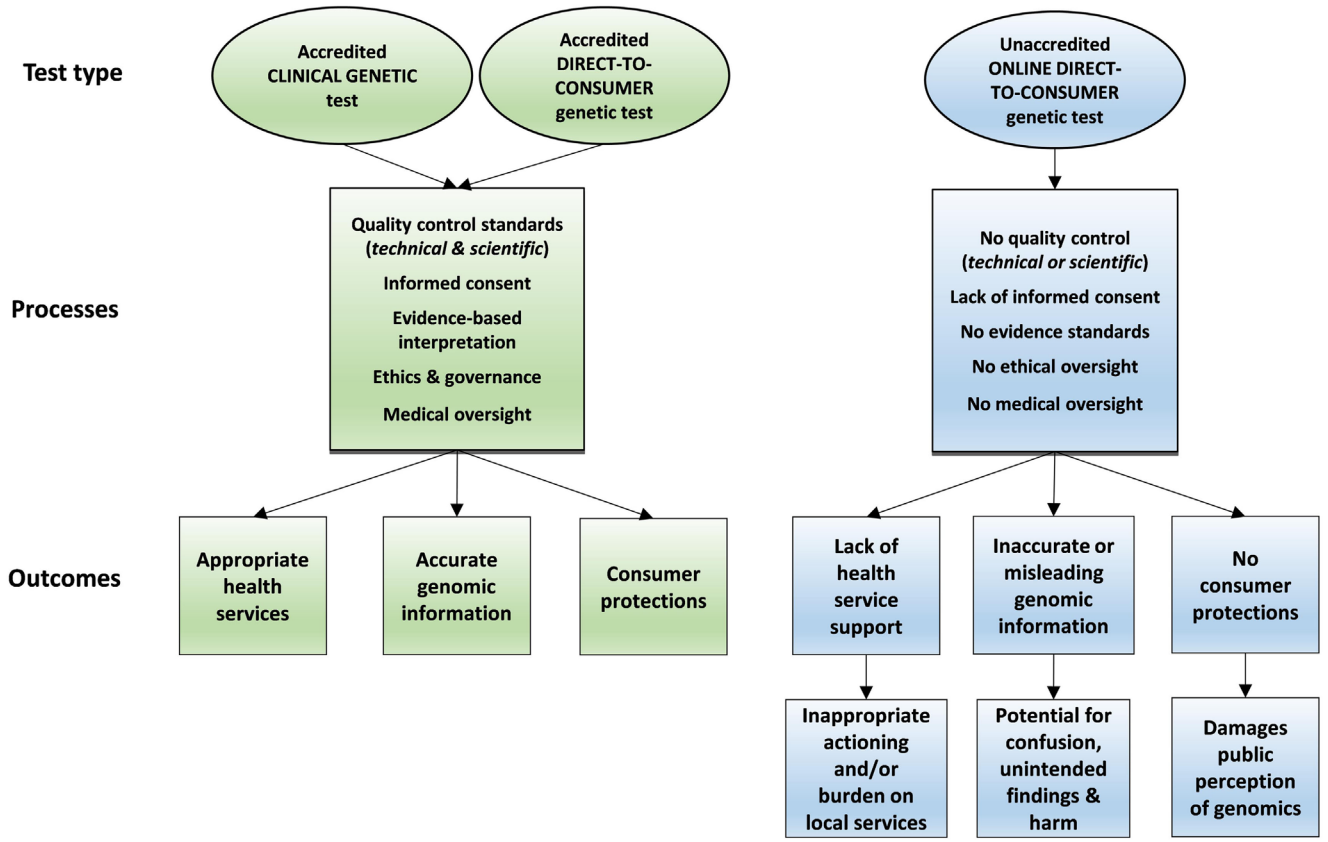

FIGURE 1 | Processes and outcomes for accredited versus non-accredited genetic testing pathways.

genetic services for assistance with interpretation or management of DTC genetic findings, posing an emerging challenge for the medical community (6, 7).

Many online DTC genetic tests originate in the USA, where the Food and Drug Administration (FDA) has ongoing challenges in maintaining regulatory oversight (8). Online DTC tests originating from the USA under FDA approval do not necessarily obtain country-specific approval elsewhere in non-US jurisdictions. However, many are still available and accessible *via* the Internet from any country, essentially by-passing local testing regulations in non-US countries. Some online DTC tests, if sold locally in non-US jurisdictions, would be in violation of local guidelines for genetic testing. However, direct access *via* a global online marketplace creates challenges for non-US authorities in enforcing local regulations on Internet-based products.

How local jurisdictions, such as Australia, the UK, and Europe, should approach regulation and quality control of Internet-based genetic testing is uncertain (9–12). The immediate availability and direct nature of access pose new challenges. Although difficult, many of these challenges are not necessarily unique to the field of genetic testing and have been mirrored in other regulated industries recently disrupted by the emergence of a global online marketplace, such as the online prescription drug sector (13).

CURRENT REGULATION OF GENETIC TESTING IN AUSTRALIA

Under current Australian regulation, there is a strict regulatory regime governing the registration and provision of human genetic tests offered by Australian companies (14–17). Furthermore, laboratories which carry out genetic testing must be accredited for technical competencies by the National Association of Testing Authorities (18). These standards mandate a level of quality control for genetic testing services in Australia. However, compliance with these standards makes it challenging, and relatively expensive, for Australian companies to provide price-competitive DTC testing services compared with offshore DTC companies. Such offshore companies can access Australian consumers *via* the Internet, but are not subject to any Australian regulation.

Consumers may have difficulty distinguishing between locally accredited Australian products and unaccredited, offshore products marketed online. The inability of local authorities such as the Therapeutic Goods Administration (TGA) to regulate online DTC genetic testing and advertising leads to a multitude of regulatory, medical, and ethical concerns, which are set out below and summarized in **Table 1**. In addition, Australian regulation explicitly allows consumers to access non-accredited overseas

TABLE 1 | Concerns with unaccredited online direct-to-consumer (DTC) genetic testing.

Regulation/quality	Challenging for local authorities to regulate online products
	No technical standards for quality control
	No scientific standards for evidence of significance or actionability
Medical	Return of actionable genetic findings without medical oversight
	DTC customers seek interpretation from local health services
	Potentially damaging to the reputation of medical genomics
Ethical	Return of actionable genetic findings without genetic counseling
	Disclosure of risk variants for non-treatable conditions
	Erosion of informed consent
	Recreational intent versus unintended genetic findings
Privacy	DTC companies retain consumer data and DNA samples
	Access to genetic data by third parties, without consumer consent

tests through a self-importation exemption [(14), Reg 7.1 and Schedule 4].

CONCERNS WITH UNACCREDITED INTERNET-BASED DTC GENETIC TESTS

Regulation/Quality

Although stringent standards apply to genetic testing conducted in Australia, the TGA and other regulators are not empowered to prevent access to or regulate the quality of Internet-based DTC genetic tests conducted overseas. Similar issues are faced by other international regulators (9), with issues reported such as difficulties determining whether DTC samples were being processed locally or sent overseas (11). Given the challenges of genomic literacy in the general population (19, 20), many consumers may not be aware of the quality of online genetic tests. Thus, consumers are vulnerable to online marketing by overseas companies, especially for some of the more questionable products generally opposed by the scientific and medical community (10, 21).

Medical Issues

There is evidence consumers of Internet-based genetic tests are increasingly seeking the advice of general practitioners or clinical genetics services for interpretation of results (22). This risks placing an increased burden on existing local health services, which are often publicly funded with limited resources. Funding of additional services to accommodate a growing influx of DTC consumers may not be sustainable in Australia and other comparable nations (23), particularly when results can be ambiguous, uncertain, or confusing, and often identified in individuals not at genuinely increased risk of disease. With some Internet-based DTC companies returning significant genetic risk information of medical and psychological gravity, such as variants in the BRCA genes, without any genetic counseling or medical support, there is also scope for potential harm (24) and/or inadequate care for those who need it.

Furthermore, consumers may have difficulty in distinguishing between established locally accredited clinical genetic testing services (meeting high standards of quality control), versus cheaper online options not subject to the same quality measures. This has the potential to confuse consumers and may compromise long-standing efforts of local genetic services (25).

