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Personalized health and precision medicine in practice

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Personalized health and precision medicine in practice

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Table of contents

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Editorial: Personalized health and precision medicine in practice

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Editorial on the Research Topic
Personalized health and precision medicine in practice

Social scientists have scrutinized extensively so-called personalized health and precision medicine. "Precision" and "personalization," these scholars argued, are buzzwords of biomedical research: at best, they are umbrella terms that cover a diverse array of practices, technoscientific innovations, and biomedical scenarios (Abettan, 2016). At worst, these terms conceal perilous rhetoric: they operate a worrying brokerage of scientific promises and political reform of healthcare that make up a social meaning of innovation disjoined from its value for patients and the healthcare system (Prainsack, 2017). More recently, social studies of biomedicine have addressed the practical settings (e.g., public health; clinical sciences; environmental health sciences, etc.) in which normative, practical, organizational and technoscientific processes related to "precision" and "personalization" take place (Bourret and Cambrosio, 2019; Chiapperino et al., 2020; Bourret et al., 2021; Crabu, 2021; Polk et al., 2023). Leaving aside the question as to whether innovations will deliver on their promises, offers the opportunity for a different social and humanistic scrutiny of contemporary biomedicine: what are the specific institutional, local, practical, technical and scientific reconfigurations of health and medicine required by "precision" and "personalization?"

This Research Topic dissects how personalized health and precision medicine happen in these kinds of practices. Taken together, the nine articles composing the Research Topic demonstrate how these sociotechnical configurations are a diverse patchwork of healthcare experimentations and innovations in need of stabilization, validation, and standardization. Aspects concerning the implementation and validation of infrastructures of personalized health and precision medicine are best represented in the Research Topic. Taking personalized stem cell therapies for thalassemia as a case, Panwar documents the gamut of social, historical, ethnic and cultural categories that enter in the constitution of a biobanking infrastructure in Chennai, India. Caught up with considerations of caste, language and family relations, the personalization enacted in this biobanking infrastructure resembles a searching for definition of community and collective identity, rather than a technical process of biomedical research. Bühler analyzes the assemblage of a human biomonitoring cohort in Switzerland. Upstream

from the detailed personalization of public health interventions for Swiss citizens lies the implementation of a longitudinal population-based cohort that can offer the tools, data and knowledge needed to assess the impact of the environment over health. The infrastructuration of precision public health, Bühler argues, rests upon challenging enactments of biosocial complexity in postgenomic sciences; that is, on the pragmatic and strategic choices made by scientists to render the complexity of social conditions, environments, relations and experiences amenable to biomedical research.

Another subset of articles in the Research Topic shows how the infrastructures and sociotechnical configurations of personalized health and medicine are no less dependent on often-neglected human labor. As argued by von Arx, data-intensive medical practices in cardiology may have profound implications not just for how, but also as to when a diagnosis is made. Her case study of remote cardiac monitoring illustrates the relevance of time in the development of precision cardiology: the alleged immediacy and continuity of telemedical devices does not automatically translate in a medicine of anticipation and early diagnosis. Rather, this promise of immediacy clashes with the need for human synchronization of these technologies: without adapting to the temporalities of the nurse ward the data-intensive monitor cannot produce meaningful knowledge of the patient's heart condition. Froger-Lefebvre et al. observe the same need for human labor and collective action. The authors analyze the implementation of an electronic prescription software for the use of genomic analyses in France. Vital to the introduction of this software is (what the authors qualify as) the dirty work of invisible professions: administrative and time-consuming tasks, such as the tuning of the new software into existing software, or the adaptation of established logistical workflows. All this essential work is often performed by overqualified workers in precarious jobs and raises profound questions about the invisible organizational choices and hierarchies of professions in precision medicine.

The political dimensions of practices developing personalized health and precision medicine are fleshed out more explicitly in two further contributions to the Research Topic. Pillayre and Besle analyze the mixed biomedical, organizational, and political aspects that partake to the definition of "rarity" in oncology. Documenting the constitution of validated lists of rare tumoral entities, the authors unpack a recursive tension in this process. On the one hand, the definition of rare cancers is intimately connected to the rise of genomic technologies: a growing number of cancers can in fact be defined as rare due to the availability of technologies that can measure their unique biological characteristics. On the other hand, rarity merely depends on negotiations between medical and political actors aiming to affirm the relevance of these clinical entities and direct toward them expert work in the international community. Pinel et al. emphasize instead how the development of epigenetic tests, known as biological clocks, renders specific forms of decay observable and socially relevant. Researchers assemble these tests by selecting specific sets of data and resources. In doing so, they also produce the relevance of specific collective approaches to aging in science and society. While the biological clock portrays aging as inevitable decline in the laboratory, the clock's transition into the market transforms aging into a modifiable trajectory, which demands action from allegedly empowered individuals and health consumers.

Of note is also the heterogeneity of the contributors to the Research Topic, including expertise in law, sociology, philosophy and anthropology, but also public health, epidemiology, clinical genetics and data sciences. This testifies to two intersecting points. On the one hand, this heterogeneity illustrates the topicality and relevance of STS analyses for the actors who are actively pursuing this new kind of medicine, healthcare and health promotion. As exemplified by the article of Walton and Christensen—two authors who can claim decades-long professional experiences in the development of genomic medicine—the change required to bring the tools of genomics in healthcare systems are neither merely technological nor just clinical or scientific. The authors underline the often-neglected social, organizational and policy dimensions of the genomic transformation of medicine. Hospital workflows, institutional standards, billing procedures, professional education or even the architectures of hospitals should be the target of change in the healthcare system to accelerate the use of genomics in medicine. And the importance of bringing "the social" into the development of personalized health and precision medicine is of no less relevance at an epistemic level to these actors. As pointed out by the perspective article of Delpierre and Lefèvre—two public health scholars—models of personalization are too tied to a biomedical model of health, which often neglects the interactions between the environmental, socio-economic, psychological, and biological determinants of health. Drawing upon a biopsychosocial model of medicine, the authors underline that biomedical knowledge of health—based for instance on the tools of "omics sciences" (e.g., genomics, transcriptomics, epigenomics, proteomics, metabolomics, and pharmacogenomics)—may not be fit for the purpose of delivering on the promises of personalization. Personalized medicine, they conclude provocatively, should be tantamount to a serious consideration of the "person" beyond the unique biological characteristics of individual patients.

On the other hand, the heterogeneity of contributions to our Research Topic points to the reflexivity on the epistemic, technical, organizational, regulatory and political dimensions of personalized health and precision medicine that can come from within biomedical practices (see Mann and Chiapperino, 2023). If anything, the Research Topic is thus a reminder of the importance of engaging with a diverse array of perspectives on personalized health and precision medicine and actors that should include citizens and patients who are the primary targets of these innovations. As Berti Suman et al. argue in their perspective article, grassroots-driven initiatives—which the authors call "personalization from below"—could help identify and develop alternative understandings of "personalization" and "precision" for the future of medicine. Reaching beyond the model of public engagement with biomedicine, their political argument for personalization from below rests upon epistemic, democratic and equality considerations that heavily challenge the hierarchical structures often dominating healthcare.

In summary, the results of our Research Topic point to the openness and situatedness of the sociotechnical configurations labeled as precision medicine and/or personalized health, and to

the much-needed involvement of heterogeneous actors (e.g., civic associations, activists, citizens, patients, researchers, healthcare professionals, and policymakers) in their making. Moreover, we believe that the Research Topic also offers a clear rationale to integrate social studies of personalized health and precision medicine with the debates on these matters internal to biomedical sciences. Future studies taking a cross-cutting, interdisciplinary, and collaborative approach may be key to realize the model of "personalization" and "precision" *we*—as a heterogeneous set of scholars and citizens—want (Prainsack, 2014): a model that is both challenging to existing hierarchies in healthcare and is attuned to its practical conditions of possibility.

Author contributions

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

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Reimagining health services provision for neglected groups: The "personalization from below" phenomenon

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How can data-driven citizen science activities supporting health research and services provision meet the needs of unrepresented and neglected groups through increased personalization? In this short Perspective, we explore "personalization from below" as a concept designating forms of citizen science-based data altruism that specifically push for and enact a different understanding of both health services and personalization. We develop the argument that such phenomenon taking place outside "institutionalized" health-related practices could make health services provision more inclusive of values that matter to people. We contextualize instances of "personalization from below," discuss related data governance models and alternative public health interventions, and conclude by outlining three key arguments in favor of "personalization from below" and future research avenues.

KEYWORDS

health, public services, personalization, citizen science, data altruism, data governance

Introduction

The notion of "personalized medicine" is often understood in relation to medical treatments tailored to individual needs and based on a pool of digitalized data pertaining to the biological, behavioral, social, and environmental determinants of health (Maughan, 2017; Prainsack, 2017). This notion mostly acts at and for an "individual" level (critically Juengst et al., 2012; Prainsack, 2018). However, there are signs for a *reconfiguration* of this notion of personalization. Certainly, the fact that professional, institutional, commercial and research practices have been opening participatory avenues to involve patients has long been part of the narrative of "personalized medicine" (Swan, 2009, 2012; Prainsack, 2017). However, new and more grassroots-driven approaches of health-related citizen science activities (Vayena et al., 2015) and health data governance (Blasimme et al., 2018) have emerged, reconfiguring boundaries between experts and ordinary people. We add that crises, such as the COVID-19 pandemic and environmental or climate disasters, may further accelerate this already ongoing blurring of divides between experts and ordinary people, changing the borders of institutional territories of knowledge. Thus, a new understanding of personalization might emerge, this time enacted "from below," where *below* stands for deriving from/produced by ordinary people (i.e., the grassroots) but does not imply a hierarchy.

Given such a reconfiguration, the traditional understanding of personalization might need to embrace dimensions that go beyond an individual-centered view of a person's wellbeing, including more collective and *altruistic* understandings of services. Furthermore, traditional (health) services provision is generally still based on the expert/practitioner-layperson divide and on a rather "paternalistic" approach to the person that needs such services (Chiapperino and Tengland, 2015; Prainsack, 2017). We argue that a valorised inclusion of contributions from below in health services provision would imply reforming hierarchical structures dominating

in "institutionalized" health-related practices. In addition, we posit that this reconfiguration demands a consistent commitment from institutional actors to embrace the contribution that ordinary people, well-organized and aware of their health needs, could bring.

In this perspective article, we explore practices that signal forms of "data altruism" aimed at personalizing health services to the needs of *unrepresented* and *neglected* groups. We regard these groups as those that do not feel sufficiently or at all included in the design and implementation of health services because their particular health conditions have been under-researched and/or neglected by policy-makers due to entrenched bias and structural forms of discrimination.

Data altruism is understood as the situation in which some people decide to voluntarily donate their personal data for a common goal such as scientific research. Health *services* include both those organized by the government or any other institutional body to the benefit of a particular society or community, and those that are "auto-organized" from below, by grassroots actors that complement or substitute "official" service provisions. We explore whether grassroots-driven data altruism strategies could make health services provision more inclusive of people's values and experiences, bringing in a form of "personalization from below."[1]

As a start, we contextualize these practices as a specific form of science-based knowledge production which has been called personal health science elsewhere (Heyen et al., 2019). We then elaborate on some real cases and their data governance models, before we reflect on the implications of "personalization from below" for alternative public health interventions. We conclude by outlining future research avenues.

"Personalization from below" as a form of personal health science

Whereas the vision of "personalized medicine" focuses on the core of the healthcare system, thus on medical treatments, there have been other developments in the context of personalized health that take place largely *outside* established medical or scientific institutions. Two very prominent examples are Direct-to-Consumer (DTC) genetic tests provided by private companies such as *23andMe*,[2] and digital self-tracking *via* wearables and digital health apps. The promise of the commercially operated DTC services is to enable everyone (with a sufficient level of technology access/ability/understanding) to produce personalized knowledge about one's own body (e.g., *via* genetic tests). The promise of digital self-tracking tools is to enable individuals to obtain greater knowledge about their health status than they used to have in the past. Both cases have been the subject of numerous, also critical, analyses (e.g., Van Dijck and Poell, 2016; Sharon, 2017). As Juengst et al. (2012) argue, for instance, such practices often depict patient empowerment as "the solution" to an ever-present healthcare crisis, but at the same time risk to center responsibility for healthcare excessively on the patients. In any case, both examples represent activities and practices of science-based knowledge production which are initiated (in the case of DTC tests) or operated (in the case of self-tracking) by ordinary people and relate to their own personal health.

Heyen and Dickel (2019) have summarized these activities and practices under the term *personal health science*. Linguistically, Personal Health Science (PHS) is a term built by the authors through the coupling of three sub-terms: personal health, health sciences, and personal science. First, personal health refers to the individual health of one single person. The term suggests a personal view of one's own health and thus a (lay) perspective commonly distinguished from professionals and experts. Second, health sciences refer to the interdisciplinary field of professionally conducted research on human health. Finally, personal science means both research into one's own person and *a specific form of citizen science*, since it is usually laypersons and not professional scientists who become scientifically active and research themselves (Heyen, 2016, 2020; Senabre Hidalgo et al., 2022). Already on the basis of this simple conceptual chain, Heyen and Dickel (2019) argue, PHS can be located at the interface of health (or the healthcare system), science (or the science system), and society (or the public): laypersons research and care for their personal health. Thus, PHS practices always have both a scientific reference, since the knowledge production has at least a scientific or scientific-technical basis, and a self-reference, since the knowledge concerns the health of a concrete person engaged in these practices.

The phenomenon of "personalization from below" seems to represent a third type of PHS practices. It is neither about the commercially-driven and professional-based scientific analysis of personal health data for the benefit of science and the individual user or data donor (such as the DTC genetic tests and also platforms like *PatientsLikeMe*,[3] representing a first type), nor is it about the pure individualistic practice of ordinary people doing research on one's own body and health without striving for any additional common good-oriented purpose (such as personal science, representing a second type). Instead, "personalization from below" in our framing:

- Is the scientific research on one's own health organized and led by civic organizations, patient groups, local communities, or even individual patients or laypersons;
- Aims at the production of knowledge that is both (potentially) generalizable for science and applicable for personal health purposes of the participants (or even for wider public health services); *and*
- Creates an added value for more collective or even altruistic purposes beyond commercial profit and one's personal health.

Health data production and governance in "personalization from below"

Instances of "personalization from below" in the health sector can be found in data altruism initiatives and emerging data governance models. With data altruism we indicate the donation of (personal health) data for public interest purposes by single individuals, such as in citizen-science studies, art projects or civic-led initiatives.

1 Prainsack (2017, p. 11) in her work used the term "personalization from below," yet with a different understanding than what embraced in our contribution. In our opinion, she refers to the general data contribution and other efforts of patients within the paradigm of personalized medicine. In contrast, our proposition orients this concept towards "neglected" groups operating from below that—through contributing health data—demand to make (health) services provision more inclusive of values that matter to people.

2 See https://www.23andme.com/.

3 See https://www.patientslikeme.com/.

Data altruism differs from other forms of data generation, in which laypersons produce data about their health status (i.e., with self-tracking apps) and third parties get access to it according to the terms of service of the platform. It refers to data exchanges established explicitly for public interest purposes. Data subjects collect new data or share information with a third party for a public interest purpose, like for research and advocacy. For instance, data altruism initiatives have been launched to address structural gender-based discriminations in health research and to reconfigure healthcare *via* new forms of data collection, sharing and use. These are based on bottom-up participation, *via* donation of information about various aspects of personal health, from weight to menstrual cycle, in certain cases obtained through self-sampling kits. Initiated by different social actors, ranging from research institutions, artists, grassroots movements and civic organizations, these initiatives advocate for better and fairer healthcare for all (Salas Seoane et al., 2022).

An example is Isala,[4] a citizen science project at the University of Antwerp, developed within the framework of the larger Lacto-Be project,[5] which involved over 4,500 participants who provided detailed information about their health status and sent samples collected with vaginal swabs. The study allowed to increase understanding of the female microbiome, which is crucial for women's health and reproduction but whose ecology and determinants in the general population are still unclear with severe consequences on women wellbeing (Lebeer et al., 2022). A project with a similar goal is Transbiome,[6] developed to provide a basic understanding of the vaginal microbiome for transwomen who undergo gender-affirming to surgeries, with the aim to fill the knowledge gap about transwomen's microbiome. A related topic has been addressed by Alma,[7] an art project based on a participatory methodology. Women have been involved through the use of special sensors, for monitoring information in vaginal fluids, with the goal of creating an atlas of female intimate health and of helping those suffering from recurring gynecological conditions. Another relevant case is that of a participatory research conducted within the framework of the EU-funded project "TRANSFORM,"[8] where women acted as co-researchers talking in first person about endometriosis in Catalonia, a matter on which they felt that their voice was under-represented. The initiative embraced citizen science methods to raise awareness on how endometriosis is experienced by the affected women, and produced first-person recommendations to improve diagnostic and care services (Salas Seoane et al., 2022). Overall, these initiatives are "altruistic" insofar as data collected/shared not only lead to better knowledge about the self for each participant, but also produces collective benefits, increasing knowledge on under-researched topics, and advocating for more research and better healthcare.

Instances of "personalization from below" in the health sector can also be found in an emerging model of data governance that enables collective control over data and its use: data cooperatives. Data cooperatives have been flourishing especially in the health sector to enable citizens to control their personal health information and donate for research, see for instance initiatives such as Salus.Coop,[9] MiData[10] and OpenHumans[11] (Greshake Tzovaras et al., 2019). They allow individuals to exert direct control over their personal data, by aggregating information collected from multiple sources and integrating it with that of all members, to increase knowledge and purse collective goals that benefit members of the community and the wider society (Blasimme et al., 2018). Data cooperatives are part of a wider constellation of "alternative" data governance models, which contest the dominant logic of accumulation and extraction in the current data economy according to which data is merely a driver for economic growth (Mulgan and Straub, 2019; Micheli et al., 2020; Korjan and Narayan, 2021; Sadowski et al., 2021; UK AI Council, 2021). Mainly adopted by Big Tech and large companies, who collect data on their customers, the extractive logic is starting to permeate also States and public health authorities, that "no longer maintain a monopoly on large-scale data collection, but find themselves competing with businesses for a share of revenues to be extracted from data from the population" (Tupasela et al., 2020, p. 5).

Data cooperatives, instead, are a response from below to those trends, as they are led by civic actors (civic society organizations, citizens, informal groups), are based on different values (inclusion, equity, redistribution of value and public interest) and aim to reshape power relations around data control and value. At the moment, these are small scale and niche initiatives, yet, they are shaping the debate on how alternative governance approaches to (health) data might occur (Sandoval, 2019). In fact, not only data cooperatives are mentioned by a growing body of literature, but they are also supported by the EU Data Governance Act, a regulation included in the European Strategy for Data, which is meant to increase trust in data sharing fostering the establishment of neutral data intermediaries and data altruism.

Health data cooperatives are instantiations of what "personalization from below" could look like, as they stand in stark opposition, both in terms of scale, governance and values, to top-down initiatives by governments or big tech companies aimed at building large personal data repositories for research on personalized medicine (Blasimme et al., 2018). Not only they allow individuals to have control of their own health data, steering its use according to their motivations and concerns, but they also produce collective benefits through a more democratic governance approach: they are inspired by a political drive to increase the possibility to govern data from below. Members of data cooperatives are not just seeking individual benefits, they act as a community with shared interests and use data to satisfy collective interests (e.g., increased knowledge on a rare disease), which cannot be pursued individually (UK AI Council, 2021). Marginalized social groups and underserved communities can organize data cooperatives to make their voice heard, taking control of their data and influencing the direction of scientific activities, for instance redressing the under-representation of neglected communities in health research databases (Blasimme et al., 2018). Data cooperatives can offer access to aggregated data that did not existed before, for under-researched themes or on

4 See https://isala.be/.

5 See https://cordis.europa.eu/project/id/852600.

6 See https://www.transbiome.org/.

7 See https://al-ma.org/Smart-Underwear.

8 See https://www.transform-project.eu/transforming-the-patients-experience-through-citizen-science/.

9 See https://www.saluscoop.org/.

10 See https://www.midata.coop/en/home/.

11 See https://www.openhumans.org/.

under-represented populations, which can have a transformative power for health public service delivery.