Ethical Issues

Consumers purchasing DTC genetic tests may be motivated by curiosity, ancestry, or recreational motivations rather than medical reasons. However, they may uncover serious medical risk factors, non-paternity, or other unexpected genetic information in the process of testing, without having considered the implications beforehand (5, 26). In addition, some online tools can now be used to analyze raw genetic data from non-medical DTC tests (such as ancestry tests), to generate interpretations of medical risk. This means individuals can now access medical risk information from raw genetic data online, without any regulation, quality control, or medical oversight after undertaking an ancestry test. This opens up the potential for incorrect interpretation as well as the return of genuinely medically significant risk information without informed consent, genetic counseling, or medical oversight (27).

Genetics services providing clinical testing in Australia follow international guidelines regarding the evidence required to substantiate medical risk information before it is provided to the consumer (28). Model guidelines have also been developed for the evaluation of genetic tests (29), but online DTC companies can provide medical risk information to consumers without fulfilling these evidence requirements (30). Informed consent for Internet-based DTC products does not meet traditional clinical genetic standards, with most DTC companies currently not providing pre- or post-test genetic counseling or medical support (10).

Some DTC tests return genetic risk information for untreatable conditions prior to symptom onset, such as the APOEe4 risk allele of Alzheimer's disease (31). Although some studies have shown such results can be used by at-risk individuals to plan ahead (3), direct provision of this information without access to genetic counseling or medical oversight is generally not standard practice in the clinical genetics community, and is considered by many to be unethical (32). Media reports have detailed anecdotes of individuals who have unexpectedly received risk information for Alzheimer's disease through DTC testing and experienced distress as a result (33).

Privacy Issues

The increasing number of consumers providing DNA samples to online companies also raises concerns around the privacy of genetic data. Recent studies have shown that many online DTC companies do not consistently meet international guidelines regarding data use and privacy (34), and consumers' expectations around privacy and use of their genetic data can be inconsistent with companies' practices (35). Many online DTC companies retain DNA samples for subsequent use, including research, with potentially ambiguous consumer information about the use and

storage of DNA samples (36). Furthermore, it has been suggested that online DTC companies are selling access to their databases of genetic information to third parties, or providing samples for research purposes, potentially without the knowledge or consent of consumers who provided the data (34, 35).

Future Considerations and Recommendations

Given the growing fascination with genetic testing, it is inevitable consumers will continue to seek Internet-based DTC products. The demand for cheap, Internet-based DTC genetic testing may also be fueled by the lack of access to, and cost of, locally accredited clinical genetic testing options in some countries, especially those with publicly funded health systems (37).

There is currently no international association tasked with regulating the online DTC market. The Global Alliance for Genomics and Health (38) is developing standards for the sharing of genomic data, but does not have regulatory powers. The limited amount of public funding allocated for clinical genetic testing in most countries, combined with the increased demand for clinical genetic testing, means many individuals who do not qualify for publicly funded testing under current guidelines may seek alternative, low-cost ways of obtaining genetic information directly.

Unless governments take steps to inform consumers of the dangers of some online DTC genetic testing products, or provide alternative testing pathways, it is likely that consumers will continually have difficulty distinguishing between quality (locally accredited) and non-quality (unaccredited) online products. Many consumers may choose low-priced, low-quality tests and therefore be vulnerable to many of the medical, ethical, and privacy concerns. The potential for confusion, unexpected outcomes, and harm will increase and could threaten the public perception of genomics at a critical time. It is vital that public faith and engagement are safeguarded during the ongoing period of evidence generation for implementation of genomic medicine.

In the future, the concept of governments or public health systems providing access to universal, population-wide genomic screening for disease prevention needs to be considered. This would provide an alternative testing pathway to unregulated Internet-based DTC testing accessed through the private sector. It would ensure stronger quality control, appropriate informed consent, and implementation of evidence-based prevention following national screening principles (39). A recommendation in this regard is set out below. If publicly funded screening is not implemented, it is likely Australia and other jurisdictions will continue to see consumers gravitate toward cheap, Internet-based genetic testing options, especially when genomic literacy remains low.

We recommend the Australian government and comparable jurisdictions take the following steps:

1. Promote education of the public regarding DTC genetic testing, including publicizing warnings in prominent and widely accessed media about risks of unaccredited online DTC genetic testing products.
2. Publicly endorse any local or international companies whose genetic tests meet local accreditation standards, though an easily recognizable accreditation icon, so that consumers can readily identify valid and approved tests.
3. Amend current regulations so that personal importation of unaccredited genetic tests is not sanctioned.
4. Prohibit Internet advertising of non-accredited offshore tests and engage with overseas regulators regarding strategies for regulating advertising of, and access to, online tests.
5. Implement compulsory guidelines requiring the application of evidence requirements for interpretation of genetic tests before the return of results to consumers.
6. Consider a proof-of-concept study to pilot the development of a low-cost, publicly funded, population genomic screening program for young adults, linked with the health system, accompanied by education, focused on the delivery of evidence-based, medically useful risk information for those who seek it.

The implementation of these recommendations would require significant allocation of resources by the government, both toward regulation of online tests and steps toward building a health system capable of undertaking population genomic screening, including scaling of genetic counseling and other medical services. Significant feasibility studies and health-economic modeling will be required before this can become a reality.

The future landscape of genetic testing in countries with strong public health systems, such as Australia, remains uncertain. Many individuals will continue to seek DTC testing *via* the online marketplace regardless, especially for recreational purposes such as ancestry testing, which have limited potential for harm. However, for medical risk information, there are more complexities to consider.

The prospect of a national genomic screening program in Australia to identify actionable genetic risk in consenting adults could be considered. This could potentially identify preventable disease risk early, which if linked to public health system services, could enable closer and more appropriate medical, scientific, and ethical oversight for mainstreaming of genomic testing. A public health screening strategy would ensure those genuinely at-risk are identified and offered appropriate clinical genetic services when needed. Under this model, only established actionable genetic findings, supported by clinical guidelines and standard-of-care for preventable disease, would be disclosed (meaning most individuals would not be receiving results). This may make interpretation of genomic results and subsequent medical risk assessments more achievable.

Screening could be accompanied by national education and genomic literacy programs. These efforts may deter people from seeking unaccredited DTC testing products online for medical disease risk assessment and encourage appropriate management for those genuinely at risk. The prospect of genomic population screening linked to a public health system would require significant bolstering of Australian clinical genetic services, far beyond the current scope. This would need substantive increases in public

funding and infrastructure. Steps in this direction will need to be considered as the wave of consumers turning to DTC testing will continue to rise in coming years.

The Internet, combined with an increasing public fascination in genomics, is currently resulting in an unprecedented access to genetic testing. This will continue to rise and present new challenges for nations in regulating testing and interpretation services. It is likely a pro-active and forward-thinking approach to regulation will be required.

AUTHOR CONTRIBUTIONS

JT drafted the initial manuscript. JT and PL contributed to each draft of the manuscript.

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Phenotypic Heterogeneity in Dementia: A Challenge for Epidemiology and Biomarker Studies

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Dementia can result from a number of distinct diseases with differing etiology and pathophysiology. Even within the same disease, there is considerable phenotypic heterogeneity with varying symptoms and disease trajectories. Dementia diagnosis is thus very complex, time-consuming, and expensive and can only be made definitively post-mortem with histopathological confirmation. These inherent difficulties combined with the overlap of some symptoms and even neuropathological features, present a challenging problem for research in the field. This has likely hampered progress in epidemiological studies of risk factors and preventative interventions, as well as genetic and biomarker research. Resource limitations in large epidemiologically studies mean that limited diagnostic criteria are often used, which can result in phenotypically heterogeneous disease states being grouped together, potentially resulting in misclassification bias. When biomarkers are identified for etiologically heterogeneous diseases, they will have low specificity for any utility in clinical practice, even if their sensitivity is high. We highlight several challenges in in the field which must be addressed for the success of future genetic and biomarker studies, and may be key to the development of the most effective treatments. As a step toward achieving this goal, defining the dementia as a biological construct based on the presence of specific pathological features, rather than clinical symptoms, will enable more precise predictive models. It has the potential to lead to the discovery of novel genetic variants, as well as the identification of individuals at heightened risk of the disease, even prior to the appearance of clinical symptoms.

Keywords: Alzheimer's disease, biomarkers, clinical symptoms, diagnosis, dementia, heterogeneity, pathophysiology

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INTRODUCTION

Dementia is a major public health problem, with enormous social and economic costs, and substantial burden for the individual, their caregiver and families (1). By 2050, it is estimated that over 130 million people will be living with dementia (2). This sharp increase from the 2015 estimates of 48 million reflects not only the aging population worldwide, but the current lack of effective treatments or cures. The results of drug trials to slow or halt the progression of dementia have so far been unsuccessful (3). This emphasizes the need for more research into the etiology of the diseases which cause dementia, with better characterization of genetic and environmental risk factors (4). There is also an increasing push to identify valid disease biomarkers, which would aid in diagnosis, and could be used to predict individuals at future risk (5).

CHALLENGES WITH DIAGNOSIS

Dementia is an overarching term used to describe a group of symptoms that results in severe long-term decline in cognitive function that is significant enough to affect daily function (6). Dementia can result from a number of complex disorders which damage the brain. The most common includes Alzheimer's disease (AD), vascular dementia, frontotemporal dementia, dementia with Lewy bodies, and Parkinson's disease. Typical symptoms of dementia can include a decline in memory, language deficits, and impaired visuospatial skills, as well as a loss of executive function and attention. Associated mood and behavioral disturbances, including delusions, are also frequent (6). However the exact symptoms a person experiences depends on the disease that is causing dementia, as they are distinct diseases with differing etiology and pathophysiology. Symptoms also depend on the parts of the brain that are damaged and the complexity of these conditions is such that even within common underlying conditions, presentation of symptoms differs between individuals (7). For example, there are now classifications of both typical and atypical AD (8). Further, these diseases exist on a continuum of severity and with varying disease trajectories (9). When mild, dementia can be dismissed as "normal" age-related cognitive decline, and some individuals are able to mask symptoms in the early stages (7). The extent to which dementia progresses is also highly variable. Further, given the common behavioral and mood disturbances, dementia can also be misdiagnosed as symptoms of a psychiatric disorder (10). This presents an important challenge for the field (7).

In the absence of clear biomarkers, dementia diagnosis is very challenging. Neuropsychological evaluation with profiles of cognitive strengths and weaknesses are used by both clinicians and researchers to define the likely form of dementia. This information is used in combination with reports of clinical symptoms, the results of blood tests and neuroimaging, and is in accordance with diagnostic criteria which are continually evolving (11). As such, diagnosis is often a very expensive, long and time-consuming process which does not always result in a clear outcome. The heterogeneity in symptoms within different diseases, combined with the overlapping features (both symptoms and neuropathology) across many of the diseases (**Table 1**) further complicates the issue. However the importance of early and accurate differential diagnosis of the underlying dementia condition is crucial. It has implications for prognosis, longer term health planning, and heritability, as well as symptom management, which could potentially be made worse by the use of incorrect treatment (20, 21). Given the continual advances in disease-modifying treatments, it also will have implications for future therapeutics (22).

ALZHEIMER'S DISEASE

The most common form of dementia is AD, an insidious and incapacitating neurodegenerative disorder which accounts for ∼60% of all dementia cases (23). The defining pathological features of AD are the presence of two proteins in the brain, amyloid, and tau. Accumulated amyloid beta (β) peptides clump together forming extracellular neurotic plaques, while hyper phosphorylated TAU proteins form intracellular neurofibrillary tangles (24). A definitive diagnosis of AD thus requires histopathologic confirmation via post-mortem. In living individuals, AD is diagnosed as probable or possible according to set criteria (often DSM) by a panel of expert clinicians who review a range of documentation (25). The guidelines established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association work group (NINCDS-ADRDA), updated in 2011, are the most frequently used for dementia diagnosis (11). An expert panel review the results of extensive neuropsychological testing, detailed medical history, blood tests and imaging, such as magnetic resonance imaging (MRI), positron emission tomography (PET), and/or computerized tomography (CT) and reach a consensus.

OVERLAPPING FEATURES AND MISDIAGNOSIS

However studies have shown that a significant proportion of individuals diagnosed with probable/possible AD by experts, do not display the hallmark neuropathological criteria for AD on post-mortem examination (26). In many other cases, more than one form of dementia is identified ("mixed dementia"), and this becomes increasingly more common in later life (27). Vascular dementia is caused by stroke and/or small vessel disease and includes a number of different sub-types (12). It occurs frequently with AD and the presence of both could exacerbate the development of dementia compared with either condition alone (28). Coexistent Parkinson's disease changes also occur relatively frequently in individuals with AD (29). Dementia with Lewy bodies sometimes co-occurs with AD or vascular dementia or can be misdiagnosed as these conditions depending on the presence of symptoms of cognitive impairment or Parkinsonism (30). In fact, Dementia with Lewy bodies and Parkinson's disease are now considered as a continuum of the same disease (Lewy body dementias), with Dementia with Lewy bodies being an early manifestation in patients with Parkinson's (15).

Adding further to these complexities is the overlap in neuroanatomical features of these disorders (**Table 1**). The hallmark features of AD are the accumulation of amyloid-β and tau protein, yet neither is sufficient to cause dementia nor unique to this disease (31). Tau may be present from early adulthood and could only become problematic once amyloid accumulates (32). Even then, around 30% of people may have amyloid accumulation without any obvious clinical symptoms (33, 34). Dementia with Lewy bodies also shares the neuropathology characteristics of amyloid-β and tau (REF), and the latter is also found in other neurodegenerative conditions such as chronic traumatic encephalopathy (30). Parkinson's disease and frontotemporal dementia both involve tau alterations, but these are a loss of function rather than phosphorylation (35). Likewise, hallmark characteristics of Lewy body dementias, such as α-synuclein inclusions, are also found in many cases of AD (36).

Increasingly evidence from studies investigating neuropathology and molecular genetics has demonstrated that clinical symptoms (phenotype) are not always tightly linked with

TABLE 1 | Common neurodegenerative disorders characterized by dementia symptoms in older individuals, and characteristic features.

Condition	Estimated frequency of dementia cases[a]	Clinical symptoms	Neuropathology	Genetics
Alzheimer's disease (11)	Most frequent, 60–70%.	Memory problems and other cognitive domains can also be affected (e.g., problem solving, finding words, making decisions)	β-amyloid protein plaques & neurofibrillary tangles composed of tau protein. Brain atrophy	Amyloid precursor protein (APP), Presenilin-1 &-2 (*PSEN1, PSEN2*), Apolipoprotein E (ApoE)
Vascular dementia (12)	10–20%. Multiple subtypes (e.g. multi-infarct dementia, subcortical vascular dementia)	Impaired judgement or decision making. Varies depending on position of strokes/infarcts	Blood vessel & vascular related brain damage. Caused by chronic reduced blood flow to the brain, usually as a result of a stroke or a series of strokes	Very rare: cerebral autosomal dominant arteriopathy with subcortical infarcts & leukoencephalopathy (*CADASIL*)
Frontotemporal dementia (13)	10%. Multiple subtypes (e.g., behavioral-variant frontotemporal dementia & primary progressive aphasias)	Changes in personality & behavior, & difficulties with speech. Behavioral variant: progressive deterioration of personality, social comportment & cognition. Primary progressive aphasia: impairments in language production & speech, impaired comprehension	Atrophy in one or both of the frontal or temporal lobes. Highly heterogeneous depending on subtype. Can include Pick bodies, which are positive for Tau and ubiquitin proteins.	Progranulin (*GRN*), Microtubule-associated protein tau (*MAPT*), Chromosome 9 open reading frame 72 (*C9orf72*), Valosin-containing protein (*VCP*) (14)
Dementia with Lewy bodies (15)	5% (16)	Confusion, attentional deficits in visuospatial function. Apathy & hallucinations are common. Absence of motor alterations seen in Parkinson's disease	Abnormal aggregates of α-synuclein proteins, which form spherical structures (Lewy bodies) in nerve cells. β-amyloid and tau accumulation	Rare autosomal dominant inheritance: Alpha synuclein (*SNCA*), leucine-rich repeat kinase family (*LRRK2*), glucocerebrosidase (*GBA*)
Parkinson's disease (17)	Up to 80% of patients with Parkinson's disease progress to dementia	Motor alterations including tremor, rigidity, bradykinesia, changes in gait. As it progresses, dementia like that seen in dementia with Lewy bodies or AD is common	Accumulation of α-synuclein aggregates in diverse brain regions, often begins in the substantia nigra. Result in degeneration of dopaminergic neurons. β-amyloid and tau accumulation	Rare autosomal dominant inheritance: *SNCA* and *LRRK2* genes