Alternative public health approaches triggered by "personalization from below"

The illustrated experiences suggest three main arguments for how "personalization from below" can support alternative public health approaches. First, an epistemic argument, which is that knowledge of health issues can be overall improved by "personalization from below." The data that people share in these initiatives are often shedding light on under-researched matters and come from the knowledge of under-represented groups. Furthermore, the data that people share are frequently enriched with people's values and their demands for a different way to imagine health services provision. By relying on such data, personalization approaches can represent more members of the population and the knowledge stemming from said practices becomes more generalizable.

The second is a democratic argument to favor "personalization from below," as the political legitimacy of any public health intervention in any group can benefit from considering the initiatives that are manifestation of this trend and the related data produced. Indeed, when institutions manage to "embrace" the good of these practices, methodological and socio-political innovation can occur. Launching, joining or embracing an initiative can be regarded as a *political act* that inform policy discourses on public health promotion. The said practices may embody expressions of rights (for example, right to participation, to healthcare, to dignity, to representation) and of values (for example, respect for and inclusion of unrepresented and neglected communities and their understanding of services). Data stemming from such initiatives could help institutions in making services provision more attentive of different worldviews, re-shaping them in a way that is more centered on actual needs of specific communities. This could make services arguably more democratic.

A third aspect, connected to the first two, it is an equality argument in praise of "personalization from below." Promoting the said practices can help making visible the issues, concerns, needs and health priorities of neglected groups. At present, this is found first and foremost in scientific research arenas. Synergies are indeed multiplying between researchers and social groups that feel "neglected" which demonstrates that researchers recognize the value of "personalization from below." Just to highlight some European cases, in the previous section we mentioned the Isala project, an initiative deployed in the framework of a research project funded by the European Research Council, which engaged women as citizen scientists to advance the understanding of lactobacillus' beneficial potential for vaginal health. In other instances, neglected groups stood up on social media without the "mediation" of researchers. An example is offered by the movement for the recognition of Vulvodynia[12] in Italy.[13] The initiative adopted a bottom-up approach based on sharing of information and community-building on social media to increase public awareness of an illness perceived as largely ignored and misunderstood. By posting personal stories on social media, participants (both patients and doctors) shared health data and created a (digital) space for discussion (Pieri, 2022). Recently, the mobilization led to the first proposal for a law for the recognition of Vulvodynia as a medical condition.[14]

Conclusion and future research

Our reflection, situated at the intersection of personalized health and knowledge co-production based on altruistic health data sharing, builds an alternative understanding of "personalization" that differentiates itself from a more individual-centered notion of what "personalized" means. We illustrated examples of grassroots-driven triggers to innovate health services provision. By contributing their data and time, people demonstrate that a certain matter is important to them because it is affecting them directly (e.g., a personal illness) or it is putting at risk values in which they believe (e.g., lack of recognition for the needs of an underserved group). Such flourishing small-scale initiatives shape the debate on health data governance and they shed light on under-represented health concerns or disparities that are not prioritized by policy or market agendas. They also push for regarding data as a common resource for the benefits of a (more or less extended) group of people, defining themselves how these benefits are understood and should be pursued. We speculate that in a near future people might increasingly shift from demanding data and services from "official" channels to openly providing data and even services that can be of value for institutions and other citizens. Institutions in charge of services provision should look at these practices as possible models of alternative public health interventions and design appropriate "policy uptake" strategies (Berti Suman, 2021).

Institutional support to these initiatives would entail a twin transition, pairing socially just interventions with data-driven innovation, and shaping both according to civic values. In addition, these practices will need regulation, validation and standardization to avoid abuses and misinformation masked under the vests of "good data." Such task could be performed by gate-keeping actors and stewards, which could be practitioners, researchers and research institutions, and civil society's associations. The role of institutions in the field could be to oversee the quality of data collected by the grassroots groups, and to promote digital literacy and equal access for disadvantaged communities. The question on how can these communities' values, demands, and imaginaries be embedded into data and how can governance models accommodate this in a way that they translate into services is still open. However, we believe that institutional support to scale up successful, but still niche, civic experiences could enable or at least facilitate this outcome. This implies challenging hierarchical structures often dominating healthcare, and adopting concrete interventions to embrace the contribution from small scale grassroots initiatives and help them scaling up.

12 Vulvodynia is a persistent, unexplained pain in the female genital area which can become a long-term and very distressing ailment.

13 See https://www.vulvodinianeuropatiapudendo.it/.

14 See https://www.quotidianosanita.it/governo-e-parlamento/articolo.php?articolo_id=104439.

In this brief Perspective, we could not fully grasp the epistemic, organizational, legal, regulatory, and political heterogeneity of the discussed developments. We also could not make justice to the diversity of social actors (e.g., civic associations, activists, patients, healthcare professionals, and policy-makers) that play a role in the field. In this fascinating, yet still largely unexplored field we deem that further research is needed along the following lines, among others. Empirical research should review scenarios—such as crises and disasters—that can act as enabling factors spurring "personalization from below." Furthermore, inquiry is needed to explore which values, demands and rights' claims people embed in the data they produce. Investigation on how public actors can make wise use of them through a benefit sharing approach could be useful. Research should also assess more in-depth the ruptures and continuities with traditional personalized health approaches. Comparative case study analyses could help refine and describe the said model(s) and approach(es), and assess their impacts on service provision in specific domains and contexts. A comparative investigation can also shed light on the values traditionally present in initiatives that are manifestation of "personalization from below," compared to those typical of personalized medicine initiatives. Legal implications should be explored, for example, regarding the potential risks for privacy and data protection of the participants and the likelihood of market capture, especially when there are hidden interests to profit (Berti Suman and Pierce, 2018). Answering these and further questions will be pivotal to shape agile and just health services provision in the near future. We hope our Perspective added a viewpoint and a step ahead in this direction.

Data availability statement

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

Author contributions

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

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Conflict of interest

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

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Precision and personalized medicine: What their current definition says and silences about the model of health they promote. Implication for the development of personalized health

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The US National Human Genome Research Institute defines precision medicine as follows: "Precision medicine (generally considered analogous to personalized medicine or individualized medicine) is an innovative approach that uses information about an individual's genomic, environmental, and lifestyle information to guide decisions related to their medical management. The goal of precision medicine is to provide a more precise approach for the prevention, diagnosis, and treatment of disease." In this perspective article, we question this definition of precision medicine and the risks linked to its current practice and development. We highlight that in practice, precision medicine is based on the use of large volumes of biological data for individual purposes mostly in line with the biomedical model of health, which carries the risk of the biological reductionism of the person. A more comprehensive, precise, and even "personal" approach to health would require taking into account environmental, socio-economic, psychological, and biological determinants, an approach more in line with the biopsychosocial model of health. The role of environmental exposures, in a broad sense, is highlighted more and more, notably in the field of exposome research. Not considering the conceptual framework in which precision medicine is deployed leads to the concealment of the different responsibilities that can be mobilized within the health system. Anchoring precision medicine in a model that does not limit its definition to its biological and technical components makes it possible to envisage a personalized and more precise medicine, integrating a greater share of interventions centered on the skills and life contexts of individuals.

KEYWORDS

precision medicine, personalized health, health model, challenges, risks

Some elements of definition

The last 20 years have seen the emergence of the concepts of P4 medicine, that is, participatory, personalized, predictive, and preventive medicine (Hood and Friend, 2011), and this has occurred mainly in parallel with the developments in clinical genetics, artificial intelligence, and digital technology. P4 medicine reflects fairly well the consideration of developments mainly driven by technology rather than theory. P4 medicine is particularly based on the now almost ubiquitous nature of digital technology, whether in terms of data collection (e.g., *via* internet browsing, or simply the use of smartphones), storage, and computing capacities (especially for data genome sequencing in clinical routines), or in terms of the development and use of algorithms. It updates an old idea and desire: that of gaining knowledge and information that is more specific, more targeted, and more adapted to the pathology of a given person, and to be able to analyze these data in an intelligible and useful form in order to be able to propose personalized treatment and care.

The concept of P4 medicine is thus mainly based on the use of large volumes of data, mostly biological (omics data). This is particularly the case for personalized medicine, which is one of the foundations of P4 medicine. The US National Human Genome Research Institute defines personalized medicine as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. Knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen" (National Human Genome Research Institute, n.d.). It is specified that "personalized medicine is being advanced through data from the Human Genome Project," highlighting the crucial importance of genetics to this approach.

This definition is similar to the definition given by the US National Cancer Institute, which defines personalized medicine as "a form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease. In cancer, personalized medicine uses specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis." It is interesting to note that the US National Cancer Institute uses the same definition for precision medicine (National Cancer Institute, n.d.).

In practice, precision medicine and personalized medicine are often used interchangeably. This is recognized by the US National Human Genome Research Institute in its definition of precision medicine: "Precision medicine (generally considered analogous to personalized medicine or individualized medicine) is an innovative approach that uses information about an individual's genomic, environmental, and lifestyle information to guide decisions related to their medical management. The goal of precision medicine is to provide more a precise approach for the prevention, diagnosis, and treatment of disease" (National Human Genome Research Institute, n.d.).

According to the US National Research Council, "personalized medicine is an older term with a meaning similar to precision medicine. However, there was concern that the word "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual. The Council therefore preferred the term precision medicine to personalized medicine" (National Library of Medicine, 2019).

We believe that these two terms are not interchangeable, as personalized medicine incorporates broader dimensions than those explored in practice in precision medicine as explained below.

What is done in practice when we talk about precision and personalized medicine?

In practice, the notion of precision medicine remains centered on the use of large volumes of data, in terms of the people included but also in terms of the data used, the latter being largely biological (for example, genomics, transcriptomics, epigenomics, proteomics, metabolomics, and pharmacogenomics) and for individual-centered purposes and applications. In fact, it is largely intended for predictive medicine, for the determination of risks calculated from groups of individuals with the same biological and clinical characteristics, or for diagnostic decisions, by multiplying individual biological data, for "à la carte" health. The overall aim is to offer patients a treatment adapted to their biological and clinical characteristics. Precision medicine consists of identifying which approaches/treatment will be effective for which patients according to the group to which they belong on the basis of their biological characteristics. In this sense, it is more stratified medicine than personalized medicine. As an illustration of what precision medicine means in routine practice, we can refer to oncology, where there has been significant developments in this type of medicine. The French National Cancer Institute states that precision medicine is currently based on two types of treatment, targeted therapies and specific immunotherapy (144 drugs available, including 107 targeted therapies and 37 specific immunotherapies) (French National Cancer Institute, n.d.). These treatments are mainly used for patients with advanced forms of cancer or who have relapsed. It is thus used to offer patients a treatment adapted to the characteristics of their tumor, and has had success in cases including chronic myeloid leukemia, lung and breast cancer, and metastatic melanoma (Gambardella et al., 2020).

Precision and personalized medicine: A definition that implicitly reflects one of the two main models of health

Historically, there are two main models of health representation: the biomedical or biological model (Yuill et al., 2010) and the biopsychosocial model proposed in the 1970s by Engel (1977). The biomedical model intends to define health on the basis of the individual's health, this health itself being defined and determined by the biology of the individual at different scales: for example, genetics at the most basic scale today, and the molecular, cellular, histological, and anatomical scales. This representation centered on the individual is supplemented with the notion of the environment, to take into account everything that is not the individual. To refer to health as a whole, we then speak in a very broad and not very explicit definition of a gene ×

environment interaction model. It is therefore initially a deeply reductionist and materialist representation. This model of health is the one on which precision medicine as described above is built, which is largely aimed at characterizing individuals by their biological characteristics. Conversely, the biopsychosocial model defines individual health by taking into account at least three complementary dimensions: the biological, psychological, and social dimensions. This definition is in accordance with the WHO definition of health as a "state of complete physical, mental, and social wellbeing, not merely the absence of disease or infirmity" (World Health Organization, 2013). This definition of health is then not entirely covered by that of pathology, and therefore covered even less by the reduction to the biological determination of a pathological risk. It also proposes to take into account environmental, socio-economic, and psychological determinants in addition to the biological dimension, and makes health a complex, interdisciplinary, and transdimensional field. By proposing to integrate other dimensions than the biological, this model offers a more global approach to health that is more comprehensive, more precise, and even more personal since it considers a person in multiple dimensions. The biopsychosocial model is therefore more in line with a medicine that could be defined as personalized.

However, the practice of precision medicine, maintaining health essentially as a matter of disease and biological reductionism, can distract from the need to consider the social and environmental determinants of health (Mentis et al., 2018). This model is all the more relevant as it is becoming increasingly clear that taking into account omics characteristics (primarily genomic ones) alone is not sufficient to perfectly predict the phenotype, such as the risk of developing a disease or the response to a treatment, and that the role of environmental exposures (including physicochemical, behavioral, and psychosocial exposures) is fundamental in the way genes are expressed. According to the International Agency for Research on Cancer, 40% of cancers in France can be attributed to lifestyle or environmental factors (International Agency for Research on Cancer, n.d.). The development of the so-called exposome science highlights the rebalancing of the environmental gene balance in favor of the weight of the environment in a broad definition. The concept of the exposome refers to all the exposures to external and environmental factors that an individual undergoes during his or her life from the prenatal period. It includes the external exposome, which refers to exposures outside the body that may be general (e.g., social, cultural, and ecological contexts) or specific (e.g., chemical pollutants or lifestyle factors), and the internal exposome, which refers to measurable biomarkers and metabolic and physiologic processes inside the body (Wild, 2005, 2012). Interestingly, the internal exposome builds on fields of study such as genomics, transcriptomics, metabolomics, and lipidomics, which are at the core of precision medicine. The exposome approach thus provides a conceptual framework for linking the external environment (external to the organism), including the totality of human environmental exposures from conception onwards, to internal biological functioning (internal exposome). This relationship between the environment, in particular the social environment, and biological functioning has been further conceptualized and formalized in social epidemiology. The concept of embodiment that Nancy Krieger has developed refers to "the way in which we literally incorporate biologically the material and social world in which we live" (Krieger, 2005). The way in which this biological embodiment of the social, or the social to biological transition (Blane and Kelly-Irving, 2013; Kelly-Irving and Delpierre, 2021), can take place through two broad main types of socially distributed initial mechanisms that can interact and affect each other along the life course. Firstly, mechanisms of "exogenous" origin, though which entities or conditions external to the body either enter the body and elicit a physiological response from it (for example, inert or living entities like foodstuffs, asbestos, viruses, bacteria, and pollutants) or lead to physical harm (e.g., injuries and accidents) or exertion (e.g., movements and actions). This concerns environmental exposures such as pollution, pesticides, work exposures, and lifestyle behaviors such as tobacco use, alcohol use, and diet. Secondly, mechanisms of "endogenous" origin, through which sensory interpretations of interactions with the environment elicit responses from "internal" molecules from the body mainly linked to stress perception and stress response systems as well as cognitive and psychological functions. In terms of exposures, these concern especially psychosocial exposures such adversities during childhood (for example, trauma, sexual abuse, physical violence, and neglect), occupational constraints, social support, social isolation, and experiencing discrimination, and whether they are related to age, gender, social class, skin color, sexual orientation, or disability (Blane and Kelly-Irving, 2013; Kelly-Irving and Delpierre, 2021). It is therefore scientifically inappropriate to consider genes and the social environment separately, as the biological functioning of an individual is closely linked to the environment in which he or she evolves.

Why it is important to develop a personalized medicine and health based on a broader vision of health

There is considerable evidence of the influence of various external exposures on biological functioning at different omics levels in both animals and humans, including gene expression through epigenetic changes. Among the environmental exposures studied, a great deal of data is available on the effect of physicochemical exposures or health-related behaviors. The effect of the social environment is less frequently taken into account, as a review of the literature has just shown in research on the exposome, despite research calling for them to be taken into account (Senier et al., 2017; Vineis and Barouki, 2022). However, the effect of the social environment and psychosocial exposures on biological functioning has been highlighted in the literature, including at the omics level (Lang et al., 2020; Palma-Gudiel et al., 2020; Lim et al., 2022), underlining the interest of integrating this dimension to better understand biological functioning, health, and disease. Horton has talked about a syndemic rather than a pandemic when regarding the COVID-19 epidemic, highlighting how the joint consideration of social and biological aspects improves the understanding and management of the disease (Horton, 2020).

Ziegelstein proposed that a new "omics" term called "personomics" be added to the precision medicine toolkit

(other omics approach) as the missing link in the evolution of precision medicine to a medicine that would be really personalized. He stipulated that "Personomics recognizes that individuals are not only distinguished by their biological variability, but also by their personalities, health beliefs, social support networks, financial resources, and other unique life circumstances that have important effects on how and when a given health condition will manifest in that individual and how it will respond to treatment" (Ziegelstein, 2017). This interesting proposal takes up the idea that a real "personalized medicine and health" needs to include information about the person's environment and living conditions and not only the biological characteristics of their disease. Such an approach presupposes the availability of environmental and socio-economic data which are very rarely present in medical records or simply not systematically searched for by physicians. While individuals are increasingly phenotyped at the "omics" level, they are rarely phenotyped at the environmental level (e.g., the physicochemical, behavioral, psychological, and social levels). Personalized medicine implies making the same effort to characterize the person in terms of his or her living conditions as was made to characterize the patient at the biological level.

Specificities of current personalized medicine and implications in terms of means of action and care

Technique as the main defining element of personalized medicine

Any practice is marked by the tools at its disposal, as they determine the possibilities of concrete actions, and the ways in which these actions are carried out. Thus, our conceptions of health, illness, and what can be prevented, treated, restored, or palliated are intimately linked to our knowledge, our societies, and our techniques. It is still quite rare that a technique emerges and is applied in the most appropriate and direct way for a previously identified health problem. This refers to the concept of situated knowledge, developed by Haraway (1988), which postulates that knowledge is embedded in, and therefore affected by, the concrete, historical, cultural, linguistic, and value context of the person or entity producing it.

However, it seems that the current definition of personalized medicine marks a turning point or at least an accentuation: that is, a significant imbalance between what technique determines practice and knowledge, and what knowledge and practice determine accepted and desirable techniques. Indeed, it appears that personalized medicine as it is presently is mainly defined by its technical aspects: the use of data, directly or *via* more or less sophisticated algorithms. Above all, it does not respond to a conceptual framework of health or healthcare. In this sense, it may seem to escape us, since we have not imposed any particular framework on it, at least explicitly. However, medicine, and more generally, health, do not have direct access to the modalities of existence and use of this technique, whose main infrastructures and proposed tools are in the hands of companies themselves unrelated to health, such as GAFAMS.