[a] *Kosunen et al. (18); Brayne et al. (19).*

etiology, as they can be influenced by a variety of other factors including prior experience, cognitive reserve, and epigenetics (37). Studies of several autosomal dominant dementias indicate that the presenting clinical phenotype may vary widely, even for those individuals with the same causative mutation. For example, mutations in the *PSEN1* gene are considered almost deterministic for earlier onset AD, yet there is considerable heterogeneity in the clinical expression of neurological features (38). This can include behavioral and psychiatric symptoms which can sometimes reflect frontotemporal dementia or dementia with Lewy bodies (38). Another example is a very rare autosomal dominant neurodegenerative disorder, frontotemporal dementia and Parkinsonism linked to chromosome 17 (*FTDP-17*) which has different phenotypes, even within families carrying the exact same mutation (39). The most established genetic risk factor for late-onset AD is the *APOE* ε4 allele, and this is also over-represented in sporadic Lewy body dementias compared with controls (40).

Other people have argued that the different dementia conditions are highly related conditions with a continuous range of abnormalities (41), although genetically and epigenetically they are distinct. Indeed, dementia with Lewy bodies has been shown to be similar genetically to AD, while AD and Parkinson's disease were only very weakly correlated (42). Similar aberrant changes in DNA methylation patterns have also been found in individuals with different forms of dementia (41). However the vast majority of genetic and epigenetic patterns are unique to each disease (37). Further, given the potential inaccuracies in diagnosing dementia, overlapping patterns may also reflect, at least in part, inaccuracies in how the conditions have been defined (discussed further below).

The inherent difficulties in diagnosing dementia, as well as the overlapping symptoms and even neuropathological features, presents a complex and challenging problem for research in the field. This is likely to have hampered progress in genetic and biomarker studies to date, as well as epidemiological studies of risk factors and preventative interventions.

PROBLEMS WITH INACCURATE PHENOTYPING

Genetic and biomarker studies rely on accurate phenotypes and diagnosis (43). Most genetic risk variants identified from such studies are either rare with moderate effect sizes or common with very small effect sizes (44). Large samples are thus needed to have sufficient power to detect true associations, especially at genome-wide significance levels (45). Mixing together diseases with different etiology, pathophysiology and potentially different genetic architecture, is obviously problematic for the

investigation of novel genetic variants, diluting out any signals (43). As an example, new genetic loci identified as being associated with clinically-defined AD, were not found to be associated with AD neuropathology at postmortem (46). Similar problems are likely to be plaguing new biomarker discovery. When biomarkers are identified, if they are in fact reflective of etiological heterogeneous disease states, they will have low specificity for any utility in clinical practice, even if their sensitivity is high (47). These issues are exacerbated by the challenges in selecting unaffected controls who are without dementia. AD for example has a very long pre-symptomatic phase (48), meaning that individuals without dementia in the "control" group, may be free of clinical symptoms, but could already have the disease. Together these issues may help explain the lack of substantial progress in this field to date.

UNIQUE CHALLENGES FOR LARGE COHORTS

Epidemiological cohort studies of dementia, often with the aim of identifying risk and protective factors for the disease (49, 50), are confronted with many of these challenges. Risk factors identified as being associated with cognitive decline and AD diagnosed solely on the basis of clinical symptoms, may in fact not be associated with AD pathology (46). Diagnosing dementia is expensive and time-consuming, which is compounded when undertaken on a larger scale. As a result, studies often only collect relatively sparse phenotypic data, without imaging, blood measures or other biological markers (51).

In recent years there have been widely commended efforts to increase uniformity around the diagnostic criteria for dementia and the underlying construct. The vast majority of publications in good quality journals now define probable AD using clinical criteria by the National Institute on Aging-Alzheimer's Association (NIA-AA) (11). However this criteria predominantly lists recommendations rather than requirements, with the acknowledgment that not all clinicians will have access to the results of the full range of tests, which are time consuming and expensive to obtain. This criteria also includes evidence of neurodegeneration, and thus recommends where possible, that MRI is used to assess cerebral atrophy, but there are no strong criteria regarding other neuropathological changes. With published studies, there is rarely detailed information concerning the information that was obtained to support a dementia diagnosis, and thus difficult for the reader to assess the strength of evidence for these diagnoses. Many studies instead broadly define dementia, and determine risk factors for this heterogeneous condition, which has obvious limitations (as discussed above).

A large number of other studies use less reliable measures of dementia, such as self-reports, linkage data (52), or community diagnoses, with no additional clinical evidence sought to confirm and establish dementia diagnosis (51, 53). This has obvious problems and would increase both the false positives and false negatives. ICD coding is also still frequently used, but has well-documented limitations (54). In other cases, exact diagnostic criteria is not stated (41). Together such studies are likely to be plagued by misclassification bias which would make it more difficult to identify true associations.

FUTURE DIRECTIONS

Currently the methods for identifying and delineating different dementia sub-types are imperfect and not scalable. For research to advance in this area there is a need for better definitions, with clearly established guidelines for the minimal information which must be collected data, and diagnostic markers are required to improve classification of the underlying form of dementia and at a level which is standardized and scalable for large studies.

Deep phenotyping is considered to be the key to advancing genetic studies (55), and this is not just unique to dementia, although it may be one of the most challenging areas. Descriptions of disease phenotypes often do not capture the full diversity of clinical and even pathophysiological manifestations. Advancing research in this area may require sub-categorization of the disease into more homogenous groups or disease states, which would permit increased precision (18, 46). Indeed, very recently there have been calls from the NIA-AA working group to establish a new research framework where AD is defined as a pathophysiological construct, rather than a clinical syndrome (56). While AD is often described by its clinical symptoms, it was identified and initially defined by its neuropathological features, namely the build-up in the brain of β-amyloid (Aβ) protein plaques and neurofibrillary tangles composed of aggregates of hyperphosphorylated TAU protein (11). The presence of these protein enables a definitive diagnosis of AD to be made post-mortem and there are now validated *in vivo* biomarkers for these. Using PET combined with MRI (to assess brain atrophy), the accumulation of amyloid-β and phosphorylated tau can be ascertained (57, 58). Defining AD as a biological construct based on the presence of these imaging biomarkers, will enable the generation of more precise predictive models for this specific neuropathological processes. This will shift away from the focus on clinical symptoms of the disease which are phenotypically heterogeneous, as discussed above, and thus problematic for biomarker and epidemiological studies.

CONCLUSION

The results of drug trials to slow or halt the progression of dementia have so far been unsuccessful (3), raising at least two important issues. Current treatments and interventions are unlikely to be effective in individuals with overt disease symptoms. However they could be effective if targeted very early in the disease process, before the appearance of clinical signs. Hence the need for clear biomarkers which would permit timely diagnosis and accurate characterization of the underlying condition resulting in dementia. Secondly, disease prevention is recognized as increasingly important, given the current lack of therapeutics. This is particularly pertinent for individuals identified at high-risk of the disease. This stresses the need for accurate risk prediction models, and thus the identification of the full range of genetic risk variants, as well as environmental factors through large epidemiological studies. This will also facilitate the

categorization of subgroups within the population most suited for studies of new pharmacological and non-pharmacologic interventions. Adding to this is the increasing focus on precision medicine more generally.

Accurately determining the condition resulting in dementia is critical for research, including epidemiological, genetic, and biomarker studies (46). It is also of particular importance for treatment and prevention trials. Currently there are many challenges with diagnosing dementia, and as such it is a long, complicated and costly task, and misdiagnosis remains an issue. The emergence of new disease biomarkers will have a considerable impact on clinical diagnostic procedures. However, advances in biomarker research have been limited the inability to define a "clear" homogenous dementia phenotype with current biomarkers having considerable overlap with a number of dementia conditions. This creates a circularity problem which is difficult to resolve. However these challenges must be addressed if the likelihood of success for future genetic and biomarker studies is to increase. As an initial step, the focus on neuropathological markers of dementia and defining dementia as a biological construct will enable more accurate characterization of risk factors specific for this disease, shifting the definition from syndromal to biological (56, 59). It has the potential to lead to the discovery of novel genetic variants, the identification of readily accessible peripheral biomarkers reflective of these neuropathological processes, as well as the identification of individuals at heightened risk of the disease, even prior to the appearance of clinical symptoms (60). This will also become an increasingly important issue as new drug treatments are developed (61).

AUTHOR CONTRIBUTIONS

JR and PL conceived the idea. JR wrote the first draft of the manuscript. All authors contributed to revising the final manuscript.

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Public Involvement in Global Genomics Research: A Scoping Review

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Public involvement in research occurs when the public, patients, or research participants are actively contributing to the research process. Public involvement has been acknowledged as a key priority for prominent human genomics research initiatives in many different countries. However, to date, there has been no detailed analysis or review of the features, methods, and impacts of public involvement occurring in human genomics research projects worldwide. Here, we review the reported public involvement in 96 human genomics projects (initiatives), based on a database of initiatives hosted by the Global Alliance for Genomics and Health, according to information reported on public domain websites. To conduct the scoping review, we applied a structured categorization of criteria to all information extracted from the search. We found that only a third of all initiatives reported public involvement in any capacity (32/96, 33%). In those reporting public involvement, we found considerable variation in both the methods and tasks of involvement. Some noteworthy initiatives reported diverse and comprehensive ways of involving the public, occurring through different stages of the research project cycle. Three notable initiatives reported a total of eight distinct impacts as a result of involving people. Our findings suggest there would be intrinsic value in having more public involvement occur in human genomics research worldwide. We also suggest that more systematic ways of reporting and evaluating involvement would be highly beneficial, to help develop best practices.

Keywords: genomics research, public health, public involvement, scoping review, co-design and co-production, patient and public involvement and engagement, patient participation [MeSH term], public health genomics

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INTRODUCTION

In human genomics, there is a growing need to increase involvement of the public in research and policy development. This has been identified as a crucial aspect of responsible research practice (1, 2). The concept of "public involvement" in research is defined as research that is carried out "with" people rather than "on" them (3). Public involvement can also be defined as when the public, patients or research participants actively contribute to the research or policy development process (4).

The number of people involved in genomics research is predicted to grow substantially in coming years (5, 6). By 2025, it is estimated that nearly 2 billion people worldwide will have had their DNA sequenced, creating a global imperative for responsible and effective

public involvement in research (7). Many high-profile genomics research initiatives have already made public statements about the importance of involving people, with some governments positioning public involvement as a democratic right (8–10). For example, in the report "Generation Genome," the UK's Chief Medical Officer suggested that shaping the future of genomic research requires the "active involvement of many stakeholders including patients, health professionals, researchers, policymakers, and wider society," with a "key role for public engagement and involvement" (10).

The benefits of involving the public in research are wide-ranging. They include improving trust and public influence over research (1, 7, 8); ensuring that research is conducted in an ethical, accessible and transparent manner; and ensuring that research reflects the balance and diversity of priorities within populations (11, 12). However, with the growing interest and importance of large-scale human genomics initiatives worldwide, there has been limited research into how the public are currently being involved. There has also been no structured assessment of the resulting impacts and benefits, including genomics initiatives that have involved the public.

While involving the public in other types of health and medical research has been the subject of previous systematic reviews (13–15), comparable reviews have not been published in human genomics. Many of the existing reviews on other areas of medical research conclude that reports of involvement activities are inconsistent or under-reported (15–19) and that the precise ways in which people are involved in medical research are not well-reported, including any impacts from involving people (7, 14, 16).

Our review provides a summary of reported public involvement in 96 global human genomics projects, listed on a database managed by the Global Alliance for Genomics and Health (GA4GH), a recently formed international organization seeking to enable responsible genomics data sharing within a human rights framework (20). The list provides a representation of the current landscape of human genomics research worldwide, and a snapshot of contemporary practice with regards to public involvement in human genomics research.

This scoping review provides a new perspective by exploring how these genomics initiatives have conducted and reported public involvement to date, including any impacts, facilitators and barriers of involvement. The intention is that resulting data will help inform future directions for integrating public involvement into genomics research and policy development, and inform the development of ways of routinely reporting and evaluating any involvement.

METHODS

Source

Using a list of human genomics research projects (referred to as "initiatives") from a database hosted by the GA4GH (see **Table S1**), we systematically searched public domain websites for information reported on involving the public in research. The database was curated by GA4GH staff, last verified August 2016, and contains information about the type of the genomics research initiative (i.e., consortium, data-sharing initiative, organization(s), repository or research project), the type of data gathered (i.e., whole-genome or whole-exome sequencing), the geographical scope of the initiative, number of participants (cohort size), relevant disease areas, and the public domain URL of the website for the organization or initiative (as some "initiatives" involve a number of organizations). The scoping review methodology can be summarized in three stages (see **Figure 1**).

Stage 1—Defining "Involvement" and the Search Strategy

We developed a criteria to define "involvement" and refine our search terms, informed by the International Association for Public Participation's participation spectrum and other studies (4, 8, 21, 22). This included reports of "consultation," "involvement," "collaboration," and "empowerment" (23). Involving people in genomics research was defined as the "active involvement" in shaping and guiding research, rather than only providing data (17, 23, 24). We defined specific tasks related to involvement at different stages of the research cycle (3), such as the sharing of views to influence research, or co-creating the research (19, 25, 26). "Consequential" involvement is when involvement contributes to the research process, as distinct from involvement which is ignored or not incorporated (27–29). We could not always determine whether involvement was consequential based on the available information, so an assumption was made that all methods reported were "consequential."

Stage 2—Searching Websites (Data Extraction)

Public domain websites of all the initiatives in the GA4GH database were searched for reports of involvement and associated impacts. The date range for website searching and data extraction was 16th August to 28th November 2017. The exact text from the URLs where data was extracted from was collected to allow reanalysis, with all relevant URLs archived using an online archive service to preserve the content and the date of extraction (30).

After a manual search of each domain, search engine operators were entered into the Google "site search" function in order to systematically scan the text of each public domain website for relevant phrases, including all grammatical variations of the words used (for example, deriving "involvement," "involves," "involved," and "involving" from the root word "involve"). Grammatical variations of specific phrases (denoted by inverted commas) were generated using tables to systematically create a series of search strings for each domain. For example, this search string returned 4 results:

> *site:www.ukbiobank.ac.uk/* "public involvement" OR "involves public" OR "public involved" OR "involving the public" OR "involve public"

Reports of involvement were assessed by a member of the research team (JN), then independently assessed by an additional