The choice and explanation of the conceptual framework of health and care from which personalized medicine is defined and practiced determine the possible means of action

If we choose to anchor personalized medicine, i.e., its definition (what it does, how, and why) and its means of action, in the biomedical model, the implications in terms of the responsibility of the actors and the means of action will be essentially centered on the individual. In particular, the debate around individual responsibility, and therefore the financing of health and healthcare according to individual health risks, is making a comeback: data-driven techniques and tools are deemed to provide more resources, the purpose of which is to screen the risks and quantify them, more or less upstream. The means of action are and will remain mainly directed toward the individual and the biological levers. If we anchor personalized medicine in the biopsychosocial model, the implications are different, again in terms of responsibilities and means of action. The individual responsibilities and biological actions of the previous model are replaced or supplemented by shared responsibilities and funding mutualized or endorsed by actors other than the individual (particularly in the case of environmental risks linked to several types of pollution), and also by broader means of action. We have mentioned the possibility of taking into account the patient's environment and living conditions in the physician-patient relationship, but this goes even further, since we are also dealing with public health policies, as well as collective means of action. Moreover, we must consider that health crosses a large number of policies that are not specifically restricted to public health, e.g., industrial, agri-food, education, and housing policies. The prescription of diets and physical activity, for example, is part of this logic if we consider behavior. Interventions for stress management are also part of this logic. This opens up a range of actions and professionals who can intervene in individual health management. Inhibiting the conceptual framework in which personalized medicine is deployed means obscuring the various responsibilities that can be mobilized within the healthcare system, but also depriving ourselves of additional means of action, including more precise means: since 2015, there has been talk of "precision public health." Finally, anchoring personalized medicine in a model that is not only biomedical but also does not restrict its definition to its technical components, makes it possible to envisage a personalized and more precise medicine—more relevant?—integrating a greater amount of interventions and human interrelations centered on personal skills and contexts (e.g., therapeutic education and patient empowerment). Of course, the alternative to the two existing models, the biomedical and biopsychosocial, may no longer be sufficient, and a new framework must be proposed.

Data availability statement

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

Author contributions

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

Conflict of interest

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

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Slowing down decay: biological clocks in personalized medicine

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This article discusses so-called biological clocks. These technologies, based on aging biomarkers, trace and measure molecular changes in order to monitor individuals' "true" biological age against their chronological age. Drawing on the concept of decay, and building on ethnographic fieldwork in an academic laboratory and a commercial firm, we analyze the implications of the development and commercialization of biological clocks that can identify when decay is "out of tempo." We show how the building of biological clocks rests on particular forms of knowing decay: In the academic laboratory, researchers focus on endo-processes of decay that are internal to the person, but when the technology moves to the market, the focus shifts as staff bracket decay as exo-processes, which are seen as resulting from a person's lifestyle. As the technology of biological clocks travels from the laboratory to the market of online testing of the consumer's biological age, we observe shifting visions of aging: from an inevitable trajectory of decline to a malleable and plastic one. While decay is an inevitable trajectory starting at birth and ending with death, the commercialization of biological clocks points to ways of stretching time between birth and death as individuals "optimize" their biological age through lifestyle changes. Regardless of admitted uncertainties about what is measured and the connection between maintenance and future health outcomes, the aging person is made responsible for their decaying body and for enacting maintenance to slow down decay. We show how the biological clock's way of "knowing" decay turns aging and its maintenance into a life-long concern and highlight the normative implications of framing decay as malleable and in need of intervention.

KEYWORDS

biological clocks, aging, decay, maintenance, personalized medicine, unknowing

Introduction

This article is concerned with technologies aimed at measuring and quantifying aging, which are commonly referred to as "biological clocks."[1] As we unpack what the building and commercialization of such a technology entail, we examine the associated implications for how we understand aging processes and the aging person. While for a long time, aging was commonly viewed as an inescapable trajectory of decline, today's biomedicine construes aging processes as modifiable and amenable to interventions (Moreira, 2015; Blasimme, 2021). Biomedicine, and aging research more specifically, place their gaze on the molecular, by studying biological processes underpinning aging and considering how such processes can be manipulated to slow down aging (Moreira and Palladino, 2009). The

1 This focus differs from the metaphor of the "biological clock" in reproductive health to describe the time constraints on fertility, usually that of women.

notion of "healthy aging", which is ever present in health policy recommendations about old age (World Health Organization, 2015), suggests that every person differs in their aging processes and that personalized strategies are needed to control or "optimize" aging (Lassen and Moreira, 2014). Crucially, such strategies rely on measurements of aging that can assess a person's health and his or her rate of deterioration compared to a reference population (Green and Hillersdal, 2021). Drawing on various methods, such as molecular biomarkers, measures of body composition, or questionnaires collecting anthropometric and health behavior data, these technologies promise personalized assessments of a person's biological, functional or "real age" (Moreira et al., 2020). The biological clocks discussed in this article are one example of such measurement technologies.

In our empirical field, biological clocks are technologies aiming to calculate a person's biological age, which is traditionally understood as a measure of the effect of time on a body, in contrast to a person's chronological age, which refers to how many years a person has lived (Nathan, 2021). In practice, biological clocks are based on biomarkers of aging that trace and measure molecular changes. Or as geneticist Macdonald-Dunlop et al. (2022, p. 623) put it:

> We all become acquainted with visible changes that accompany aging, such as graying hair, baldness, loss of skin elasticity and worsening of posture, and that these vary noticeably amongst individuals of the same chronological age. However, there are also molecular hallmarks of aging such as telomere shortening, genomic instability and cellular senescence that also show variation in individuals of the same chronological age.

In other words, Macdonald-Dunlop et al. (2022) suggest that aging leaves molecular traces, which technologies of biological clocks aim to make visible. Biological clocks are studied for the purposes of better understanding aging at multiple biological levels, but they are also intended to help better prevent age-related diseases. In such cases, aging is understood as a risk factor for multiple diseases, and measurements of biological aging are considered possible predictors of, and intervention sites for, the speed of decay (Green and Hillersdal, 2021). Or as science scholars Müller and Samaras (2018) put it, like much of contemporary aging research, biological clocks focus on the aging body to map out and intervene upon aging processes, rather than the aged or old body.

One of the most well-known biological clocks is the epigenetic clock developed by bio-mathematician Steve Horvath and colleagues (Horvath, 2013; Horvath et al., 2014). Drawing on earlier insights that aging is related to changes in DNA methylation in cells, they used epigenomics data to precisely track CpG methylation patterns[2] across the genome to estimate a person's biological age. Biological clocks have since been constructed using a variety of omics technologies, such as metabolomics, proteomics, microbiomics, and glycomics. The development of biological clocks is thus deeply intertwined with and dependent on the ever expanding technologies and data, which can be utilized to build a new biological clock. Common to these efforts is the understanding that molecular changes can provide information on dynamic phenomena ranging from trauma, environmental exposures, lifestyle, or socioeconomic status. By incorporating information about the nature of a person's life through factors such as lifestyle or exposures, biological clocks building on these omics technologies promise dynamic and personalized measures of our health and bodies, while leaving open the possibility of change over time (Knoppers et al., 2021). However, one should not just take for granted the realization of such promises. Biological clocks are still uncertain and controversial epistemic objects, with many actors in the field showing skepticism about their accuracy, validity, reliability, and even their purpose (Moreira, 2015).

As technologies offering personalized measures of aging based on individuals' molecular markers, biological clocks serve the broad agenda of personalized medicine—a term referring to a shift within healthcare and the medical sciences from a one-size-fits-all approach toward the tailoring of diagnostics and therapeutics to individual characteristics (Collins, 2010). For Moreira (2015, p. 20), growing interest in biological age in fact represents a shift in the ways biomedicine approaches and segments the life course, from relying only on chronological age toward "destandardized, individualized life course trajectories." As we study biological clocks, we thus point to how technoscientific practices enable new ways of individualizing life course trajectories, which, more broadly, helps map out what personalized medicine looks like in practice.

It is also worth noting that biological clocks, while representing an expanding academic research field, also constitute a growing industry (Dupras et al., 2020). Biological clocks make commercial products, increasingly available as online services, where individuals can get tested to be informed about their "true" age through personalized age measurements. We empirically study biological clocks both in academic research and in the commercial world, drawing on ethnographic fieldwork in a research laboratory and in a commercial firm. Across these two sites, we take a specific interest in the development of such technologies. While biological clocks are becoming popular, little is known about how biological clocks are developed and commercialized as direct-to-consumer products on the online market. This means that little is known about what drives the technologies available today, what resources and methods are utilized to create biological clocks, or what discourses and concepts are mobilized to enable possibilities and address specific concerns. In this article, we focus on the imaginations and conceptualizations of aging that support the development of biological clocks in both the laboratory and the commercial world. Our aim is to unpack how aging processes are conceptualized and the aging person enacted in contemporary health technologies, and to discuss the implications of such technologies for understandings of individual agency over the aging trajectory. To help us do this, we draw upon the concept of decay. In the next section, we

2 Methylation of cytosines in the cytosine-guanine nucleotide pair is the most common DNA-change in mammalian cells (Moore et al., 2013).

explain our use of the concept of decay to theorize the making of biological clocks.

Decay as analytical framework

To "decay" means to decompose and deteriorate. Anything and everyone decays: bridges (Gupta, 2021), prisons (Kohn, 2021), communities (Schubert, 2021), as well as bodies and minds (Gjødsbøl et al., 2017). Decay thus constitutes a normal process that comes with being, but also one that can process at an unwanted pace. In the case of human bodily decay, anthropologist (Hage, 2021, p. 3) reminds us that one can distinguish between normal and pathological decay, whereby pathological decay is:

> The decay that marks us experientially such that we end up noticing it, is a decay that is happening at what we consider an unusual rhythm, often too quickly, but sometimes too slowly, and a decay that is progressing outside the confines of where we expect it to exist.

Decay is thus defined by a norm. Importantly, norms of decay do not just "exist" as universal standards. Rather, conceptions of aging are socially constructed through particular cultures, groups, and contexts, which are themselves dependent on socially constructed standards of living. This is illustrated in the "bio-medicalization of aging" (Estes and Binney, 1989), which is tied to societal challenges of aging populations in Western societies. Moreira (2015, p. 27) exposes how the organization of biomedical research and "institutional configurations of expertise" within biomedicine in the Global North led to the now dominant understanding of aging as a medical problem to be addressed at the individual level and through biomedical interventions. In other words, norms of decay are tied to particular places, cultural contexts, and politics, which dictate at what tempo decay is deemed acceptable, as well as what constitutes appropriate ways of intervening upon it. Thus, decay has a temporality—it operates according to a pace—as well as a spatiality—it occupies and evolves in particular places. In this paper, we draw on decay as an analytical category to problematize such norms about tempo associated with the development and marketing of biological clocks, and reflect on how these norms are tied to particular places.

Although decaying buildings or communities may seem very far from decaying bodies, the conceptual framework emerging from the decay literature is helpful in excavating how bodily decay is approached in personalized medicine. From this literature, we learn that there are different processes that can lead to decay. Anthropologists (Klein, 2021; Klem, 2021) studying narratives of decay in particular social groups such as settler colonial Australia or post-war Sri Lanka distinguish between *endo-decay*, to refer to when things are thought to decompose from the inside, from *exo-decay*, whereby disintegration is understood to be caused by external factors. This distinction is hardly ever neat, and the two processes often entangle and shift from one to another. Crucially, the distinction between what counts as endo- vs. exo-decay is closely tied to norms and values about decay. In his study of urban decay in Rome, Herzfeld (2021) points out how different narratives and interpretations are mobilized to discuss the cause of urban decay, pointing to endo- vs. exo-processes. He specifically points to an ambiguity: on the one hand, citizens of Rome cherish the genteel patina of urban infrastructures in the city, investing in and restoring old neighborhoods; on the other hand, citizens are anxious about the perceived degradation of cultural and moral standards, what Herzfeld refers to as "social decay." Interestingly, a particular interpretation of the causes of these two forms of decay is put forward: the former is deemed to be the inevitable result of time and endo processes, while the latter is attributed to increased human circulation and exposure from migrants coming into the city, and thus the result of exo-processes. In this example, the distinction between endo- and exo-decay differentiates between processes that are considered generic or determined (endo-decay) and processes that are thought to be related to human agency (exo-decay). When it comes to human bodily decay, some aspects of decay may similarly be considered endo-processes (e.g., a genetic disposition for disease) while other aspects may be considered exo-processes (e.g., diet or exercise). More broadly, this literature helps us reflect on what factors are understood to be causing decay, and how such factors are approached, studied, and intervened upon to act upon decay. In other words, it points to particular ways of "knowing" decay.

This point connects with discussions about maintenance, which is essential to stave off or slow down decay. The notion of maintenance is by some social science scholars approached as a care practice that takes into account decay and vulnerability (Tronto, 1994; De Laet and Mol, 2000).[3] Similarly, we see maintenance as starting from the fragility of life and things and involving practical tinkering. But noting that decay not always leads to maintenance work, we explore what maintenance to resist decay entails, where and when it takes place as well as who is involved. Decay is only deemed problematic at certain times, places, and when it touches certain people, such as valued members of society. This comes to the fore in Kohn (2021) study of processes of decay in the US prison system. Prisoners may be left to decay physically, mentally, and socially in buildings that are themselves physically molding and crumbling, without many noticing or paying attention. But this would not be the case for high schoolers, especially in a well-off district—one could imagine how a rotting and molding high school building would cause outrage and be the subject of interventions to repair the visible decay. This example illustrates how maintenance to slow down decay, whether that is of buildings or of bodies, targets specific places and people, especially the Global North and the already well-off. This is something we too observed with the development of biological clocks, which are predominantly aimed at wealthy customers of the Global North (see also Müller and Samaras, 2018). More broadly, decay implies a politics, whereby some things and people are left to rot, their decay being considered normal, while others are attended to and maintained so as to stop or slow down their decay, which is deemed pathological. In addition, there are different ways of maintaining entities (Denis and Pontille, 2017). If we take the example of a high school building

3 They approach care as "persistent tinkering" to improve life by attending to people and their relations "in a world full of complex ambivalence and shifting tensions" (Mol et al., 2010: 14).

prone to mold, maintenance can take the shape of an organized monthly clean-up where staff and students take turns wiping out mold. But maintenance could also mean investment from regional authorities to carry out structural works on the building, with better ventilation and insulation, as an attempt to solve a more general underlying problem. As such, different approaches to maintenance put different emphases on who is responsible and who should do the maintenance work. Investigating what form of maintenance is encouraged in connection to aging is particularly telling of what is understood as factors of cause and control. As we highlight in this paper, promoting control of decay as a practice of *self*-care frames individuals as agents of responsibility for their trajectory of aging.

Finally, the concept of decay brings to our attention a particular conception of time and of the person. Bodily decay positions individuals on a trajectory of functional decline with an inevitable ending, that of death. This trajectory is marked by feelings of loss. That is, as people decay, they lose capabilities or prosperity. However, with maintenance work, a person can suspend or slow down decay in the present, which offers the promise of a longer and healthier future. The human body, while always decaying and moving toward death, is improvable and "plastic," offering the possibility of slowing down the pace of decay. In other words, while people cannot stop their own decay from happening, it can be slowed down. It is an inevitable fate, yet one that can be monitored, managed and controlled.

In our study of biological clocks, we employ these insights to better understand how the bodily decay measured by the clocks is approached and made sense of as a problematic phenomenon that needs addressing, and crucially, to examine who and what is held responsible for decay and for enacting maintenance work to keep it at bay. As an analytical lens, the concept of decay is particularly useful because it renders visible how processes of decay (and maintenance) are inherently cultural and political, as they rest on particular understandings of what and who is valuable, and who is responsible for taking action. Drawing on the concept of decay, we thus ask: How are biological clocks developed and commercialized to assess when decay is out of tempo? What are the temporalities enacted through biological clocks and what do they mean for understandings of the person and the person's agency? Who is implicitly held responsible for managing bodily decay?

The study

This article is based on a study investigating the contemporary data ecosystem of personalized medicine, specifically interrogating the flows (of data, people, funds, etc.) making and maintaining this ecosystem. To this end, the first author conducted ethnographic fieldwork in empirical sites connected by data, the first of which is the Wilson Lab. Based in Scotland, the Wilson Lab is an academic research laboratory well known for its database of phenotypic and genotypic data originating from a cohort of healthy volunteers from the Northern Isles of Scotland. For Jim, the PI of the lab (and many others in the scientific community), the people of the islands represent "isolated populations," which make excellent study samples for various genetic investigations, ranging from the identification of genes involved in rare diseases to the characterization of interactions between genes and the environment (Kristiansson et al., 2008). The Wilson Lab is composed on the one hand of staff managing the cohort and curating the resulting database, and on the other hand, researchers utilizing the available data for the production of knowledge. Based on their cohort data, staff at the Wilson Lab study population and disease genetics with a focus on the genetic architecture of complex traits. While ethnographic fieldwork looked to explore the making of data in the cohort and its uses in biomedical research by the lab, the first author also came to learn more about the work of one particular team member, who was building biological clocks in an attempt to learn about aging processes.

The second site is a biotechnology company called Genos. Based in Croatia, Genos is specialized in the study of glycans—sugar molecules surrounding proteins in the blood that influence the immune system. Having developed a method for the high-throughput analysis of glycans, Genos sells analysis services to institutions conducting cohort studies for research, turning biological materials into glycomics data. As part of an EU-funded consortium, the Wilson Lab and Genos collaborated, which entailed Genos analyzing samples from the Wilson Lab, turning them into high-throughput data to be added to the Wilson Lab's database. The first author conducted ethnographic fieldwork at Genos to learn more about their work producing high-throughput omics data for a wide range of customers around the globe. During fieldwork, the first author learned about a biological age test, called GlycanAge, which they sell online to individual customers for a fee. The test was developed by Genos staff at the bench, based on their expertise in the analysis of glycans, but its running and marketing are now overseen by a dedicated team of three employees, led by a project manager.

The first author conducted ethnographic fieldwork in October 2019 at Genos and February 2020 at the Wilson Lab. In both sites, it involved observing data practices. The first author observed laboratory staff working at the bench with biological materials, witnessed database workers processing omics data, or watched researchers analyze large datasets using computational methods. Fieldwork also entailed sitting in meetings, attending seminars, and sharing lunch or coffee breaks with team members. The first author gained consent from participants by cultivating ethical mindfulness (Sleeboom-Faulkner et al., 2017), actively situating ethics within the research process, and securing relationships of trust with participants. The ethnographic data consists of field notes from participant observation, informal conversations with staff, reflections from meetings, as well as in-depth semi-structured interviews with members of the teams carried out by the first author (seven at Genos and 12 at the Wilson Lab). All informants were pseudonymized. We then coded all materials thoroughly following network thematic analysis (Attride-Stirling, 2001). We specifically draw upon interview data with the people in the two laboratories who were involved in building and commercializing biological clocks. In addition, we draw upon promotional materials from the GlycanAge website.

In what follows, we discuss our empirical results. We start in the laboratory to unpack how researchers develop their biological clocks by drawing out the norm of decay against which individuals are assessed, analyzing the particular conception of aging—as an inescapable and uncontrollable trajectory—that is enacted through this work. Then, we follow how biological clocks are transformed

into wellness technologies that can be sold on the market, and how this transformation shifts understandings of aging. Finally, we discuss the particular forms of maintenance that are advocated to control the forces of decay identified through the biological clocks, pointing to how it turns aging into a space of intervention, while it transforms the individual into the agent of cause and control.

Aging as endo-decay

The development of a biological clock starts with the making of what practitioners call a "baseline," that is, a basic standard that can serve as a comparison or control. A baseline is needed to draw out the norm of decay against which individuals can be assessed and their biological age calculated. This norm suggests both the appropriate effect of time on human bodies at specific time points and a pace at which decay happens over time. In this section, we discuss what goes into the building of a norm for biological decay and analyze what this norm tells us about understandings of aging processes and the aging person.