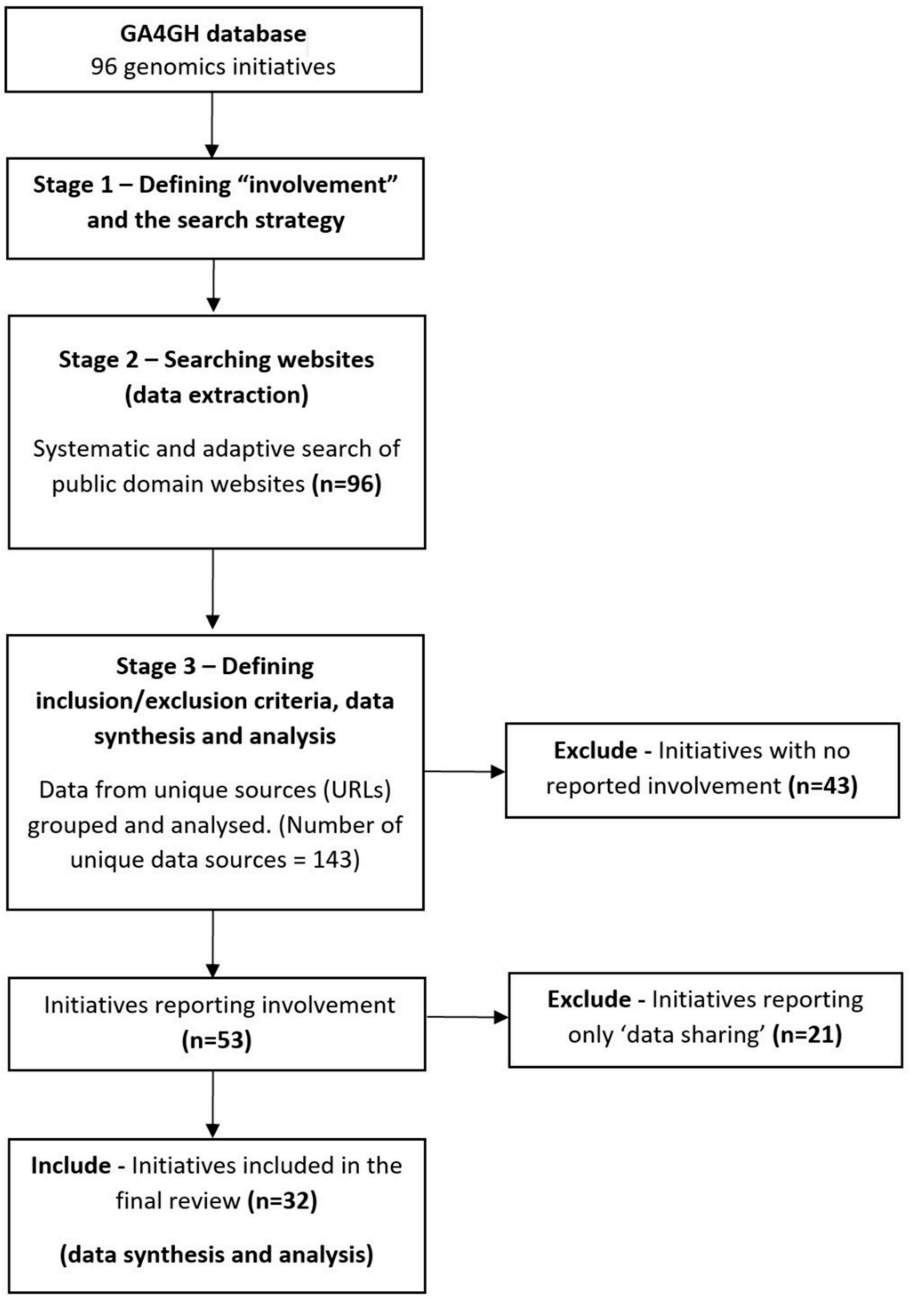

FIGURE 1 | Scoping review study overview and results summary.

member of the research team, with a random sample assessed by a third investigator (PL). Any disagreements between the team on the data included was discussed until a consensus was reached. Informed by previous reviews, the search terms for the concept of involvement were; "engagement," "involvement," and "partnership" (21, 31–34). The search terms to describe the people involved were; "citizen(s)," "community," "consumer(s)," "lay," "patient(s)," "public," "stakeholder(s)," and "user(s)."

In addition to using a standard list of terms, adaptive (context dependent) search terms were sometimes required when searching domains where terms were specific to the region or initiative. Adaptive search terms were; "advocate(s)," "carer(s)," "civil society," "client(s) (35)," "customer(s) (35)," "group(s)," "participant(s)," "payer(s)," "population(s) (29)," "PPI" (an acronym commonly used in the UK which stands for "patient and public involvement"), "residents" (geographical grouping) (36),

"representative(s)," "taxpayer(s)," and "volunteer(s)." For more details on search method, see **Systematic search method**.

Stage 3—Defining Inclusion/Exclusion Criteria, Data Synthesis and Analysis

Defining the inclusion and exclusion criteria was an iterative process informed by published scoping review methodologies (37, 38). Initiatives reporting no involvement were excluded from further analysis. Initiatives were categorized as "no involvement" if the context of words such as "participation" were used to describe "research participants" (research subjects) only, rather than aligning with the concept of involvement already articulated (4). Reported impacts were excluded if they were phrased as anticipated future impacts (using terms such as "we expect"), rather than reporting real results. Initiatives reporting "data sharing" as the only type of involvement were also excluded. Initiatives reporting any other type of involvement, according to our definition, were included and proceeded to data extraction (structured categorization of extracted search data).

Extracted data was categorized (data synthesis) based on the following types of information; (**a**) the *method* of involvement (*how* people were involved) (24); (**b**) the *tasks* they were involved in (what people *did*) (24); (**c**) the *stage* of the research (using an expanded version of an existing framework (15), informed by INVOLVE) (39); (**d**) *who* was involved, for example "research participants," "patients," and "public" (informed by the Concannon "7Ps Framework" taxonomy) (16); (**e**) *reported facilitators or barriers* of involvement; and (**f**) publicly-reported *impacts* (informed by section 7 and 8 of the GRIPP2 framework) (16, 24).

As there is currently no standardized way to report and group methods of involving people or descriptions of people involved (24, 29), grouping was informed by methods of previous reviews [for example, grouping similar methods of involving people (24)] and by using previously established nomenclature (26, 33). The initial grouping (JN) was reviewed by other authors (PL). While previous reviews have used frameworks to label the "roles," "degrees," or "levels" of involvement or "control" (19, 24), we did not use these frameworks as they require subjective judgements to be made, often with insufficient data (26, 40–42).

RESULTS

Of the 96 initiatives searched, based on our criteria, only a third reported involving people in some capacity (32/96, 33%) (**Table 1**). These 32 initiatives were included in the final analysis (data synthesis).

Reported Methods of Involvement

The reported methods of involving people were organized into categories, shown below in **bold**, with the number of total initiatives reporting each method shown in brackets:

- **Citizen science** ($n = 2$)—people involved beyond data collection, research design or data analysis, toward co-creation across all aspects of the scientific process (43);
- **Consultation** ($n = 4$)—an organized consultation or dialogue process;
- **Formal discussion** ($n = 8$)—formalized "focus groups," forums or interview structures;
- **Formal groups** ($n = 20$)—a working group or committee (including ethics and data access committees, "scientific advisory groups" and "steering groups");
- **Generic involvement** ($n = 11$)—informal, such as meetings, "partnership," or an unspecified method;
- **Newsletters** ($n = 2$)—or mailing lists;
- **Online tools** ($n = 7$)—websites, social media, or online community hosting;
- **Public events** ($n = 13$)—with discussion—including initiatives hosting public debates, workshops, discussion spaces, or conferences;
- **Surveys** ($n = 10$)—including questionnaires; and
- **Other** ($n = 7$)—methods not described by other categories.

Some initiatives reported using multiple methods to involve people. Reports of involving people also showed that some methods, for example "formal discussion," can use different modes of communication, including face to face, online (for example, "massive open online courses"), or a combination of the two.

Figure 2 summarizes overall findings from data synthesis. There was variability in the methods and tasks of involvement reported. This supports previous findings that involvement in biomedical research is diverse, varied, and described using different language (44).

Reported Tasks of Involvement

The tasks people were involved in (what people did when they were involved) were diverse. Tasks included identifying research priorities related to people with specific diseases; communicating priorities to scientists, clinicians and health policy makers [IDs 11, 37, 50, 74]; designing or improving how people will be involved in the research [IDs 41, 50]; educating professionals involved in the research [ID 8]; developing workshops and conferences [IDs 44, 94]; offering culturally appropriate information about research to people in community groups [ID 37]; providing feedback on the cultural and linguistic appropriateness of public domain research documents [ID 96]; and translating information into "lay" language [ID 92]. Tasks also involved sharing views and perspectives about multiple aspects of research projects [ID 37, 92, 96]; articulating phenotypes [ID 65]; and being a project co-investigator [ID 21].

Some initiatives reported involving people in the task of giving feedback and sharing views and perspectives about the "acceptability" of specific aspects of the research design. For example, research management, governance [IDs 27, 41, 92, 72], accountability, planning, policy, protocols, data access, and data use [IDs 37, 74, 84, 92], consent, re-contact, withdrawal, confidentiality, benefit sharing, project closure, and recruitment [IDs 37, 62, 74, 92]. A number of initiatives also involved people in the task of sharing views and perspectives on issues of perceived social and ethical importance (including being told about potentially serious incidental findings) [IDs 37, 74, 96], or to scrutinize a project to ensure it aligned with public interest [ID 11].

TABLE 1 | Summary of G44GH initiatives reporting public involvement.

Name of Initiative/Organization	ID	Geographic Region (cohort size)	Reported methods of involving people
100 k Wellness Project	1	North America (100,000)	Online tools, Other
Australian Genomics Health Alliance (AGHA)	8	Australia (1,800)	Formal groups, Other, Public events
Biobanking and Biomolecular resources Research Infrastructure (BBMRI)	11	Europe (N/A)	Formal discussion formats, Public events
Cancer MoonShot 2020	16	North America (20,000)	Generic involvement
Clinical Sequencing Exploratory Research (CSER)	21	North America (6,000)	Generic involvement
DECIPHER	24	International (21,475)	Formal groups
East London Genes and Health	26	Europe (100,000)	Formal groups, Generic involvement
Electronic Medical Records and Genomics (eMERGE)	27	North America (55,028)	Surveys
ELIXIR	28	Europe (N/A)	Consultation, Formal groups, Public events
France Genomic Medicine 2025	33	Europe (N/A)	Consultation, Generic involvement
Genome in a Bottle	35	International (N/A)	Generic involvement, Public events
Genomics England	37	Europe (100,000)	Consultation, Formal discussion formats, Formal groups, Generic involvement, Other, Public events, Surveys
H3Africa	41	Africa (60,000)	Formal discussion formats, Generic involvement
Implementing Genomics in Practice (IGNITE)	44	North America (73,000)	Formal groups, Public events
International Rare Diseases Research Consortium (IRDiRC)	50	International (N/A)	Formal groups, Generic involvement, Other, Public events
Kaiser Permanente Research Program on Genes, Environment, and Health (RPGEH)	52	North America (500,000)	Formal groups
Kaviar	53	North America (N/A)	Formal groups
Matchmaker Exchange	57	International (N/A)	Formal groups, Online tools
MSSNG	60	North America (10,000)	Formal groups
MyCode Community Health Initiative	62	North America (250,000)	Formal groups
MyGene2	63	International (500)	Online tools
openSNP	65	Europe (2,500)	Citizen science, Online tools, Surveys
Precision Medicine Initiative /"All of Us"	69	North America (10,00,000)	Citizen science, Formal groups, Formal discussion formats, Generic involvement, Online tools, Other, Public events, Surveys
Public Population Project in Genomics and Society (P3G)	72	International (N/A)	Formal groups, Online tools, Public events, Surveys
Qatar Genome Project	73	Asia (1,161)	Surveys
RD-Connect	74	Europe (2,500)	Formal discussion formats, Formal groups, Generic involvement, Newsletters, Online tools, Surveys
The Clinical Genome Resource (ClinGen)	84	North America (N/A)	Formal groups, Other
Tohoku Medical Megabank Project	86	Asia (150,000)	Formal discussion formats, Public events, Surveys
Transforming Genetic Medicine Initiative (TGMI)	88	Europe (N/A)	Public events
UK Biobank	92	Europe (500,000)	Consultation, Formal discussion formats, Formal groups, Generic involvement, Newsletters, Other, Public events, Surveys
Undiagnosed Diseases Network (UDN)	94	North America (8,000)	Formal groups
Vanderbilt's BioVU	96	North America (215,000)	Formal groups, Public events

Initiatives from a database provided by the Global Alliance for Genomics and Health were searched for reports of public involvement (based on public domain websites). Each initiative has been assigned an ID number. The type (method) of involvement was categorized using specific criteria.

While there are commonalities with the principles of involvement in other kinds of biomedical research, the review identified three novel tasks in relation to human genomics research not found in other reviews. These included involving people in phenotype articulation [ID 65], where people can describe the lived-experience of having specific genomic variations; articulating the variation in perspectives of people affected by different rare diseases [ID 74]; and collective governance, problem solving and improving code [ID 53; 65]. For example, Open SNP shared the code for the entire initiative using Github (a platform for sharing open-source code), inviting participants and other members of the public to scrutinize, contribute, and improve the code.

Reported Stages of Involvement

Most reports of involvement were at the "implementation and management" stage of research (19/32, 59%), followed by "dissemination" (12/32, 38%), "evaluation," and "study

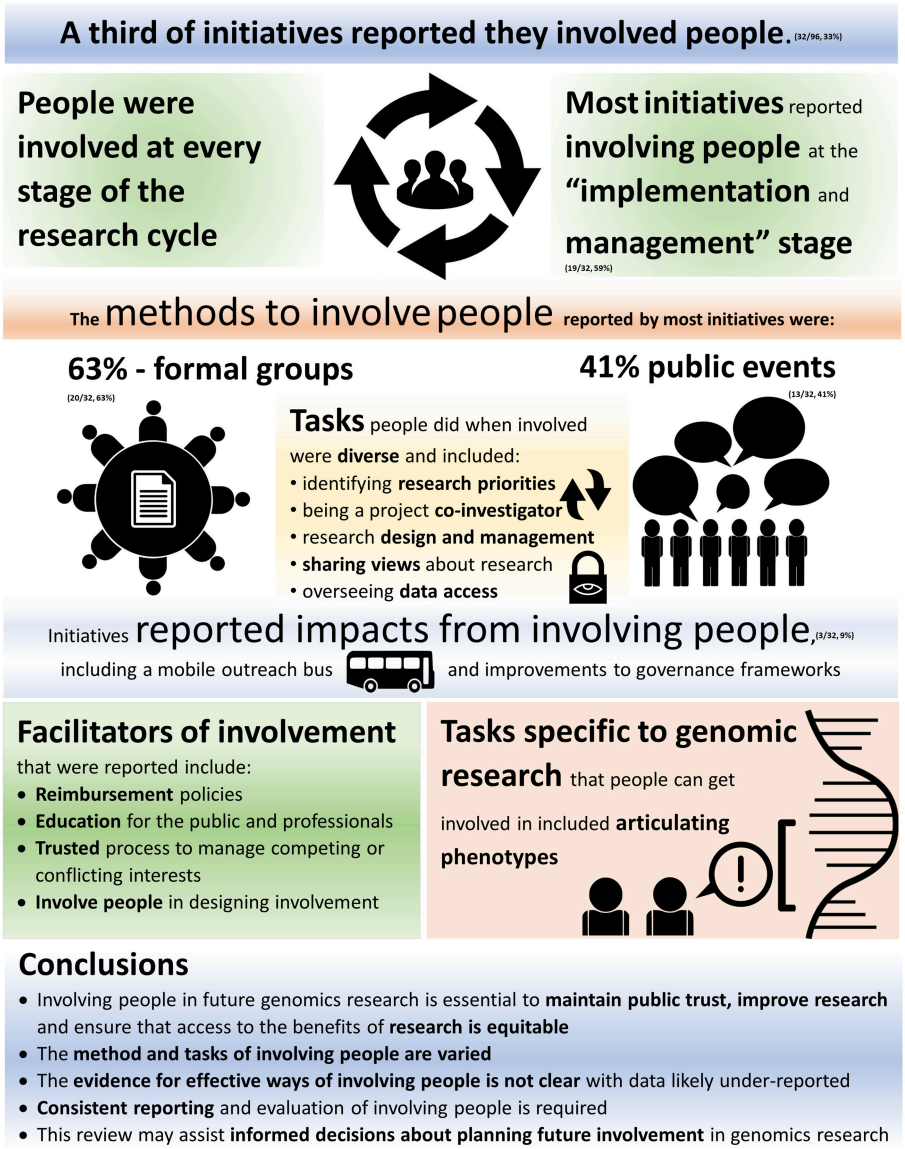

FIGURE 2 | Summary of results.

design" (both 9/32, 28%) and "data analysis" (8/32, 25%). The stage with the lowest number of initiatives reporting involvement was "funding" (1/32, 3%) with the next lowest being "identifying topics" and "prioritization" (both 4/32, 13%). Four initiatives reported involving people at every stage of research [IDs 21, 50, 69, 74].