Establishing the norm for biological age first means mobilizing population data. At the Wilson Lab, PhD student Anna drew on the cohort data the lab owns and manages so as to develop a number of biological clocks. The population recruited in the cohort is a general population, all of whom share roots in the Northern Isles of Scotland. They are predominantly healthy individuals. To study this population, Anna used particular sets of data, from nine different omics technologies, including epigenomics, glycomics, proteomics, and metabolomics. She explains:

> Particularly with [cohort name], not all two thousand, but over half, a thousand people have all of these multiple omics assays, like protein and certain lipids, and that sort of thing. And we want to have a measure of biological age, measure how your body deteriorate differently from just how old you are. People mainly looked at DNA methylation data, but a couple of people have looked at other types. And because we are in the position of having different data than other people [have], we want to see if you can compare whether actually you could, so that's my project. (Anna)

Anna drew on the availability of data at the Wilson Lab—high numbers of individuals and data of different sorts—to build a baseline for biological age. Crucially, Anna focused her attention on some data rather than others: she explored various omics data to trace the effect of time on human bodies, while leaving out other data also available, such as individuals' clinical history. The choice to focus on omics data alone was driven, first, by the epistemic approach of the lab when it came to the study of aging, which was to learn about aging processes by tracing molecular markers. This reflects current scientific strategies for monitoring and measuring aging based on molecular signs known as "aging biomarkers" (Green and Hillersdal, 2021). Second, the focus on omics data alone can be explained by the availability of different omics data in the lab. As mentioned, the Wilson Lab invested heavily in the development of a rich database composed of phenotypic and omics data from the people living in the Northern Isles of Scotland. For analysts like Anna, these data can be mobilized as a resource to study different molecular mechanisms, such as telomere shortening, genomic instability and cellular senescence, as well as for identifying molecular markers of biological decay that can be used as biological clocks to measure aging.

Also noteworthy is how omics data are approached and interpreted by Anna. Omics technologies are widely considered to be capable of capturing, at a molecular level, the impact of environmental exposures and individuals' experiences such as trauma or socioeconomic status (McGuinness et al., 2012; Pinel et al., 2018; Knoppers et al., 2021). This potential was indeed recognized by Anna and her peers. However, what surprised us was that in practice, when developing biological clocks, the role of environmental factors shaping their omics data was not explicitly studied. While the researchers acknowledge that environmental factors influence processes of aging, their analysis of omics data does not present or explore environmental factors as difference-makers. Rather, omics data are studied for what they can tell them about the internal molecular processes leading to a person aging. In this process, the measurement of biological age becomes disconnected from the environment. This observation echoes critical social science analyses of epigenetics (e.g., Lock, 2013; Chiapperino, 2021). Authors discuss how scientists navigate this post-genomic science, where biology is assumed to be open to the environment and plastic, by pointing to new forms of reductionism. They specifically show that while research in epigenetics pays attention to the social and material environment by producing an "embedded body" (Niewöhner, 2011: 291) imprinted by its environment and its past, in practice aspects of the social world are bracketed and situated in "quasi-natural experimental system". In the case of the Wilson Lab, the norm of biological age constructed turns aging into an internal process. With their focus on the molecular mechanisms of aging traceable through sophisticated omics technologies, researchers conceptualize aging as processes of endo-decay.

Similarly to the Wilson Lab, at Genos, the available data drive the building of the baseline. The baseline for their biological age test is derived from their work analyzing samples and producing glycan data on behalf of cohorts and research institutes around the world, who approach glycans as causal factors for many diseases (e.g., rheumatoid arthritis, lupus, etc.). Katja, the GlycanAge product manager, who oversees the development and marketing of their biological clock, explains in an interview: "This is how we use older research; GlycanAge is like a commercial product based on all the research that has been produced at Genos so far." Over the years, through a series of collaborative arrangements and contracts, Genos analyzed samples from about 100,000 individuals. Genos researchers draw on the resulting glycomics data to build a norm of biological age. According to the GlycanAge website, they understand aging as "the accumulation of damage in your body over time, caused by a long term over-activation of the immune system." In that sense, they too studied aging at a molecular level, by tracing molecular changes linked to glycans.

Using the biological clock to measure an individual's biological age requires that multiple baselines are developed, as there is no universal molecular measurement of biological aging time. In addition to age, Genos staff also differentiate their data populations according to sex and ethnicity. The ethnic origins of their population data were often mentioned by Genos staff, and it

constituted an important biological parameter when building the norm of biological age. In part, this is because Genos provides analysis services for cohorts around the world, and as a result, the population they curate through their data has varied origins. However, as we learn from Katja in the quotation below, the building of several baselines according to ethnicity was not only biologically justified, but also commercially motivated:

> The idea is that since glycans are in a way dependent on the genes, different ethnicities have different IgG glycosylation patterns. So ideally, whenever we move to a new market we would need to define a new baseline. … Sometimes we try to cope: if the changes are not big, then we try to correct that on the data analysis level, but sometimes you cannot do that. As we spread worldwide we would definitely need… This is something we always include in the business development plan. If we go for China we first need to make a baseline for China. … Whenever we change markets or adapt to new markets, we need to develop new baselines. Like, you can use the same baseline when you're comparing Austrian and Croatian population, or like you know, something that is 300 kilometers apart, but you cannot move to Mozambique with a Croatian baseline. (Katja)

To be able to deliver testing services to individuals in all parts of the world with different ethnic backgrounds, Genos needs several baselines. Concerns about consumer markets drive the building of baselines and their efforts at including diversity. We find Genos's approach to data collection and the building of baselines to contrast with contemporary discussions about the health "data gaps," whereby the data collected in health data infrastructure do not capture certain portions of the population. In such discussions, efforts to address the health "data gap" emphasize inclusion and justice as the motivation (Shim et al., 2022). At Genos, their approach to addressing "data gaps" seems to be directly driven by the identification of commercial market gaps.

In practice, having several baselines according to ethnicity is used to compare individuals to the "right" biological age trajectory. Individuals are plotted against a baseline according to their own ethnicity, as well as their sex. Or as Katja further puts it in an interview: "What is necessary for the test is actually the gender and the ethnicity, so we can choose which baseline we plot you on." "Plotting individuals on the baseline" means comparing individuals' glycan profile to the norm. Katja continues:

> Then according to your IgG glycan, or glycosylation pattern, we estimate for, you know, females this type of glycosylation pattern corresponds to a Caucasian female of 53 years old, for example. And this is what you get as a read-out. (Katja).

The number Katja mentions here is a person's biological age as it reflects the molecular pattern of the person compared to the average population. However, that number only makes sense when compared to the person's chronological age—that is, by comparing how "old" your body is to how many years you have actually lived. By comparing the two numbers, analysts come to differentiate normal from pathological decay, whereby any biological age above a person's chronological age is deemed pathological—it signifies decay that is out of tempo. When analyzing samples, researchers place individuals on the trajectory of aging, and their position below or above the trajectory decides on their individual pace of decay. This resonates with findings from Moreira et al. (2020), who show that individual users of biological clocks, instead of substituting chronological age for biological age, estimate the difference between the two in order to qualify their life trajectory. In our case, we see how measures of biological age coexist with, and are even dependent on, measures of chronological age. It is by comparing the two measures that one can determine when decay is out of tempo and offer personalized assessments of possible interventions, as we will show below.

We want to draw out a few lessons about the development of biological clocks in the cases presented. First, what unites the laboratories is the great extent to which the available data determine how they develop their biological age clock and baseline. The design of the model for biological age does not come before data. Rather, data availability drives them to decide what biological clock to design and develop. In this sense, their work building baselines based on data availability resonates with the concept of "data-driven" research, which captures research thought to be led by the generation and collection of vast quantities of data in order to identify new processes and phenomena. However, while developing hypotheses from patterns identified in large datasets may be data-driven, decisions still have to be made about what data to include, how to classify data, and how to interpret data and resulting models (Kell and Oliver, 2004; Leonelli, 2012). Similarly, biological clocks are developed from decisions on the most salient features of data populations, as well as scientific and normative norms for the interpretation and use of biological clocks.

This takes us to our second point, which is that baselines for biological age are constructed. They are the result of labor, resources, and choices. This resonates with critical discussions of the reference problem, which point to the implications of pragmatic choices concerning the selection of reference populations (Green and Hillersdal, 2021; Binney, 2022). In our case, the baselines are shaped by several factors, including data availability, a particular epistemic strategy to study aging, as well as considerations about the intended consumer populations and markets. Depending on what goes into the baseline, radically different biological clocks leading to various results can be produced. This point confirms the epistemic uncertainty about what is measured by biological clocks, which we hinted at in the introduction.

Third, across the two laboratories, their respective attempts at building baselines for biological age draw out a particular vision of aging. Namely, aging is seen as the result of endo-processes of decay, which can be studied molecularly using sophisticated omics technologies. Aging follows a unidirectional and inevitable trajectory, which begins at birth and ends with death, thus echoing the historically common view of aging as an inescapable trajectory of decline (Grmek, 1957; Gjødsbøl and Svendsen, 2019; Blasimme, 2021). In this vision, aging is a measurable process tied to molecular markers at specific time points, which means that individuals can be placed along that trajectory and their own aging measured. While aging is understood as a normal and physiological process, at times aging can become pathological. In the vision of aging

enacted by Wilson Lab and Genos staff, what we also find striking is what becomes invisible—namely the role of socio-economic factors shaping longevity and life expectancy. While aging is situated at the molecular level and tied to internal and biological processes, the "social" roots of aging, with factors such as living or working conditions, are bracketed. As practitioners place the emphasis on the molecular and bracket the social, they enact a very particular way of knowing decay. Crucially, they conceptualize decay as an internal process tied to biological patterns and differences, while the person decaying is depicted as isolated from the immediate and wider environment. In other words, scientists turn aging into a de-socialized and de-contextualized phenomenon of the inner body.

Aging as exo-decay

Biological clocks, while born in the laboratory in an epistemic attempt to better understand the molecular underpinnings of aging and biological decay, travel beyond the laboratory as products that can be sold to individual customers and wellness businesses. In this section, we discuss how biological clocks are packaged as direct-to-consumer tests, and show how the making of a biological clock into a product shifts understandings of aging from an inescapable trajectory, to a malleable and controllable one over which individuals have responsibility and agency.

At Genos, the biological clock designed in the lab was turned into a patented product called GlycanAge. The test is marketed as a general health and wellness test, rather than being aimed at any particular disease. Or as their website states, taking the GlycanAge test means "start[ing] your wellness journey." Consumers are also informed that:

> GlycanAge is your key to healthy aging. It is the only biological age test that accurately measures your unique response to lifestyle change. (GlycanAge website, November 2022)

Yet, the researchers behind GlycanAge caution against interpreting the biological clock as a diagnostic test. As Katja, the GlycanAge product manager, explains:

> So it is basically a test that is intended not to diagnose anything. Because it is too unspecific because it basically measures the glycans on IgG that are related in some kind of chronic low-grade inflammation, mostly. That is associated with aging and aging is related to diseases. And therefore basically what you measure, these glycans on this IgG molecule, it's one of the most common analyses we actually do here, it's like bread and butter. We try to assess what is this inflammation level in your body and which age group it actually corresponds to. (Katja)

The differences between the two quotations highlight how the accuracy of measurement is not necessarily matched by conceptual precision of what is being measured. We grasp from Katja the particular pathway through which glycans are approached as proxies for inflammation, which is itself a proxy for aging, which again constitutes a risk factor for multiple diseases. In other words, for Genos researchers constructing their biological clock, glycans are connected, in a long chain of relationships, to various age-related diseases or disease risk. This comes up in Genos's research publications, many of which are concerned with particular diseases, such as COVID-19, cardiovascular diseases or cancers, and how glycans can be understood as causal factors impacting the individual's susceptibility to, or response to, such diseases. However, when glycans are studied in order to develop the GlycanAge biological clock, the relationship between glycans and specific diseases is broken up: glycans are framed as potential predictors for general processes of inflammation and aging, while researchers are hesitant to reach conclusions about causality. This approach resonates with how Anna, at the Wilson Lab, describes her work developing biological clocks:

> I'm attempting to treat them as potential biomarkers, and not check for causality and because I'm trying to, eh, trying to treat them all as sort of as naïve predictors, with not really any hypothesis about which ones should help predicting age. What I have done is I have just standardized all the measures, so they are all, they will all be on the same scale, in the hope that it then cancels out the fact that they were all in different units. … Because, again, it's just predicting and not looking for causality. It's a lot of association that are just associations, they are indicative, they are not really proving anything. (Anna)

Biological clocks are here treated as "naïve predictors" of age rather than technologies that can tease out causal patterns between aging and diseases. Staff look to learn how individuals' bodily decay compares to the average population, and come up with a number to reflect that pace. If individuals' decay is deemed pathological, researchers are not looking for causality in diseases. In part, that's because staff find that interpreting the number they produce is difficult. This is something Anna mentions in an interview:

> At the moment we find that tackling that number is quite easy, but whether that number is meaningful in prognosis is probably more difficult. That's what I have been doing and it's a lot of "meh" [i.e., inconclusive] results, which is not great. [Laughs] … The aim would to be able to say this number, say plus 5—if you're predicted to have the health of an average 55-year-old, if you're only 50, … that number plus five would indicate that you're more likely to have a cardiac event or develop this disease. But at this moment, it is not also always showing that. And the effect sizes are tiny. So, actually, what we found is that, very normal things like the normal blood test you would have at your GP is more indicative of that, than very fancy assays. (Anna)

While Anna's PhD project is entirely dedicated to the development of biological clocks, she shows ambivalence about the technology. Specifically, she suggests here that there is uncertainty in the results produced by the biological clocks. Because of such uncertainty, researchers prefer to approach the biological clock as merely revealing associations with aging. But we also learn that, for Genos, focusing on aging, rather than diseases, is strategic. As Katja explains, they were able to formally disconnect GlycanAge from diseases by avoiding a clinical label:

> We deliberately opted out of clinically validating this as a clinical test. We even went so far as to ask for the Croatian counterpart of FDA to issue us a statement that we are not a clinical diagnostic test. (Katja)

Making sure GlycanAge is not labeled as a clinical test is important because it keeps Genos out of the more tightly regulated space of pharmaceuticals and medical devices (Simon et al., 2022). As a health test rather than a diagnostic test, GlycanAge is made to fit into the ever-expanding wellness and lifestyle market. While pathology is ever present in Genos's work, and in the references on their webpage to multiple scientific publications in biomedical journals, their commercial strategy to focus on wellness exemplifies the very thin line that exists between diagnostic tools and wellness technologies.

This shifting and often fluid relationship between biological clocks and diseases also comes across when considering the type of individual Genos targets and studies. On the one hand, in the laboratory, when Genos researchers analyze samples and turn them into glycomics data, they mostly study sick individuals who are part of disease-specific cohorts. On the other hand, when they develop and market their GlycanAge test, the individuals they focus on are healthy customers. Specifically, they have a particular healthy individual in mind. From Katja, we learn that this individual is first a customer, who is "mostly over 40" and "in the upper spending bracket, because the test is now 350 euros." Then, from a conversation with Ivan, the CEO of Genos, we learn that this individual is aware of his or her own health "risks" and how "changing their lifestyle" can reduce those risks. We see here how norms of decay are related to what Chiapperino and Tengland (2015) term a "new wave of empowerment", which promote proactive civic agency and private voluntarism in health promotion. In fact, in their promotional material, the GlycanAge test is presented as a tool for self-empowerment and improvement:

> Discovering your biological age will provide you with the confidence that your current lifestyle is optimal, or empower you to make changes if there could be room for improvement. (GlycanAge website, November 2022)

The webpage also presents numerous examples of consumers who have managed to reduce their biological age through lifestyle interventions. Figure 1 illustrates a person's trajectory of decay through lifestyle intervention (red line) in comparison to their chronological age (black line) over a 2.5-year period. This figure shows how an individual was able to reduce their biological age from 45 to 28 in only 2.5 years. In other words, this person was able to slow down the speed of decay to an extent that graphically looks like one can "turn back time" and regain (molecular) youth. This indicates how a quite significant part of the aging trajectory is taken to happen through processes that are plastic and modifiable.

While healthcare technologies are promoted as means for enacting individual freedom in health promotion, the new wave of empowerment also comes with new responsibilities for citizens and questions about *who* is empowered and *how* (Chiapperino and Tengland, 2015). The biological clock designed by Genos is aimed at the aging population of the Global North, and specifically targets

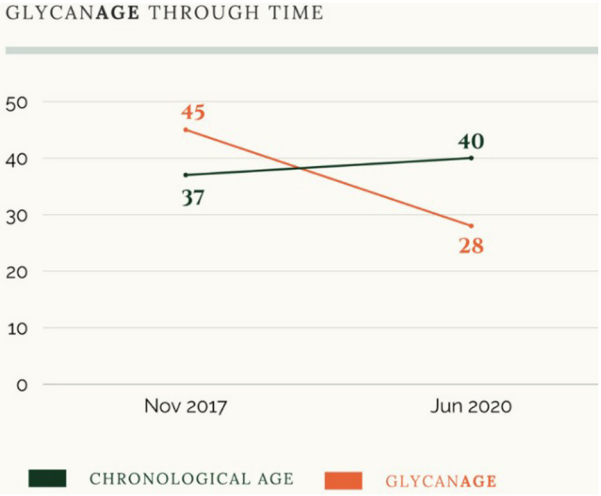

FIGURE 1
Screenshot from the GlycanAge website illustrating a person's biological age over time in comparison to their chronological age (November 2022).

patients turned consumers who can afford to buy the test and take action to improve their health. Along with critical scholarship of personalized medicine (Prainsack et al., 2008; Harvey, 2009; Juengst et al., 2012; Prainsack, 2017), we argue that a consequence of the conceptualization of health maintenance at the individual level may be that those unable to enact maintenance may be deemed irresponsible and unfit to be self-governing citizens. Moreover, empowerment comes with exclusion: many people are excluded from even considering the test, either because Genos does not have the relevant data on specific populations to produce an accurate test, or because individuals do not have the financial means for testing or resources to follow health recommendations.

With this focus on lifestyle and individual behavior change, we move from the focus on molecular endo-decay to exo-decay, as the aging person becomes a responsible agent of control. What is also worth noting is that GlycanAge, as a personalized wellness technology, puts to the fore a very particular understanding of exo-decay. For Genos staff, only certain things count as "exo," or the environment, in this form of decay (Pinel, 2022). In their website, the environmental factors emphasized as shaping the GlycanAge are individual lifestyle behaviors, such as diet or exercise, or personal life events such as divorce, stress or "the loss of a loved one". Here again, structural and socio-economic factors, which may also shape exo-decay are invisible. By defining "exo" as individual lifestyle, Genos leaves unaddressed what Marmot (2005) termed the "causes of the causes"—that is, the socio-economic determinants that make certain lifestyles harder to achieve for some, or environmental determinants related to these such as exposure to pollution (Valles, 2018).

When the biological clock becomes a wellness technology on the market, decay shifts from being an inevitable trajectory to a plastic state that can be acted upon by empowered individuals who—through the test—gain knowledge of their personal decay and possible intervention options (Blasimme, 2021). In this

scenario, the aging person is understood as responsible and seen as an agent of cause and control, capable of affecting their own malleable trajectory of aging. This particular understanding of aging echoes recent trends in aging policies, which emphasize the plasticity of aging and human agency in impacting one's aging, with for example global initiatives such as the healthy aging program developed by the World Health Organization (2015). The notion of healthy aging specifically underlines that while the rate of deterioration differs among individuals, it is modifiable through individual actions, and programs for healthy aging usually point to a set of concrete practices individuals can enact to modify their aging trajectory (Lassen and Moreira, 2014; Lamb, 2017).

In summary, while the test places individuals on an aging trajectory that inevitably ends with death, it suggests that there is significant room for interventions to slow down decay or even "turn back time" to reach a younger biological age than before they took the test. Thus, individuals can move along this trajectory if they enact change in their lifestyle. While aging becomes a malleable process, the temporality drawn here is that of an indeterminate future which is open to interventions, the actors of change being individuals acting on their lifestyle. Specifically, intervening upon the aging trajectory implies maintenance work, a responsibility which is shifted onto the shoulders of individuals. And as we show next, a particular form of maintenance work is advocated to control the forces of decay identified through biological clocks.

Maintenance work to slow down decay

As the GlycanAge promotional materials promise, buying the test means embarking on a "wellness journey." This starts with taking the test and being delivered results about one's biological age. Next comes a consultation to discuss the results and receive advice in order to "optimiz[e] your health and longevity." Or as one can read on the GlycanAge website:

> Our plans come with complimentary guidance for your health and wellness journey. Once you receive your results, you will be able to book your free one-to-one video consultation with a Care Team Specialist, who will work with you to discover where you may like help in improving. (GlycanAge website, November 2022)

Members of the GlycanAge Care team include a health coach, what they call a "Lifestyle Medicine doctor," nutritionists, personal trainers and fitness instructors. In the consultation, care specialists and Genos customers discuss and interpret the results of the biological age test, but this interpretation is highly dependent on the individual providing "profile details," or as Katja explains:

> We collect also different information about your lifestyle, previous disease history, you know, medication, also stress level. Anything that could actually correlate with results. Because very often clients come to us and tell us "OK, now I get a number, like I'm 63 my GlycanAge is 83, why?" And then it's easier for us to try to… So we are not MDs [medical doctors] here. We don't claim that what we are selling is any kind of diagnostic test, but we have to look at the data that they provide us. They can choose whether they want to give this data or not. It's optional. But if they choose to give it to us, you can try to indicate what might be the reason for the result of their test and then they can choose whether they want to take that further. (Katja)

Based on the information provided by people taking the test, the GlycanAge care specialists offer an interpretation of the results. For example, a biological age result above the norm can be deemed to be linked to high-stress levels and poor nutrition. In this context, Genos staff do not hesitate to reach conclusions about causality—specifically, they establish a causal pathway between GlycanAge results and lifestyle. Such interpretation then leads care specialists to formulate advice about areas in the individual's life that could be "improved" in order to promote healthy aging. In other words, Genos and their care specialists encourage customers to convert the measurements of their biological age into actions. In line with Moreira et al. (2020) study of biological clocks, we thus observe a pragmatic engagement with the measurements, whereby they are translated into concrete practices to enhance one's aging prospects, regardless of the uncertainties about the test and which health domain the results should inform.

Concretely, much of the advice given to individuals focuses on diet. For example, their website displays tips concerning ways to prevent "weight-gain during menopause," "anti-aging foods," or again "anti-aging supplements." The solution offered to a decaying body is thus maintenance through lifestyle. The emphasis on lifestyle as a course of action may be linked to the absence of more specific advice (Juengst et al., 2012). In effect, with Genos's focus on lifestyle and diet, we observe a particular form of care being advocated to slow-down decay: rather than a relational form of care like the one depicted by anthropologist Moser (2011) in her study of dementia in nursing homes where the aging individual is thought of in a web of relations, what is put to the fore is self-care while aging becomes a matter of individual and isolated practices. Individuals are made responsible through several steps. First, they are responsible for taking the test and for filling out information that could be used to interpret their test result. Second, after receiving lifestyle counseling, they are responsible for enacting the suggested changes to improve their health and wellness.

This form of maintenance work is in fact commodified, since GlycanAge offers a subscription model whereby individuals take several tests at regular intervals to monitor their biological decay and to assess the impact of the lifestyle interventions on the pace of decay. Or as the GlycanAge website states: "We highly recommend dual testing to track your progress toward slowing aging." Katja explains this strategy:

> Ideally we would actually use the GlycanAge test to monitor your speed of aging. To kind of have control over your healthy aging. You could do like the test once a year. Or if you want more information within your lifestyle change cycle, then you can do it every 6 months for example. And see whether this intervention works for you or not. Because the thing is, the same intervention might work for you but not for me or for her. … So what we are saying now is, this is your first read-out, you know, go out there in the world, make a change that you think

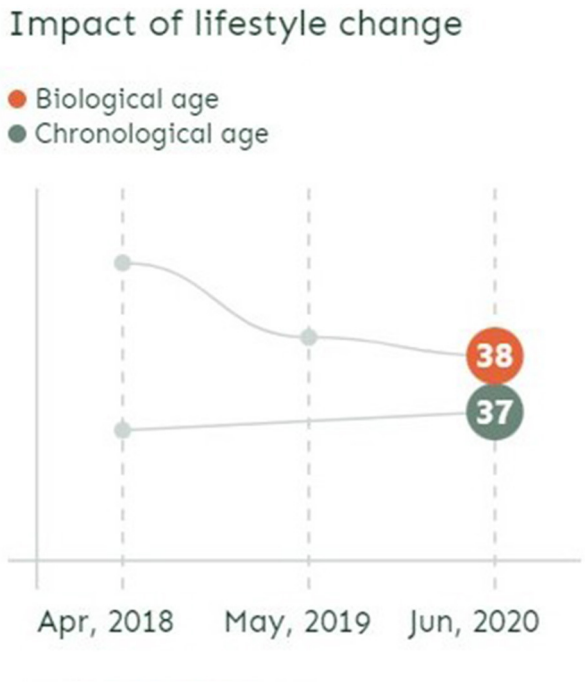

FIGURE 2
Screenshot from GlycanAge website illustrating the possibility to change biological age over time (November 2022).

> might benefit you. And then come again for the next round of testing. If it works fine, continue with that, you know you can read that, but if it doesn't, change it and do something else and then come take a new test. So, what we will also try to develop now is some kind of subscription model where we can actually test. … Plus for us of course commercially it's good. Yes, but this is like, as I said, this is the closest to personalized medicine we have gotten so far. (Katja)

The implicit claim is that taking regular tests enables individuals to keep their bodily decay in check while monitoring the impact of their maintenance work. On the GlycanAge website front page, the personal stories displayed showcase regular testing. With graphs showing two curves (one for chronological age, the other for biological age), the stories look to illustrate the significant impact of lifestyle change by pointing to important fluctuations in biological age over rather short periods of time (from half a year to 2 years) (see Figure 2).

The figures on the GlycanAge webpage present biological age as a relatively stable, but modifiable, trajectory in time. However, according to other researchers, there is another side to that story, which is that under normal conditions, biological age naturally fluctuates over time. A recent study (Komaki et al., 2022) of epigenetics biological clocks shows that epigenetic age can change by more than 3 years from day to day in apparently healthy individuals without intervention. In one customer story on the GlycanAge webpage, we also learn that a COVID-19 infection impacted the test results as he "had aged 4 years" from the initial result. This raises further questions about what is measured and about the basis for recommending and evaluating specific lifestyle interventions based on "snapshot" testing at specific time points.

In the vision articulated by Katja, the responsibility of the person taking regular tests goes even further. The individual is not just a customer following professionals' advice, but also an experimenter urged to try out different lifestyles and monitor the effect on their measured biological age. It is the responsibility of the individual to figure out what interventions work best—and buying new tests is the way to know what works. Crucially, bodily maintenance—in this vision—becomes a life-long project. Individuals are urged to keep on making adjustments to their lifestyle in order to improve their health, while they should keep taking biological age tests to check how their actions affect their aging trajectory. This particular vision of bodily maintenance corresponds to what Blasimme (2021) calls "ground-state prevention." This form of prevention focuses on signs of declining bodily functions, rather than specific diseases, and seeks to enhance human capacities by attempting to control and postpone aging. In other words, rather than living longer or preventing specific diseases, "ground-state prevention" is about gaining healthy life-years by attacking "ground causes" of multiple age-related diseases, e.g., through geroprotective drugs or, as in our case, personalized recommendations for lifestyle changes.

From Katja's words above, we also learn how for GlycanAge staff, biological age tests come to represent personalized medicine. For them, what makes it personalized medicine is that individuals not only receive a personalized assessment of their biological decay but are also given access to specialists, who can design a tailored plan to slow down their trajectory of decay based on this information. However, the biological clock represents a very particular version of personalized medicine, as it takes the shape of a wellness technology, a commodity sold directly to individuals. In fact, the sort of personalized medicine offered by GlycanAge reminds us of what Prainsack (2022 p. 211) refers to as "boutique practice", whereby data interpretation and personalized health strategies are available to a select few who are wealthy enough to afford the time of human experts. One is also left wondering whether GlycanAge indeed represents a more "precise" approach than traditional healthcare, where general health advice is formulated based on individual's clinical data. The GlycanAge test in itself is not suggestive of personalized interventions. Rather, the maintenance work suggested to individuals taking the test is based on staff's interpretations of biological decay, supplemented with additional information from the individual. It is also worth noting that examples of health advice featured on the GlycanAge webpage resemble general advice about healthy lifestyle. This raises questions about the necessity and basis for individualizing agency in aging *via* biological clocks.

Discussion: The politics of preventing decay

Biological clocks are human constructions that make particular forms of decay visible, and encourage specific types of maintenance work. According to the intended purpose of the clock, researchers make decisions about what data to include, what resources to draw upon, and what epistemic approaches to aging to

mobilize. When restricted to the confines of the laboratory, the biological clock brings forward a vision of aging as an inevitable trajectory of decline. However, when the biological clock moves to the market, aging becomes a malleable and plastic trajectory over which individuals can (and should) act. In other words, we come to see how biological clocks are not neutral technologies assessing decay that just "exists" within individuals' bodies, but rather are man-made technologies that bring to light particular conceptions of aging and of the aging person. As they do so, we argue, biological clocks enact a politics of decay.

In the social study of medical technologies, there has been a great interest in promise and potentiality (Brown, 2003; Martin et al., 2008). This literature directs attention to how politics of potential facilitate hope and futurity, while shaping science and financial investments (Svendsen, 2011; Taussig et al., 2013). The concept of decay helps us see that in the field of aging, such articulations of future potential are closely linked to a politics of decay. "Optimizing" or "potentializing" aging through biological clocks embody and rely on ideas about decay. In particular, the politics of decay we identify in the development and commercialization of biological clocks is concerned with the biological enclosure of existence and the dependent opposition of life and death (cf. Povinelli, 2016). While decay is an inevitable trajectory that starts at birth and ends with death, the individual endowed with life and agency has the potential to stretch time between birth and death. Biological clocks, and the maintenance work that is promoted along with them, thus articulate and bring together two distinct temporalities: one where decay constitutes an inevitable trajectory with death as the ultimate end, and one where decay can change from one day to the next and can be intervened upon, controlled and managed. Biological clocks bring these two temporalities into tension by emphasizing how individuals can stretch out time and have agency over an inevitable trajectory of decay.

Thinking about biological clocks through the lens of politics of decay helps problematize dominant norms regarding whose and what aging is deemed problematic, in what context, and who should be made responsible for managing it. It helps us see how the development of biological clocks rests on particular ways of approaching, studying and knowing decay. Specifically, our case shows how researchers bracketed knowledge about aging as either endo- or exo-processes of decay. At the Wilson Lab, researchers draw on omics technologies to build their biological clocks, and as they do so they invite the "environment" to the molecular level (Landecker, 2011). However, this is not followed up in their study and aging is bracketed as endo-processes internal to the individual. This particular way of knowing decay is unknown in the translation of biological clocks into commercial products. With GlycanAge, decay is approached as exo-processes, yet only certain things count as "exo," specifically those related to lifestyle. Echoing anthropologist Geissler (2013, p. 16) who argues that "zones of unknowing" are created and maintained "in the pursuit of scientific knowledge," we see how the development of biological clocks rests on particular ways of knowing decay that come together with forms of "unknowing." What we find particularly remarkable is how the building of biological clocks in the laboratory and commercial products in the biotechnology company unknowns decay as a multifaceted and complex relationship between individual and environment. Rather, an individual's bodily decay is reduced to molecular processes which may be related to individual lifestyle, while this individual is treated as if they are cut off from their family, neighborhood or social class.

The biological clock's way of "knowing" decay turns aging into a life-long concern resulting in maintenance work over which individuals have a moral obligation and responsibility. The GlycanAge webpage presents successful examples of citizens who have benefitted from taking on this responsibility. In one of the featured customer stories, we meet Christian who took the GlycanAge test because of concerns that his lifestyle could have negative long-term impacts on his health. He was surprised to learn that his GlycanAge was seven years younger than his "actual age."[4] Nevertheless, he decided to implement lifestyle changes to optimize his GlycanAge and takes tests annually to monitor his progress. While the example positively shows the motivating potential of biological clocks for lifestyle change, it also illustrates how the responsibility to age "as healthily as possible" has no upper limits. The endpoint is not merely to reach the "normal" age of the baseline. Even if your molecular clock estimates that you are several years "younger" than your chronological age, there is still room for improvement. Similarly, there is no limit to the age or period at which individuals could benefit from maintenance work. Any sign of decay, detectable as invisible molecular changes in glycans, is a target for actions to optimize lifestyle. Optimization of biological age thus exemplifies how ground-state prevention is not limited to changing the aging trajectory from "pathological" decay to "normal" decay but involves an *agification of life itself* (Blasimme, 2020, 2021). Individuals are encouraged to worry about aging at an increasingly early time in life and through increasingly encompassing dimensions of measurements and age-preventive actions. Optimizing biological age is a life-long preoccupation, regardless of the admitted uncertainties about what is measured and the connection between ground-state prevention and future health outcomes.

We are left to wonder who is to benefit from such specific ways of measuring and slowing down decay. Put differently, who is the technology of the biological clock for? Decay is not always considered a problem, but rather, decay is seen as problematic at certain times, places, and when it touches certain people. On a global scale, it is in the Western world that bodily decay is seen as especially problematic and is regularly intervened upon. This can seem paradoxical since it is also in this part of the world that people live the longest and healthiest lives. It is there that geriatrics medicine has flourished over the 20th century, thus turning aging into a legitimate site of medical care and prevention (Blasimme, 2021). As such, decay is deemed out of place when it touches the already healthy and wealthy of the Global North. The vision of aging enacted through the biological clocks we studied speaks to Western conceptions of aging and developed countries' approaches to gerontology that see aging as a modifiable

4 https://glycanage.com/self-care/lifestyle/ensuring-work-life-balance-and-getting-over-covid-19/

trajectory. One can argue that technologies of biological clocks are intended to serve the already healthy individuals of developed countries, rather than improve life expectancy of the majority across the globe. This underscores how biological clocks are not neutral scientific facts emerging from the statistics of omics data but are performative technologies that shape how we view aging and health. Biological clocks are—according to those promoting and selling them—constructed through a selective focus on forms of decay which are measurable only through patented technologies, yet—it is claimed—modifiable through individual lifestyle changes. Meanwhile, efforts to make molecular signs of decay visible leave other aspects invisible, such as socio-economic aspects that affect aging and life expectancy both locally and globally.

Data availability statement

The datasets presented in this article are not readily available because the data contain personal information. Requests to access the datasets should be directed to CP clemence@sund.ku.dk.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. According to Danish legislation, study participants were orally informed about the purpose of the study and gave their consent. All data were handled and stored according to the rules of the Danish Data Protection Agency.

Author contributions

CP led the design of the ethnographic study, collected empirical material, led the analysis and conceptualization, and led the writing and editing of the manuscript. SG and MNS acquired funding, supported the analysis and conceptualization, and supported the writing of the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Paving a pathway for large-scale utilization of genomics in precision medicine and population health

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Having worked with two large population sequencing initiatives, the separation between the potential for genomics in precision medicine and the current reality have become clear. To realize this potential requires workflows, policies, and technical architectures that are foreign to most healthcare systems. Many historical processes and regulatory barriers currently impede our progress. The future of precision medicine includes genomic data being widely available at the point of care with systems in place to manage its efficient utilization. To achieve such vision requires substantial changes in billing, reimbursement, and reporting as well as the development of new systemic and technical architectures within the healthcare system. Clinical geneticist roles will evolve into managing precision health frameworks and genetic counselors will serve crucial roles in both leading and supporting precision medicine through the implementation and maintenance of precision medicine architectures. Our current path has many obstacles that hold us back, leaving preventable deaths in the wake. Reengineering our healthcare systems to support genomics can have a major impact on patient outcomes and allow us to realize the long-sought promises of precision medicine.

KEYWORDS

precision medicine, genomics, population health genomics, bioinformatics, whole genome sequencing, implementation science, genetic testing, reimbursement

Introduction

The separation between the potential for precision medicine and the current reality have become abundantly clear. This became evident in my work with two large population sequencing initiatives, the MyCode program at Geisinger (Carey et al., 2016), and the HerediGene program at Intermountain Healthcare (IH) (Walton et al., 2022). As a clinical geneticist with a professional background in programming and information technology, I have gained insight into both the clinical application of genomics as well as the technical infrastructures required to support it. At both Geisinger and IH, hundreds of thousands of patients have available sequencing data, creating a daily struggle to push actionable data into the clinical space across a large healthcare system. To do so efficiently and at scale requires workflows, policies, and technical architectures that are foreign to most healthcare systems (Walton et al., 2022). Many historical processes and regulatory barriers currently impede the ability to realize the ultimate vision of precision medicine (Klein, 2020; Walton et al., 2020, 2021; Abdelhalim et al., 2022; Schaibley et al., 2022; Stenzinger et al., 2022). Technology and the cost of sequencing are no longer significant impediments in the US healthcare system, but rather the efficient and proper utilization of such technologies holds us back. New possibilities depend on our ability to diverge from conventional processes justified

primarily by historical context rather than current utility. While some of these barriers are necessary to ensure patient safety and allow for evidence-based approaches, there is certainly ample room for improvement and failure to increase efficiencies may leave us well behind. Many historical conventions lose relevance in the face of new technologies and scientific discovery. While other industries blossom through the grasp of these technologies, medicine grinds slowly forward. Additionally, newly proposed regulatory measures may also threaten innovation and progress in this space (HR4128, 2021; ACMG Group Sign-on Letter, 2022; FDA, 2022; HER, 2022).

Sequencing, aside from interpretation, is rapidly approaching the cost of other regularly ordered laboratory tests, with the $100 genome clearly within our grasp (Philippidis, 2022). Several initiatives exist that use whole genome sequencing (WGS) for newborn screening (Buxton, 2022), and it is likely that in the future, genome sequence will be part of every medical record. Healthcare systems must be prepared for the tsunami of clinically actionable information generated from this data. We have previously described IH's work to deploy a precision health framework (Walton et al., 2022). As we pushed through this deployment, glaring deficiencies presented themselves as barriers to fully realizing precision medicine. This perspective presents a vision for precision medicine with suggestions to expedite that vision into daily clinical care. This vision is based on my experience with genomics in the US healthcare system, though, some of these challenges may be encountered in other healthcare systems around the world.