Reported Impacts of Involvement

Nearly 10% of the initiatives reporting involvement also reported impacts of the involvement (3/32, 9.4%). Three initiatives reported a total of eight distinct impacts as a direct result of involving people [IDs 37, 73, 92]. The method with the most reported impacts was "public events" (4/8, 50%), followed jointly by "formal discussion formats" and "surveys" (2/8, 25%). Actions taken as a result of involving people (impacts) included the creation of a mobile outreach bus [ID 37]; improvements to ethical and governance frameworks [ID 92] (45); and improved participant information and consent documents [ID 37] (46). Some impacts were reported as being a result of using a combination of methods.

Reported Facilitators and Barriers to Involvement

A number of specific facilitators of involvement were reported, including: reimbursement policies [ID 21], with people involved paid for their time [IDs 92, 94], travel [IDs 74, 94], accommodation [ID 74] and expenses [IDs 74, 92]; education and learning opportunities for the general public [IDs 1, 11, 41]; ensuring people involved are informed and can make informed decisions [ID 11]; education for health

professionals [IDs 41, 50]; providing opportunities to learn about how to involve people [IDs 41, 50]; and governance which is trusted by all stakeholders to be able to manage real or perceived competing or conflicting interests [ID 50]. The only barrier reported was limited venue size, which restricted the number of people who could be involved [ID 92]. This also implies a limited budget, which is an important but likely under-reported implicit limitation on all involvement methods.

DISCUSSION

This review provides an overview of reported public involvement occurring in prominent human genomics projects worldwide, during a period of rapid growth for genomics research. We identified significant variability in the way in which involvement occurs and is reported. The variation in reported involvement suggests diversity in both the ways people are being involved in genomics, and in the varied and emergent language used to report and describe involvement, consistent with other areas of biomedical research (8, 21). While there are similarities with the principles of involvement in other kinds of research, this review has identified three different tasks specific to genomics, not found in other reviews (44).

Because the results from this review suggest there is currently no standardized way of reporting involvement in human genomics, and therefore evaluating how people are involved, there is a risk that best-practice will be hard to define or even absent in future evidence reviews. This has implications, as the number of people involved in human genomic research is predicted to grow exponentially. Without a standardized framework to report and transparently evaluate ways people are involved, it will be difficult to create an evidence base to inform best-practice.

While a third of initiatives reported involvement, a majority of projects did not (64/96, 66%). Some prominent initiatives involving the genetic analysis of thousands of people did not refer to public involvement in any way. This is somewhat concerning given that involving the public has been identified as a crucial aspect of responsible research practice in genomics (1). Whilst we acknowledge the probable under-reporting of involvement activities on public-domain websites, we argue public involvement in human genomics research needs to increase.

Findings from this review also suggest it is best-practice to involve multiple stakeholders (including the public) in designing how people will be involved in research (co-design of the involvement plan), and to involve the public throughout the lifetime of a project in certain tasks (such as overseeing data access) and to evaluate the involvement with both qualitative and quantitative data.

Co-design of involvement strategies may improve how appropriate, effective, efficient and equitable they are. Seeking input from people into the design of planned methods of involvement by identifying what is considered "good practice" was reported by H3Africa [ID 41] and the International Rare Diseases Research Consortium (IRDiRC), and reported as a facilitator of involvement by the IRDiRC [ID 50]. The IRDiRC [ID 50] also reported both qualitative and quantitative data should be used to evaluate involvement, although there is currently no way to systematically collect and analyze such activity (47).

If involvement is more effective when the public are invited to help plan it, standardized reporting and evaluation will help make informed decisions at every stage of involvement from co-design through to evaluation.

Implications for Policy and Practice

With the impact of some genomics research data likely to be measured in decades, some of the initiatives offer a useful insight into planning and funding of sustainable (long-term) involvement for the entirety of an initiative's lifetime (9). For example, Genomics England [ID 37] and the UK Biobank [ID92], as exemplars, both reported multiple ways of involving people, at different stages of the research cycle, conducted over a number of years. Other initiatives, such as the International Rare Diseases Research Consortium (IRDiRC) [ID 50] and the Public Population Project in Genomics and Society (P3G) [ID 72], also publicly stated the importance of planning sustainable involvement over the duration of a project. These initiatives demonstrate a standard of involving people which could eventually be used to inform international best practice.

The IRDiRC also reported that involving people throughout an entire project helped maintain trust by scrutinizing and managing competing or conflicting interests [ID 50]. Similarly, the UK Biobank reported that involving people in ethics and governance should not be one-off and must be ongoing [ID 92]. The method of using "formal groups" was more common for more complex or ongoing tasks such as overseeing data access, policy development, research management and improving research protocols.

Some initiatives, such as openSNP, reported tasks that were specific to genomics research, such as articulating phenotypes [ID 65]. Involvement in this kind of task might have important implications when working to usefully describe people's subjective lived-experiences across multiple languages, for example, rare diseases and mental health (48).

Public involvement in articulating phenotypes also suggests that the traditional boundaries between terms such as "research," "healthcare," "patients," "research participants," and "the public" may be increasingly challenged by the methodology of future genomic research (49). Findings from this review show that both "the public" and "patients" are already involved in every stage of research, including collecting and analyzing data (49). Any future standardized reporting of involvement will need to keep pace with the continually evolving language to describe not only what research is, but who is involved and how.

Limitations

While the database hosted by GA4GH includes many of the most prominent human genomics research initiatives worldwide,

the database is not exhaustive. There are several known genomics initiatives which involved people that were not part of the database. Therefore, the GA4GH selection cannot be considered systematic or representative. However, it does provide a reasonable indication and snapshot of the current global landscape in human genomics research up to November 2017. After the review was completed, GA4GH shared a new a database with 220 initiatives (50), presenting an opportunity for future reviews. The addition of so many new projects to the database reflects the rapid pace of growth in human genomics research.

Our data collection was limited to self-reported information reported on English language websites only. This likely under-reports the total amount of public involvement occurring. For example, some initiatives may have conducted involvement, and not reported it publicly. This indicates a current lack of standardization or best-practice in reporting involvement activities in human genomics research, which we feel could be improved.

Of the public involvement activities reported, we did not systematically follow up reports to confirm they had taken place, or if involvement was "consequential" (27–29). While this is a limitation of the review, it also reflects the inconsistent and often incomplete ways genomics research initiatives report impacts of involving people. For example, the impact of how involvement influenced research was only reported by three projects—Genomics England [ID 37], the Qatar Genome Project [ID 73] and the UK Biobank [ID 92].

A number of reported methods did not provide sufficient information to make a clear decision about how to group a method. For example, many reports of involvement simply referred to a "workshop," "meeting," or other "public events," where people were able to get involved by sharing views and perspectives. As a result there is potentially significant overlap between some methods, which could have been articulated more clearly if more data were available. Similarly, while detailed data was extracted about "who" was involved, ways of grouping terms such as "research participants," "patients," and "public" requires further development to co-create standardized definitions.

The systematic searching of domains with the Google site search function relies on Google servers having carried out a "website crawl," where data from the website is indexed (51). As the search and indexing process is partially opaque (not open-source), this method cannot be considered "exhaustive." However, it is an appropriate supplementary search strategy for this scoping review.

Reports of "data sharing" were excluded, as they were not considered as public involvement. While sharing data may enable people to be involved in some tasks (for example, in analyzing data), data sharing is not necessarily an indicator that people were involved in the analysis of data. The complexity within the term "data sharing" in genomics, and how people can be involved in the analysis and interpretation of data, also requires further consideration (52–54).

CONCLUSION

Involving people in the future of genomics research is an essential aspect in maintaining public trust, improving research outcomes, and ensuring that access to the benefits of genomics research is equitable (1, 14, 49). The limited number of initiatives reporting public involvement and its impact in this study suggests there would be significant value in developing a more systematic method of both reporting and evaluating how people are involved in human genomics research. Data from such reporting could provide the evidence required to inform future policy around involvement of the public, as human genomics research continues to grow.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2019.00079/full#supplementary-material

Table S1 | GA4GH database and results table. This table combines a database of human genomics research projects hosted by the Global Alliance for Genomics and Health with a summary of results from a scoping review of currently reported public involvement reported on public domain websites. The data is organized alphabetically, with organizations reporting involvement listed first.

Systematic search method | This document describes the search method, including how standard and adaptive TERMS were used to search the public domain websites of all the included initiatives in the GA4GH database for reports of involvement and any impacts.

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