The vision

Genetic testing would no longer consist of a thousand different orderable panels, as is the case today, but would instead consist of one genetic test for all purposes that could be used throughout the life of the patient. Any need for genetic interrogation would automatically initiate the process of WGS using testing modalities that capture the spectrum of genomic variation, including structural changes. The data from this test would be readily available at the point of care for a myriad of purposes, including but not limited to:

- Pharmacogenomics—Prescribing medications according to an individual's genetic profile to deliver the most suitable medication and dosage for optimal results based on their genetic characteristics.
- Gene based therapeutics—Identification of patients with disease that have genetic variation that is responsive to gene therapies or biologics and initiating those treatments.
- Disease prevention—Identification and implementation of preventative action on individuals who harbor pathogenic variants in genes known to predispose to preventable disease, including, but not limited to, those recommended for reporting by the American College of Medical Genetics (ACMG) (Miller et al., 2021).
- Disease risk modeling—Deployment of scoring models to predict patient disease and enable prevention. Such models would include polygenic risk scores and more complex models that incorporate genomic information with other patient data and/or environmental information to predict and prevent disease.
- Real-time genetic diagnosis—Facilitating genetic diagnosis in real-time as patients seek medical attention at hospitals or clinics when exhibiting symptoms. Enabling the use of faster and more effective treatment options as a result of more accurate diagnoses.
- Population health genomics—The utilization of genomic data by health systems to cater disease management strategies to the genetic diseases of the population being served.
- Reproductive decision making—The use of genomic information from individuals considering having children to help them understand carrier risks and make informed reproductive decisions that may include the use of in vitro fertilization and preimplantation genetic diagnosis.

This genomic information would travel with the patient to different hospitals and clinics in different states or countries. The clinical use of this data would be achieved almost entirely through approved bioinformatics systems that are not subject to manual review and medical director sign-out, enabling the inexpensive and rapid utilization of genomic data. Exceptions would be made for diagnostic cases that involve variation or genes that are not well characterized.

Complex clinical decision support systems (CDSS) use the genomic data to augment physician judgement, guiding them through genomic specific care pathways, adjusting prescriptions according to a patient's predicted response to medications and automatically scheduling preventative maintenance and disease surveillance. Similar systems are deployed through mobile and wearable devices that monitor and guide patient health outside the clinical setting, enabling patients to actively participate in their care. Complex artificial intelligence (AI) models using genomics project patient trajectory and allow for adjustment so the patient can reach their optimal health targets.

Clinical geneticists begin serving more in administrative roles overseeing the application of genomics and precision medicine across healthcare systems, with titles such as Chief Genomics Officer (CGO) or Chief Precision Medicine Officer (CPMO). Such officers would work with each department in the system to apply precision medicine technologies and practices to their respective domains. Clinical geneticists would retain limited practice in diagnosis and management of rare disorders, with many genetic conditions distributed to other specialties. Genetic counselors would become nearly as ubiquitous as nurses to facilitate the deployment and management of precision health systems.

The change

To fully scale and implement the aforementioned vision requires rethinking and re-engineering many processes that have been in place for decades. Though not exhaustive, the list below addresses some critical changes needed to achieve a more complete realization of precision medicine.

New paradigm for ordering and billing genetic testing

Currently, billing for sequencing is messy. Labs have found creative ways to bill that meet payers' often ill-informed demands. As an example, some payers require single gene tests before sending a panel, and others might require a panel before an exome. Today, all these tests are essentially run on the same platform, so billing for what is allowed by the payer and then reflexing to obtain more analysis such as a panel, extended panel, exome, or genome is not uncommon. This results in laboratories, who really only offer one product (genome or exome sequencing), lessening the product's value and complicating the diagnostic process to meet the demands of payers. All that comes back from these tests, which are often run on an exome or genome backbone, is a PDF that displays maybe a handful of variants, leaving gigabytes of clinically useful information outside the healthcare system.

Genetic testing should follow a model similar to medical imaging. Genome sequencing should no longer be billed as a laboratory test. It should be billed as a procedure like an MRI. This "procedure" is ordered the first time there is any indication for any genetic testing and generates sequence data accessible to the healthcare system. The interpretation occurs thereafter and would be performed and billed separately, like a radiologist billing for reading an MRI. The complete data from the genome sequencing would remain accessible to the healthcare system for serial interrogation based on the longitudinal needs of the patient. Also like an MRI, specialist physicians should be able to browse this data with the aid of bioinformatics tools at the point of care in the context of the patient. If they find something that impacts patient care, they should be able to request that this finding be reassessed by the interpretation service. Interpretation should be able to occur onsite with the aid of bioinformatic tools or remotely using specialized services. Currently, most of the cost of clinical genome sequencing is in the interpretation, not in the laboratory process. This change would make genome sequencing a readily available and inexpensive commodity and facilitates less expensive bioinformatic interpretation where there is less ambiguity around variant consequences. It would also open up substantial opportunity for research that can make the genomic data even more useful and its interpretation cheaper.

Automated bioinformatic analysis and reporting

Manual sign-out of genetic testing reports can be automated in areas where genomic variation is well understood, and laboratory processes are well defined with high levels of accuracy. Clinical Laboratory Improvement Amendments (CLIA) regulation is administered by Centers for Medicare & Medicaid Services (CMS) to ensure laboratory testing is performed accurately, reliably, and with consistent quality. Sequencing data meeting certain quality metrics coming from a CLIA certified laboratory should be able to be processed entirely by approved bioinformatics processes. These processes could provide results were there is certainty around variant classification, such as with pharmacogenomics, polygenic risk scores, and ClinVar variants with high levels of evidence. ClinVar is a publicly available database of genetic variations and their clinical significance, that is commonly used to interpret genetic test results. ClinVar variants with a 3-star designation have been reviewed by an expert panel and achieved consensus in classification and 4-star variants are considered a practice guideline. Variants with a 3-star or 4-star designation should be able to be reported in an automated fashion. Many laboratories have already automated much of this reporting while still maintaining manual signoff for the report.

As the majority of variant evaluation and sign out is clinically assessed through the analysis of bioinformatically generated information, it makes sense that these processes can be automated by analyzing the human processes taking place and replacing them with computer algorithms so long as they reach a certain threshold of validity. Arguments against trusting a computer for such processes fail in that all the information used to sign out such reports is generated by a computer, there is no human sense such as vision that is used in traditional pathology that gives a human an advantage over a machine when reporting well established variants. For example, in my experience as a laboratory medical director signing out pharmacogenomic testing reports, we had a standard pipeline and protocols, reporting only well-known variants that do not need evaluation every time they are seen. Deviations from this standard process in pharmacogenomics reporting is rare. There is no more need for a human in this process then there is for reporting a complete blood count (CBC). Of course, there will be exceptions that require medical director evaluation when things do not meet certain specifications, as is the case with any laboratory test. Additionally, there would be a medical director responsible for oversight and sign off on the process, but there would be no need evaluate each individual's report. As our knowledge about genetic variation increases, the majority of this information will be able to be reported without human intervention. While automated sign out of reports is certainly not standard practice in the field of pathology, it is something that needs to take place as the volume and use of genomic data grows and the capabilities of artificial intelligence improve and even begin to exceed that of humans. These automated reporting systems sitting on top of large amounts of genomic data can serve as powerful tools to further precision medicine and its translation to patient care. Such systems would allow for automated reanalysis and reporting on existing genomic data as new information about genomic variation becomes available. The implementation of these technical architectures would enable inexpensive reporting/interpretation on already inexpensive genome sequencing, providing significant value for genome sequencing at a very low cost.

Dynamic electronic genetic test reports

It is not uncommon for knowledge about genetic variation to change over time. This can be problematic when a change requires the reissuance of thousands of clinical reports and notifying equal numbers of clinicians and patients of the change. The dynamic nature of genetic information lends itself to dynamic electronic reporting that keeps up with the current science and automates

updates to clinicians and patients. This type of reporting may also be our solution for variants of unknown significance (VUS), which currently pose a significant clinical problem (Richter, 2013). Utilizing dynamic electronic reporting, it is possible to restrict the viewing of variants whose clinical utility is uncertain to specialist providers. Such physicians may change the interpretation of the variant and push it to the patient report if they feel confident that the variant is impactful. This would avoid confusing and inducing anxiety in patients while preventing providers with little genetic experience from misinterpreting and misusing information from the final report. We need to build a dynamic reporting system that responds appropriately to new information.

Genome first approach

Historically, the **first** visit with a geneticist involved seeing the patient and performing a very detailed physical exam to identify the right genetic test to order. As we move to genome sequencing as the first-line test, the value of this **first** visit and exhaustive phenotyping become questionable. We have begun this transition at IH, the challenge being that many payers will not pay for genetic testing unless the patient has seen a clinical geneticist. Despite this challenge, we have reduced our **first** visit encounters by 50% by implementing it where payers have allowed. Furthermore, many patients do not need to see a clinical geneticist at all with this approach because their resulting genetic conditions are referred to the specialist, who ultimately treats that condition with a genetic counselor providing counseling around inheritance and disease risk. In our early experience with this approach, it is far more valuable to have the genetic test available when seeing the patient and tailoring the exam and questioning to the discovered genetic variation. It is still required to have a major phenotype to base the initial genomic analysis on, which can often be garnered from the referral. The sequencing **first** approach becomes especially important with the current shortage of clinical geneticists and long wait times (Dragojlovic et al., 2020; Simon et al., 2022). Today, phenotype still holds significant value as we try to tease out the clinical implications of variation in 20,000 genes, but the diagnostic utility of exhaustive phenotyping is waning, and the sequencing **first** approach is gaining ground. Working with payers to clearly designate phenotype algorithms in each specialty for which genetic testing can be ordered without a prior visit to a geneticist can help drive this forward. This would ultimately save payers money by eliminating an unnecessary encounter. A brief genetic counseling session is still required to initiate the testing but even this part could arguably be replaced with technology over time.

Enabling first line providers to order genetic testing

As the importance of detailed phenotyping lessens, opportunity arises for other, less specialized providers to initiate the genome sequencing process. Pediatricians, for example, are qualified to diagnose intellectual disability (ID). The current first-line testing modality for ID includes WGS. We can enable this process with informatics support to manage the pre-counseling aspects of the test and population health genomics architectures to manage the secondary findings (Walton et al., 2022). Epilepsy also includes WGS as a first line test (Smith et al., 2022). It does not make sense to have a clinical geneticist in the care pathway for epilepsy unless the diagnosis is a complex syndrome affecting other systems since the patient will ultimately be managed by neurologists anyway. Shifting the ordering of genetic testing from clinical genetics to other providers increases the throughput of the system, thereby increasing the number of genetic tests ordered and resulting diagnoses received. We have already seen this taking place in neurology departments where there is a movement to have dedicated neurology genetic counselors who facilitate this workflow (Wofford et al., 2019). One key factor to enabling this approach is to have an infrastructure that allows for routing results to a clinical geneticist for support when necessary. Improving genomics education of frontline providers is also important. The amount of education required would not be extensive and could easily be integrated into both medical school and residency training programs.

Role of genetic counselors and genetic counseling assistants

As we enable primary care and other specialties outside of clinical genetics to take on genetic testing, genetic counselors are still critical to making these systems work. With our public health genomics deployment, we were quick to realize the limited availability of clinical geneticists. Genetic counselors are critical to the deployment and maintenance of precision medicine at scale. Furthermore, providing genetic counselor assistants to support genetic counselors increases their availability and productivity (Krutish, 2022), with the added benefit of augmenting the genetic counseling pipeline with high-quality applicants with significant field exposure. While informatics frameworks can help deliver a great deal of precision medicine, the field requires trained individuals to deploy, maintain, and operate complex frameworks. Genetic counselors have proven to have a very robust set of skills, performing well in diverse roles that support such frameworks. Their base set of skills will need to be expanded with genetic counselor training programs including more exposure to polygenic risk scores (PRS) and their associated relationships to complex disease as well as an increased exposure to pharmacogenomics. While oversight of complex precision medicine frameworks by a clinical geneticist may be desirable, such systems cannot be too dependent on this scarce resource. Increasing the number of genetic counselors in the system is critical to the success of any precision medicine program.

Increased clinical use of sequencing leads to increased clinical utility

Clinical genetics is an interesting specialty in that it sits at the intersection of clinical care and research. New discoveries are frequent but are often made through thorough clinical investigation

with the intent of diagnosing and treating the patient rather than using controlled studies with established IRB protocols. Many of the genetic disorders we know about today are the result of the clinical uptake of exome sequencing. Over 500 new genetic disorders have been discovered by providers matching their clinical findings to other providers through the Matchmaker Exchange (Boycott, 2022). Without the widespread adoption of whole exome sequencing, this progress would have been impossible. Likewise, we need large cohorts of sequenced patients that provide us with the statistical power to study treatment outcomes relative to the causal gene. We currently face the challenge of increasing the clinical use and utility of WGS. The extra information provided by WGS has little utility if we do not understand its clinical implications. We learn about the clinical implications of this information through increased use of clinical WGS. This challenge is compounded with the advent of long read sequencing, which provides even more information. It is critical that we enable the rapid clinical uptake of these technologies.

Challenging the academic model

The discovery of new variants that cause disease in a well-described gene does not get much academic attention. In fact, some of my colleagues have claimed that it's difficult to get funding for large-scale functional studies because they have lost their novelty. With the inability to publish such findings, there is little incentive to increase public knowledge on gene variation. Laboratories make significant contributions to ClinVar, but clinicians rarely do, despite being most qualified to link patient phenotype to genetic variation and ultimately determine the pathogenicity. Less than 10% of ClinVar submissions are from clinicians at the time of writing (ClinVar, 2023). Even if journals accepted publication of specific variants, the process of submitting and publishing is very inefficient, especially for clinicians whose primary focus is patient care (Vines, 2015). New academic models need to be developed that incentivize clinician contribution to public knowledge and provide an easy-to-use framework to do so. Frameworks have been proposed and even implemented with specific genes and conditions (Majumder et al., 2021). We should continue to build and improve these frameworks scaling them to all genetic conditions. As they are developed, they should account for clinician incentives, patient privacy protections, and institutional review board (IRB) requirements, to lower barriers of publication. Most clinicians will not go to the length of writing an IRB protocol to submit such findings.

Technical architectures needed

Prior work has uncovered the deficiencies of technical workflows to facilitate precision health, especially at the interface of the laboratory and the clinic (Walton et al., 2020, 2021, 2022). These processes are critical to the success of scaling precision medicine. To my knowledge, such complete systems do not exist in the commercial space and required our organization to build custom solutions. Electronic Medical Record (EMR) vendors have begun to build infrastructure to support precision medicine (Walton et al., 2020) and third-party tools with that cover different aspects of precision medicine are beginning to appear. There remains significant work to be done in this area particularly in the domain of implementation science (Wiley et al., 2022).

Prioritization and governance of technical architectures

In my experience advising other healthcare systems, implementation of precision medicine technical frameworks tends to be a low priority to organizational leadership. This is particularly true when projects require resources from the EMR technical team. As genomic information becomes more available and critical to daily patient care, healthcare systems that have avoided implementing such architectures will find themselves struggling to manage the data and the resultant clinical implications. This can result in suboptimal patient care and even legal liability. In my prior experience, one major barrier to achieving approval and prioritization from leadership is their concern over who will manage the domain specific aspects of the such architectures (Walton et al., 2020, 2021, 2022). Having a domain expert or CGO who can oversee and manage the deployment and continued use of such technical architectures is critical. Clinical geneticists are already filling such roles in healthcare systems that have progressed in this space but without formal recognition or title.

Reimbursement challenges

Genetic testing and clinical genetics encounters have been poorly reimbursed (Raspa, 2021), with many clinical genetics departments operating at substantial losses. Becoming a clinical geneticist requires two additional years of training after a primary specialty, yet financial compensation is usually less than practicing in the prerequisite field. This has led to a cohort of individuals being primarily driven by scientific interest and desire to help patients with compensation as an afterthought. Having such an altruistic workforce is beneficial, but the historical lack of financial focus of the profession may be what has led to unsustainable reimbursement models and a small workforce. As the need for such services becomes more critical, there must be financial incentives to develop the clinical workforce and required infrastructures within the healthcare systems.

Perhaps one of the most important roles for genome sequencing is in preventative care. Genetic information allows for surveillance and prevention that can significantly lower morbidity and mortality for patients which ultimately decreases their long-term cost of care. While several well studied genes have demonstrated financial value (Wordsworth et al., 2010; Lázaro, 2017; Tuffaha et al., 2018), it is especially true when the impact of multiple actionable genes is considered in concert. The challenge is that these financial incentives are long term savings and there may even be short term cost increases due to the associated preventative care. United States (US) payers have not shown much interest in

cost savings that cannot be realized in time periods shorter than their average churn, whereas national healthcare systems are more likely to see these financial benefits and adopt related policies. As there is a net national benefit in terms of reduction of cost, morbidity, and mortality, government intervention may be prudent to move the US forward.

Payers largely cover preventative care with grade A or B recommendations from the United States Preventative Task Force (USPTF) guidelines (HR3590, 2022). These guidelines are very conservative and slow to develop. Of the 73 American College of Medical Genetics (ACMG) actionable genes (Miller et al., 2021), only two currently have USPTF guidelines (US, 2019) despite significant evidence for the clinical impact of other genes on the list, including those for Lynch Syndrome [Evaluation of Genomic Applications in Practice Prevention (EGAPP) Working Group, 2009] and Familial Hypercholesterolemia (Lázaro, 2017). Using this slow gene-by-gene approach will take decades to realize the potential of genomic preventative care. IH currently considers over 200 genes actionable (Walton et al., 2022), as does ClinGen (ClinGen Curated Genes, 2022). The USPTF takes a very deliberate disease specific approach to evaluation. As preventative WGS and its interpretation drop in price dramatically its utility should be assessed as a whole for preventative care, rather than assessing the impact of individual genes. In most cases, the cost of testing one gene vs. 1,000 different genes is not significantly different as laboratories typically use an exome or genome backbone for testing. Therefore, opting for a more focused approach of testing a single gene does not appear practical as there is considerable added value to be obtained from the extra genomic data. This is especially true as we realize the growing list of genes that contribute to each disorder and how difficult, if not impossible, it is to differentiate between causal genes through clinical evaluation. Interestingly, an argument that has been made to justify testing only two genes rather than a panel is that primary care physicians (PCPs) may not have the expertise and time to handle the management of BRCA1 and BRCA2 let alone those related to other genes (Rajagopal et al., 2019). In my experience, few primary care physicians are prepared to manage any of these conditions if they do not have prior experience with them, and many have expressed concern about getting results from our population health sequencing programs. However, those concerns were largely allayed when the genetic testing results were delivered with clear concise management guidelines, or the patients were initiated on care pathways that were independent of their primary care provider. Rather than limiting the number of genes tested or returned to patients our focus should be on implementing infrastructures to manage this information and guide patients and providers through care pathways. This challenge is not going to get easier to tackle, it is going to grow every year as our genomic knowledge increases.

Data storage and access

Where genomic data should flow after it is generated is an important question. As patients navigate through various health insurance plans, seek specialized medical services, and travel to different geographic locations, it is crucial for the data to be accessible to multiple interpretive services and healthcare systems. There are still open questions of what data to store (genomic variant call format (gVCF), compressed reference-oriented alignment map (CRAM)), where to store it (onsite, federated systems, central repository, flash drive), and who pays for the storage (government, patient, healthcare system, laboratory). Additionally, as the price of sequencing comes down there is a question as to whether it is cheaper to store the data or just re-sequence the patient as needed. The relative cost of data storage is growing as a contributor to the overall cost of genome sequencing. AWS introduced S3 cloud storage in 2006 at a price of $0.15 per GB per month. Standard S3 storage in 2022 is about $0.022/GB/month (depending on usage volume), nearly a seven-fold reduction in price. The cost of genome sequencing dropped by a factor of more than 20,000 during the same period, from over $20M in 2006 to less than $1000 in 2022. The 10-year cost of storing a genome for ongoing analysis on AWS has been estimated at over $300. The cost may be mitigated by use of archival storage systems or advanced data compression. **One** strategy would be to keep variant data as gVCF files in high-availability storage while storing read data in a lossless CRAM format in deep archive storage where retrieval is delayed. Over 10 years, we estimate this approach would cost about $40, allowing for the CRAM to be retrieved from the archive at least twice. Limitations to using gVCF are having an incomplete human reference genome and persisting challenges around calling of structural variants and repeat expansions, which at times necessitates the use of CRAM format for reevaluation. Strategies for how to store and access data need more definition and study to ensure seamless precision care across systems.

Regulation

While some regulatory oversight is needed as precision medicine gains ground in the healthcare system, over-regulation could hinder progress in the field. Although often started with the intent of protecting patients, regulation can also have the effect of benefitting industry giants by creating significant barriers to market entry and thereby eliminating smaller innovative players from the market. This ultimately limits innovation by reducing competition. The recent introduction of the VALID Act (HR4128, 2021) proposing FDA regulation of genetic testing could have had a large negative impact on genomic innovation if it had passed. Such regulation would impose significant regulatory burdens and associated costs that are prohibitive to small academic laboratories who have driven a significant amount of the innovation in this field (ACMG Group Sign-on Letter, 2022). Careful analysis of actual harms vs. benefits of new regulation should be considered before any laws are passed. It is also important to realize that genetic laboratories already have oversight by other regulatory bodies. FDA regulation could impose significant braking on an industry whose rapid progress has been very beneficial to patients. With the failure of the VALID act to pass, it is uncertain what steps the FDA will take next toward regulation of genomic testing. As the FDA has asserted itself into this space, it has a responsibility to ensure that their policies enable small innovative companies to enter and operate in the market. They also need to ensure that they have the capacity to manage oversight in a way that does

not impose significant financial and temporal burdens on highly innovative laboratories. The FDA's regulation of CDSS and artificial intelligence, are equally as concerning as these regulatory measures will also have profound impacts on the delivery of precision medicine (FDA, 2022; HER, 2022). Regulation is necessary and can offer protections to patients but must be employed prudently to ensure that it does not ultimately harm patients by preventing highly beneficial products from coming to market.

Conclusion

While the world changes around us, healthcare cannot afford to stand still. Reengineering different aspects of our healthcare system to harness the power of genomics could expedite our path to reaching the full potential of precision medicine. We find ourselves at a critical intersection where we can opt to take the path of least resistance, leaving preventable deaths in our wake, or take the path of change, reducing mortality and morbidity while improving quality of life. We should implement meaningful changes to accelerate this field, as it has so much potential to impact patients and their care. This vision reflects my opinion, shaped by my experience working in two of the largest population health sequencing programs in the U.S. healthcare system. Certain principles may not be applicable to other healthcare systems, and I acknowledge that other professionals working in this field may hold divergent perspectives. My objective is to facilitate a dialogue that encourages a variety of perspectives and fosters collaboration toward leveraging genomics to advance the field of precision medicine at an accelerated pace.

Data availability statement

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

Author contributions

NW and GC performed analysis of data storage and sequencing costs for this work and contributed to the "Data Access and Storage" section of this work. Both authors contributed to the article and approved the submitted version.

Conflict of interest

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

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E-prescription and invisible work in genomics in France

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This article aims to analyze the transformations in medical prescription work and infrastructures brought by digitalization. Our fieldwork takes place in the context of precision medicine development based on genomics High Throughput Sequencing (HTS) in France, through the Plan France Médecine Génomique (PFMG 2025). The Plan aims at industrializing the production of genomic testing in clinical context at a national scale, particularly in oncology. To ensure the intensified flow of information between hospitals and HTS platforms required, a centralized process has been organized around two sequencing platforms and the introduction of a new e-prescription software (E-PRES). We start by analyzing how the e-prescription software changes the practices of health professionals by imposing new technological and professional standards. We show that, more than a mere prescription tool, this software is also a monitoring tool for the platforms and prescribers' work, and a support tool for the logistical and work organization. Secondly, we question the division of labor among the different professionals involved in the organizational or technical tasks required. We show that the feasibility of this new form of digitalized prescription relies on an important *data*work performed by "small hands" to select, translate and process a vast amount of heterogeneous data.

KEYWORDS

digitalization, genomics, electronic prescription (e-prescription), invisible work, cancer, high throughput sequencing, infrastructure studies

1. Introduction

The France Genomic Medicine 2025 Plan (PFMG2025) is a national policy organizing and financing the access to whole genome sequencing in care setting. All patients in the country, for which this analysis is deemed of potential clinical interest—either for diagnostic, prognostic or treatment- are eligible, notably rare disease and cancer patients. In this latter field, scholars have shown how the identification of specific mutations in genes such as BRCA, that strongly increase the risk of disease, has helped recompose medical nosology (Keating et al., 2016; Cambrosio et al., 2021) but also clinical work (Bourret, 2005). More recently, so-called somatic genetics turned toward the characterization of tumor cell DNA has undergone important developments. New treatments (targeted therapies, immunotherapies) whose prescription is conditioned on the presence of specific somatic mutations have been massively evaluated in clinical trials (Nelson et al., 2014; Polk et al., 2023) and commercialized. While some of these therapies are remarkably efficient, the current flow largely reflects an economy of promises (Hedgecoe and Martin, 2003) endorsed by both the drug industry and the regulation agencies (Salcher-Konrad et al., 2020). Inquiries on genomics in cancer care settings have highlighted the multiples forms that these practices of promises can take outside drug pipelines, in the patient' experiences and in professional

work (Kerr et al., 2021). The reorganization and new division of work associated with the routinization of genomic tests has also been documented and analyzed as a consequence of the specific articulation work between clinical and molecular data, that this cancer drug related genetics entails (Beaudevin et al., 2019). Yet, the French Plan, with its focus on High Throughput Sequencing (HTS) technologies[1], takes genetic analysis for the clinical care of cancer into a new dimension. In the field of rare diseases, Timmermans has proposed a rich analysis of the transformations in the genetic diagnosis work associated with HTS. He emphasizes the importance of new standards, in this work, namely international databases and the specific expertise required to use them properly (Timmermans, 2015). He also outlines the new ways in which these standards are articulated, through a collective endeavor, with both individualized molecular and clinical data to produce new forms of "causality for clinical purposes" (Timmermans, 2017).

Digital tools are a central part of this emerging HTS diagnostic process. In the case of the PFMG2025, if international databases are essential, a couple of additional tools have been developed among which a software, referred to by the actors as an e-prescription software, is of particular interest, given its role in the national access to HTS in different care context, including cancer. Digital tools have been used for decades in various fields of medical activity, including the organization of work with the so-called shared medical file (Lehoux et al., 1998), the financing of care with the National Health Insurance Interregime Information System (SNIIRAM) or the performance of medical acts with telemedicine (Mathieu-Fritz and Gaglio, 2018) or the algorithmic systems used to assist medical decisions (Anichini and Geoffroy, 2021). Informational infrastructure studies (Bowker, 2008; Bowker et al., 2010) have proposed insightful ways to consider computers, document scanning processes, software… Rather than "substrate systems" (Star, 1999; p 380), i.e. invisible backgrounds of work, these digital tool should be analyzed as infrastructures contributing to the organization of human work, with growing importance in situation where a variety of professionals performing tasks distributed over time and space are involved (Strauss, 1985; 1988). Some of this literature has renewed the analysis of "the ties between records and the social system that services and is serviced by these records" (Bittner and Garfinkel, 1967; Garfinkel, 1967; p. 192) and has highlighted the invisible work done by technicians to make the infrastructures operational (Shapin, 1989). This includes and shapes diagnostic work associated with intensive data entry, data care and logistical organization to ensure physical links between the stages of production organized from afar, that remains largely imperceptible to many members of the infrastructures when the device is working. Yet, this work of "little hands" requires specific skills (Denis and Pontille, 2012). While the updating of a database is a matter of expertise specific to so-called scriptural activities, its cognitive dimension has often been underestimated (Pontille, 2010). The invisible work behind databases consists of a set of tasks such as updating reports, cleaning fields, classifying, building a query, but also making the data compatible with the chosen digital format. These tasks must constantly be legitimized by the actors to show the extent of their work (Dagiral and Peerbaye, 2012).

The present article analyzes the implementation and the ways in which the new e-prescription software developed in the PFMG2025 is used. With this case study, we aim at contributing to the existing literature on HTS diagnostic work in care setting by introducing an analysis of the specific effects of digital tools on the organization of work and the forms of expertise involved. To do so, we draw on the informational infrastructure studies and take up their specific interest in the characterization of all forms of work, including the "invisible." Invisible work is indeed concept aligned with descriptions of the underestimated role played by paramedical staff in diagnosis and categorization labor (Seim, 2022). While physicians are historically considered as the "traditional adjudicators of whether or not someone is sick" (Dumit, 2006; p. 576), other medical laborers, such as nurses or ambulance crews, also perform essential preliminary classification work.

2. Background

Inspired by similar foreign policies, such as Genomics England in the United Kingdom or the Precision Medicine Initiative in the United States, the French Plan differs from these research-oriented initiatives in its clinical ambitions. Initiated in 2016 and endorsed by the Prime Minister, the PFMG2025 promises a revolution in healthcare through a generalized access to genomic medicine (Bourgain, 2019). Practically, the Plan has financed the setting up of two national HTS platforms where the production of whole genome sequencing is centralized. All the patients in the country with a pathology identified by professional and regulatory bodies as eligible and with a clinician prescription, should get a HTS, performed on one of these platforms and included in their healthcare national coverage.

Started in the late 90/s with the first BRCA test (Bourret, 2005), the introduction of genomic medicine in the French cancer care has undergone a first acceleration in the late 2000/s when the National Cancer Institute launched a State-funded program to settle "platforms for molecular genetics of cancer" all over the country (Nowak et al., 2012). This initiative was an answer to the first market authorizations of drugs whose prescription was conditioned on the identification of specific mutations in the cancer cells. These platforms produced the required tests for all eligible patients in the country (Beaudevin et al., 2019). In parallel, implications in precision medicine clinical trials developed in a handful of expert centers, where clinicians accumulated a rare and recognized expertise (Besle and Schultz, 2020). Many of these clinicians have been involved in the design of the FMG2025 Plan and in its implementation in hospitals. Their central position in expert centers and the competition between specialized institutions helped getting support from most health professionals in this very structured clinical field of French oncology (Castel, 2008). Facing little resistance, the HTS prescriptions provided by the Plan are gradually becoming routinized.

In a previous work (Bourgain and Lade, 2022), we have studied the impacts of the new centralized organization set by the French Plan on the production of genomically informed medical diagnoses.

1 This is high-throughput sequencing that allows the analysis of the entire human genome, and no longer only a panel of genes targeted and previously identified by biologists.

We have described the work done by the actors to ensure the quality of these diagnoses, the involvement of historical actors and the place made for new professional entrants, notably the bioinformaticians. We also highlighted the decisive role the e-prescription software, showing that its usages went well beyond this sole act. The software, we claimed, actively contributed to the coordination of the complex sequencing pathways that goes from the initial prescriptions by oncologists to their final impacts on the patients.

The sequencing pathways generate a very large amount of data for a significant number of patients, that conveys an image of abundance medicine. The handling of the case flow from a diversity of hospitals all over the country required the setting of an *ad hoc* digital infrastructure. Following the guidelines of the PFMG2025, each of the two national HTS platforms (referred to as platforms A and B) developed their own system, and referred to them as e-prescription software. Although the two have specificities, they share important common characteristics. In what follows, they will be designated in a non-specific way, as E-PRES. In the present article, we analyze the specific issues raised by the production and use of digital data associated with E-PRES, with a focus on the initial prescription stage. While this informational infrastructure links the different professions and spaces involved in the genomic analysis production chain, as a technological mediator, it also translates and distorts information (Latour, 2007; p. 58). Its impact on the ways in which professionals organize themselves is therefore significant.

Our survey has been carried out at the peculiar and transitional moment of the implementation of these new genomic analysis pathways and associated computer system, as part of the PFMG 2025. We show that this centralizing intention clashes with the information systems and genomic medicine analyses that have been in place for several years in some expert centers. E-PRES is in competition with existing software in hospitals, and around which logistical processes and work organization of health professionals are well-established. In this context, clinicians have difficulties in appropriating this additional software and its interface, and they finally organize themselves to delegate the e-prescription related work. To this aim, they negotiate with reformers (as we propose to call the health professionals to whom the State has entrusted the implementation of the PFMG2025 Plan) the creation of new positions, mostly held by women qualified as "prescription assistants" or ensure that other professionals already present, such as genetic counselors, free up time to carry out the work of monitoring, updating and validating the various stages of treatment in E-PRES. At the time of our survey, the new positions were referred to as "prescription assistants." Late 2022, their title was changed for "genomic pathway managers." Using this type of profession to perform the dirty work (Hughes, 1997), corresponding to the administrative and time-consuming tasks performed by the bottom of the hospital hierarchy, is a common practice in the medical profession. Moreover, this invisible organizational work is mostly performed by overqualified women in often precarious jobs (Avril and Vacca, 2020).

Similarly, the work of prescription assistants seems to be invisible as it is carried out in the name of doctors and in a software environment that leaves little trace of their input, except when it is not performed correctly and the production chain is blocked. The moment chosen for our survey, during the phase of introduction of the E-PRES software, enables us to reveal the importance of this work done by "little hands." Difficulties of appropriation by the clinicians, negotiations between professionals, training issues and the need to recruit professionals assigned to these technical tasks of prescription assistance are all indicative of their importance. In this context, our article examines the ways in which the introduction of the E-PRES software reaffirms the existence of little hands within the hospital, and more broadly within the medical order, and renews the forms of invisibilization of their work.

BOX 1 E-PRES: the different steps of the e-prescription software.

E-PRES is a tool that collects patients' clinical data in digital and structured form: clinical signs, diagnostic informatoin, family history, digitalized consent form for genetic analysis. From this software, it is possible to initiate but also to follow the complex logistical process that ensures the transfer of a patient's biological sample from the local hospital where it was collected to the centralized HTS platform that performs the DNA sequencing and proposes a clinical interpretation. In the case of tumor samples, this process includes an additional step at an expert biology laboratory, where the quality of DNA is evaluated. Finally, once the HTS analysis has been performed and interpreted on the platform, the result can be deposited there, along with the associated clinical management recommendations. Many actors are involved in the steps followed by E-PRES, whether they produce the data it aggregates, use them and/or are concerned by the decisions it allows to be made.

3. Methods

The data used in this study were obtained from a field survey interested in the deployment of genomic medicine in France[2], conducted from January 2021 to June 2022, in the two sequencing platforms of the PFMG (platforms A and B) and four hospitals or cancer centers in the Paris and Lyon areas. Given the COVID 19 pandemic context the fieldwork was conducted by different members of the team in the Lyon and in the Paris area. Previous fieldworks (on INCa platforms and on early phase clinical trials in several French hospitals) and contacts helped getting access to the platforms, hospitals and interviewees (see Table 1).

In the present article, we rely on qualitative data, i.e., semi-structured interviews based on grids adapted to the different interviewees and observations. Twenty six interviews were conducted with PFMG managers; staff recruited on the two platforms: managers, biologists, quality manager, medical manager; referring physicians and other professionals involved in the genomic test prescription chain, such as prescription assistants or genetic counselors. We started the fieldwork with interviews of three policy makers of the Plan, to get a general overview of the policy issues. Then, we first investigated the Parisian platform by meeting with the medical and operational managers who allowed us to interview the staff such as biologists or bioinformaticians. Although this entry through the management may have produced some bias in the information collected, it was the only way to

2 This survey is carried out within the framework of two research projects: an inter-SIRIC project (Socrate, Brio, Curamus, Lyrican) "Prescription Genomic Medicine" and an INCa project "Making sense of cancer."

proceed. In the sensitive moment of implementation, control over the information release on the platform was deemed as essential by the management. We proceeded the same way at the Lyon platform, first meeting the managers and then the staff. We were also able to visit the entire platform. Finally, the last part of the fieldwork consisted in observing sixty Molecular Tumor Boards (MTB) meetings in oncology, during which the selections of patients from three Parisian hospitals eligible for HTS were discussed. These observations were crucial for to identify difficulties linked to the handling of the E-PRES software and the decisive but often silent role of prescription assistants. Physicians, prescription assistants and genetic counselors were interviewed and a 1-day observation of the work of a prescription assistant was carried out.

Transcriptions of the interviews, subcontracted to an external provider, were analyzed with a double thematic coding and completed with the field notes from the meeting and workday observations.

Interviewees were given an information leaflet presenting the objectives of the survey and the conditions for data storage and processing. Finally, compliance with the CNIL's MR-004 reference methodology of the project was validated by the CNRS's Data Protection Department (DPD) (declaration n°220740). It also received the favorable opinion of the Groupe de Réflexion Éthique du Center Léon Bérard (GRET-CLB 2021-003) as well as that of the Inserm Ethics Evaluation Committee (CEEI-IRB00003888).

In what follows, we start by presenting the complex path of genomic analysis in a care context and analyze the ways in which E-PRES challenges existing practices. Secondly, we show that the implementation of E-PRES requires important adjustments on the part of clinicians and implies the work of "little hands" of new professions, to select and translate relevant data, sort documents and digitize the information required in the process.

4. The introduction of genomic prescription software in the French healthcare system

The introduction of e-prescription in care pathways linked to genomics appears to be a tool for controlling and transforming the nature of work. In this first part of the paper, we describe the multiple roles of E-PRES in the coordination, monitoring and organization of all stages of the prescription. The introduction of this new software, which coexists with already existing softwares and practices generates technical difficulties, but also frictions and negotiations between professionals. Finally, we discuss the transforming power of E-PRES, cognitive this time, on the prescription work itself.

4.1. Beyond e-prescription: a software for organizing and monitoring genomic testing

In order to understand the transformations caused by the introduction of E-PRES, it is necessary to look back at the complex pathway set up by the PFMG to carry out genomic analyses. Unlike the genomic tests carried out locally in some hospitals, platforms A and B centralize the sequencing of samples from the entire national territory. These platforms are thus located at a geographical distance from the professionals who order the analyses, and the various stages of the HTS test production are geographically fragmented. In this context, the care chain is distributed over more numerous and dispersed sites and IT infrastructures, primarily E-PRES, play a key role in linking and coordinating the different steps of the genomic testing pathways.

TABLE 1 Table of empirical material.

Kind of material	Number
Interviews with policy makers	3
Interviews on platform A	7
Interviews on platform B	5
Interviews with health professionnals	11
MTB observations	60

Within the framework of the PFMG 2025, the production of a genomic test is organized in several stages. The pathway begins with an initial prescription request from the clinician in charge of the patient's follow-up. This request is then sent to one of the 20 Molecular Tumor Board (MTB)[3] labeled by the Plan throughout the country[4], which assesses its eligibility before validating it. Eligibility has two dimensions. First, general clinical indications have been set by the Plan—in oncology, two broad categories: rare cancers and refractory metastatic cancers- and only patients corresponding to these indications can get an HTS analysis.

Second, the MTB also selects patients according to health indicators (number of metastases, "RMH" score[5], etc.) and sometimes, more informally, according to other individual characteristics: age, social situation, location, but also according to the lifestyle and behavior of certain patients, such as whether or not they smoke. The collective decision made during the MTB meeting are based on the information collected in the patient's clinical file and made available from a software that is different from E-PRES.

Indeed, each hospital uses a specific software to handle the consultations or medical acts, the clinical information, evolution of the disease and its management, and the results of the biological or genomic tests already performed. Once the members of the MTB have collectively validated the HTS prescription, a new entry must be created in E-PRES that includes the prescription, clinical data and the patient's consent. This registration triggers the logistical and technical process of the genomic test. New software, specific

3 Molecular Tumor Board are multidisciplinary meetings in which clinicians, biologists, clinical research associates and bioinformaticians participate. Their objective is either to refer a patient for a sequencing or to analyze the molecular results of the sequencing, in order to prescribe a treatment to the patient.

4 https://pfmg2025.aviesan.fr/professionnels/preindications-et-mise-en-place/cancers-avances-en-echec-therapeutique/

5 The RMH (Royal Marsden Hospital) score is a biological test used to assess the patient's health status.

to the PFMG pathways, E-PRES thus requires supplementary data work.

> *"There, the patient is entered into [E-PRES] which is a software that allows the follow-up of different patients, and the interface between the different centers. From there, as soon as the patient exists in [E-PRES], we can ask the pathologist to transfer the tissues to the platform where the nucleic acids will be extracted. And so, there is again a bit of... I would say formalities, trying to mediate and coordinate between different people, with the pathologists, saying that this patient has been included. You have to send the tissue. The pathologists order a transporter. The tumor comes out of the tumor library."*

Interview with a neuro-oncologist, prescription physician, June 17, 2021.

The samples are then sent to the sequencing platform, where various preparation steps are executed by specialized technicians. These final steps in the preparation of biological samples and sequencing require meticulous logistical development. The DNA must be extracted and prepared so that the molecules can be analyzed by the machines, the very high-speed sequencers, which are the cornerstones of the platforms. The sequencing of the samples is a particularly important step in the technical process: the biological material is transformed into digitalized information.

While other softwares are used during the sequencing process, E-PRES plays an important role at the end of these technical steps because it aggregates the genomic data analyzed by the biologists. Indeed, the subsequent steps of bioinformatics data processing require technical expertise developed by dedicated teams. The quality of the digital data generated by the sequencers is controlled before they are analyzed by biologists, using *ad-hoc* software, different from E-PRES, and developed by the bioinformaticians. Thus, E-PRES organizes the work of linking and articulating (Star, 1986; Strauss, 1988) data of different natures: genomic data, clinical data, legal documents such as the consent signed by the patient, but also external international databases containing, in particular, information on the role of variants. E-PRES is thus at the center of a complex, distributed information infrastructure of storage and computing, in which material and logistical issues play a key role. This makes it a priority for the manager of bioinformatics on platform B to have a system engineer in his team, who is able to operate and control the hardware infrastructure:

> *"In fact, yes, my profile [...] that I like to recruit first, [...] is the system engineer. The one who will manage all the hardware infrastructure, the calculation server. Because without it, we don't really do anything. Without a good infrastructure that holds up and with good systems engineers who monitor and manage all that, you don't get very far. It's really the essential engine."*

Interview with Platform B bioinformatics manager, April 29, 2021.

Beyond this function of organizing digital prescription, E-PRES is, for the platforms and prescribers, a tool used for logistical follow-up and work organization. Each step on the pathway is recorded in the software. The web interface displaying the list of patient files submitted for genomic testing indicates by a band at the top of the screen the number of files according to their status along the genomic testing chain: "waiting to be received," "waiting for sequencing," "waiting for results," "completed."

Similarly, on the slides used to present the genomic pathway to professionals, E-PRES is located at the center, in position to follow all steps, from the patient's registration at the MTB to the report of the clinico-biological interpretation informed by the HTS results (see Figure 1).

> *"So, we have [E-PRES], which is the electronic prescription system that actually becomes our control tower as well. We manage many things within [E-PRES]. That is, it's not just the prescription. It goes all the way to the report. The report is deposited in [E-PRES]. So, it allows us to track by theme: the physician has prescribed, the tubes arrived in the laboratory, the sequencing is done, the computer analysis is in progress... That's it. It allows us to follow the evolution of the sample, basically."*

Interview with Platform A medical director, April 06, 2021.

E-PRES is thus a tool designed to meet the organizational, technical and scientific constraints generated by this centralized HTS production scheme, through its ability to link spaces, hospitals and platforms, and professionals who are geographically distant, but also more diverse and more numerous.

4.2. The centralizing effect of E-PRES added to the localized systems already in place

In addition to its function as a tool for logistical follow-up and organization of the prescription work, E-PRES also has a role of centralizing information. Yet, as E-PRES is superimposed on existing local solutions, specific work is required to adapt to its interface and computer input. The changes in practice required are a source of resistance from certain clinicians, negotiations between professionals and, consequently, frictions (Beaudevin et al., 2019).

The PFMG 2025 aims to generalize and harmonize access to genomic medicine. In this context, the E-PRES software allows the platforms to be electronically linked to referring physicians located throughout France. As the management of platform B explains, the particularity of their sequencing laboratory is that it is entirely dematerialized and goes beyond the boundaries of the hospital:

> *Platform B medical manager: "You can't go to something like that without having a tool for prescription. So, we had to... the lab is necessarily totally dematerialized. So only that, a basic lab, it gets tubes with erasers and pencils. And we can manage a lab without having a computer system. Here, we had to totally... yes, dematerialize the entire process."*

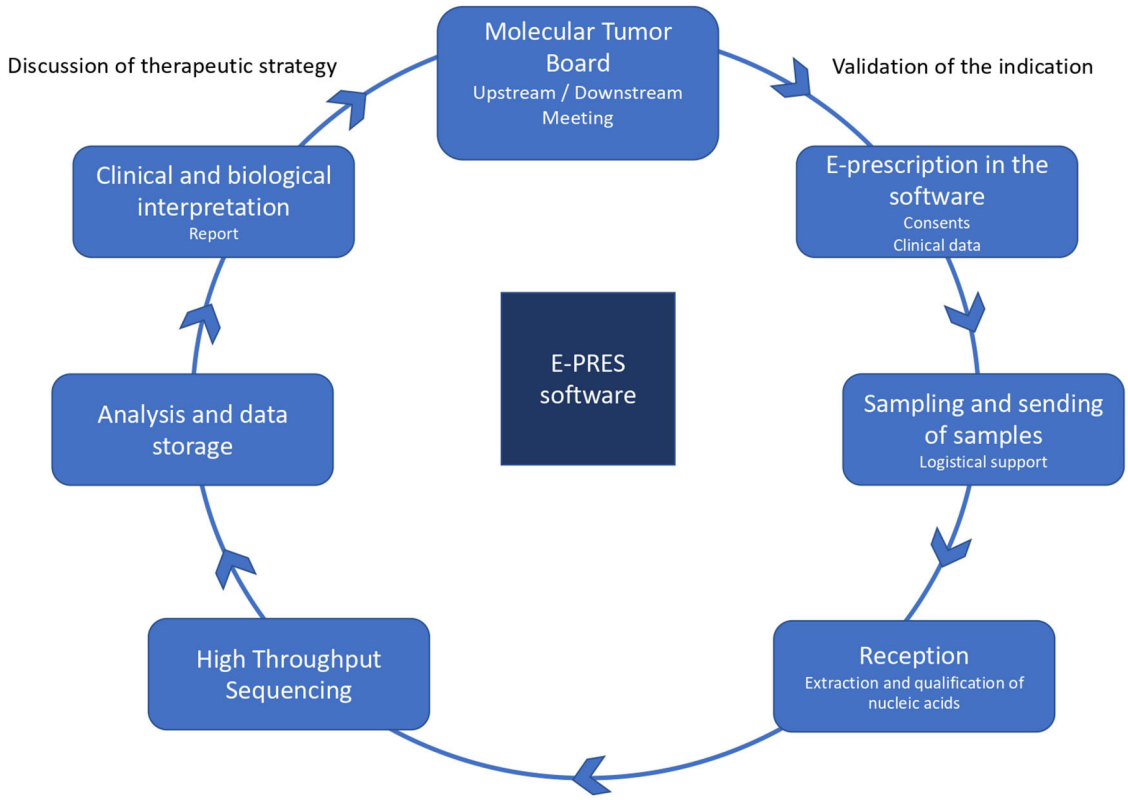

FIGURE 1
The prescription process for a genomic test. Source: https://www.oncorif.fr/professionnels/la-medecine-pan-genomique/.

> *Platform B Operations Manager: "Compared to a regular hospital, also there was the fact of going beyond departmental boundaries. In other words, whether you're in Avicenne, Bichat or Necker [three hospitals in Paris], you can send and get a result for your patient. So... and whether you are in Rennes or Lille too. So it places everyone on an equal basis [...] That is to say, if you are in Rennes and you have three patients, you will send one here, one there... So there, it is still possible to centralize."*
>
> *Interview with Platform B management, May 11, 2021.*

E-PRES has been designed to be directly used by prescribing physicians before MTB using personalized identifiers and codes. This information can be completed later, during and after MTB's discussions. However, handling the software involves additional work for clinicians: they have to get used to its interface and functioning. An important characteristic of E-PRES is that the progression throughout the different prescribing steps is conditioned on the presence of specific digital information, namely patient consent, clinical information and genomic analysis reports. The digital data management work is thus crucial to allow the progression of the prescription process.

> *"E-prescription is something new. It's a bit of a novelty in this Plan (...) Perhaps we will first make sure that they understand the tool. Because it's true that imposing e-prescription on a thousand physicians... We have very different generations. But it's true that e-prescription is a bit of an irruption in the world of some clinicians who were used to filling out notes. (...) So it's in this temporality. A bit of an immediate aspect. It's that: I have my patient and I prescribe."*
>
> *Interview with Platform B medical director, May 11, 2021.*

Moreover, E-PRES is an addition to and not a replacement for the pre-existing local software specific to each hospital. The medical manager of one of the platforms explains some of the blockages and resistance from clinicians by the "cumbersomeness" of the operations and the work involved in appropriating the software:

> *"For cancer I think, one part that is blocking is the cumbersomeness. That is to say, we had to create an electronic prescription software called [E-PRES]. Well, like any new software, you have to get used to it, and it takes some time to make an electronic prescription."*

Interview with Platform A medical director, April 06, 2021.

This implementation "cumbersomeness" also stems from the centralizing role of E-PRES, marked by technical difficulties in making the different software programs interoperable. Indeed, E-PRES has the function of monitoring the entire genomic test process and the correlated gathering of clinical and biological information. However, on the sequencing platform, part of this information is first managed through two other software, one used to monitor the biological sample preparation and the other to help interpreting the sequencing data. On one of the platforms in particular, these two software are not interoperable with E-PRES. Similar technical difficulties exist with local hospital prescription software. In this case, making the different local prescription software interoperable with E-PRES is not considered as an option by the actors.

This brings us back to the problems already studied in relation to the implementation of systems which must be made compatible with systems already in place, and for which the work of unifying and upgrading the information takes a great deal of time (Bowker and Star, 1999; p. 107–108). Indeed, the clinical information of patients, already present in the local prescription software specific to each hospital, must be adapted and re-uploaded in E-PRES by the professionals. This requires, in addition to the appropriation of a new tool, additional time for entering patient information, which is perceived as too great a burden for some of the prescription doctors. For example, a clinician involved in setting up one of the platforms described the discussions she had with the bioinformatics manager responsible for designing the e-prescription software.

"In fact, at the beginning, [the bioinformatics manager] wanted the doctor on [E-PRES] to rewrite the entire form. I told him: in fact, we'll have to do the form on [the hospital's software], then we'll have to redo the form on [E-PRES]. I said [to the Bioinformatics Manager] it's not possible, in fact. So, you have to delegate the access rights to a secretary or a genetic counselor. Because if you don't, the doctors aren't going to do it. So, we don't have the time, I tell you I don't have the time. So that's it. So that's not possible."

Interview with a physician oncologist in charge of a Molecular Tumor Board of the Plan, January 12, 2022.

This quote is revealing of the type of negotiations between professionals on the modalities of appropriation of the technology and the accomplishment of the prescription work in digital form. Although this was not the case at the beginning of the implementation of the genomic test process, prescription assistants and genetic counselors have been hired to support the clinicians in the digitization of prescriptions. Yet, prescription in E-PRES requires a specific work to translate clinical data into the standardized categories implemented in the software, which generally implies the clinician's expertise.

4.3. Translating clinical data into standardized and computerized language

The digitization of the clinical information collected transforms it by imposing a standardization of the clinical data. This requires cognitive work by professionals who must translate clinical observations into a standardized form. In local prescription software, while some of the patient information is entered directly into the interface, a significant portion of this data is made accessible to professionals through the input of scanned documents into the software. As Garfinkel (1967) has already shown about non-digitized medical records, although the complex documents included in it prevent a form of standardization of the data, they do not distort them, so that they can be used in future, yet-unpredicted, clinical contexts. On the contrary, E-PRES is designed to ensure that patients' clinical information is entered in a standardized form, according to international HPO (*Human Phenotype Ontology*)[6] codes developed to categorize disease phenotypes. They can then be manipulated directly by data processing algorithms developed by the bioinformatics platform.

"The prescription is really the entry point and we can collect a lot of information and data that are very important. [...]. On the genome, it's quite brilliant because as soon as I need data of interest that could be useful for sorting efficiently and automatically in [the other software], I just add boxes in [E-PRES] and I ask the clinicians to fill them in. And in that way, I know that I have this data that is well structured in the nomenclature that I want and I reuse it afterwards directly."

Interview with the bioinformatics manager of platform B, April 29, 2021.

The coding of patients' clinical information requires a long but also skilled work of analytical rereading of the available clinical elements. It is a matter of making the necessary decisions to decide on the most relevant codes.

"There are still [...] 15,000 HPO codes. Yes, it's not 3, there are 15,000. So, it's true that today, either you don't put in enough and you're lost. Or, you put too much and you drown the fish. So, what we're going to try to find out is that there is a middle ground in describing exactly what the patient has. There is a prescription issue."

Interview with Platform B medical director, May 11, 2021.

These issues of arbitration on the information that should be coded in HPO format are a form of "tacit knowledge" (Collins, 1974) specific to clinicians. It is not just a question of transforming information into numbers; the expertise of the clinicians is essential

6 Human Phenotype Ontology is a standardized vocabulary used for phenotype-driven differential diagnostics. It contains over 13,000 terms of phenotypic abnormalities that have been seen in human disease.

in order to identify the clinical data that will be relevant for the type of analyses planned. Moreover, a specific and collective reflection on the quantity of clinical data that must be provided, is carried out jointly by the prescription clinicians and the biologists interpreting the genomic data.

> *"Before, when we did a prescription in [E-PRES], it was frozen. It was blocked. When it was done, it was done. Whereas today, we have been able to block the identifying band [of the patient]. His consent, last name, first name, date of birth, etc. We can continue to enter clinical data as long as the data is not being analyzed. Therefore, we set up what we call CBIR, Clinical-Biological Interpretation Meetings. We have almost finished. So, it's during these CBIRs that we can collectively say: this file should be enriched on a clinical level."*

> *Interview with the medical manager of platform B, May 11, 2021.*

The HPO codes modify the prescription work because the coding implies a specific reflection of the health staff on the choice and the number of relevant HPO codes to select. E-PRES has a mediating role in this work by organizing the interactions between clinicians and biologists. This additional work thus highlights an important transforming effect of the informational infrastructures. From the point of view of the designers of one of the platforms, the objective is that the prescription work should be modified during consultations so that the physician writes it directly according to the HPO standards and, in the long run, it will no longer be necessary to translate the prescriptions according to these standards.

> *Manager of platform B: "So, we arrive and suddenly we tell them: "Guys, we're sorry, we have standards now. Okay? You have to stop sending us the exam, whatever it is, and then take this and work it out" [...] You have to write a prescription at the consultation that is as efficient as possible in terms of... data. Because it's the clinical description of the patient that is going to be essential for the interpretation."*

> *Interview with Platform B medical director, May 11, 2021.*

From the point of view of the same designers, beyond the quality of the prescriptions for each patient, it is a question of creating a database in which the clinical information can be directly manipulated by the data processing algorithms developed by the bioinformatics platform to handle sequencing data. Yet, as noted by a designer of E-PRES, this touches upon a crucial expertise of clinicians that is central to their diagnostic work and might be difficult to share.

> *"I don't know if I should say this, but [...] we have a whole area of clinical research that has been built on identifying the causes of genetic anomalies in their patients. So, it's true that we are dispossessing them a little bit... Well, if they have to put all the data in a shared database, there's a little bit of... I don't know if it's dispossession but... there's a sharing aspect that is actually quite easy in IT and quite easy in biology. It is perhaps less easy in the clinic. So, there it is, it passes time."*

> *Interview with Platform B medical director, May 11, 2021.*

It is thus the core of the prescription work that is transformed under the effect of the new importance of informational infrastructures, which are now central to logistics organization, but also to more directly cognitive work functions. In a seemingly contradictory way, this system of standardization of clinical data in HPO code, appearing to be a highly automated process, actually increases the evaluation and selection of clinical data as well as the work of adjustment between clinicians and biologists. This digitalized "precision medicine" systems increases the amount of laborious technical work involved and, as we see in the following, of feminized dirty work in particular.

5. Supporting digitalization: the invisible work of a genomic test prescription

Material, organizational and cognitive issues are at the heart of the prescription process and, as we have just seen, the digitalization of this process requires adaptations from the clinicians, centered on the integration of the E-PRES software into their practices. Yet, the appropriation of this software is not limited to the work of clinicians but is accompanied by an intensification of the dirty work (Hughes, 1997) carried out by the non-medical staff. Indeed, besides the training sessions implemented by the PFMG to facilitate the clinician's use of E-PRES, they are also supported by new professionals in charge of invisible tasks.

5.1. Training and informing on the use of e-prescription

In order to support the learning process of E-PRES, the two platforms have set up webinars. The multiplicity and geographical dispersion of clinicians likely to prescribe throughout the country have led to a digital version of these training sessions. Clinicians can therefore follow them at distance and have access to a prescriber's user manual. The objective of these webinars is 2-fold. If the modules aim first at acculturating clinicians to E-PRES, they also condition their access to the latter. For one of the platforms in particular, it is only after following the tutorial and answered two multiple-choice questionnaires that an account can be created for the clinician:

> *"So, they [the physicians] do a little 30-min learning session. And they answer two quizzes. Once they have answered… So for the moment it's still manual because... [Laughs.] We receive the answers by email [...] And once we have the answers, well, if they have more than 60% correct answers, well… On the two MCQs,*

> *in general they don't have too many difficulties. So, we ask them... well, we create an account for them. And then they can start their first prescription on the tool."*
>
> *Interview with the operational manager of platform A, March 10, 2021*

However, these distant training are not enough to get prescribers to use the software. Indeed, the implementation of E-PRES requires a succession of very physical meetings between peers to explain what it is and how it works. We find here the presence of "active relays" (Benedetto-Meyer and Boboc, 2019; p. 101) already studied in the world of private enterprise that accompanies digitalization. In the implementation of the PFMG, several actors have made the choice to familiarize their peers with digital tools and the new prescription process in the broadest sense. This need was felt by the staff of one of the platforms who noticed that prescriptions were made on the software but that they did not receive any samples.

> *"And we noticed that in some centers, there were prescriptions but afterwards the sample never arrived on the platform. So, we wondered about this. And what was happening ? The referring doctor was saying: well, I clicked, so it's good. Except that no one was informed that the sample had to be sent, etc. So, there was no way of knowing what to do. So, there was no internal follow-up. So that was one of the points that we regularly made. And in 2019, we asked all the medical oncology department heads to attend. We gave very theoretical presentations on what is the project ? How does it work? What should be done? And then, on request, [...] we did quite a few TC [teleconferences], presentations, but in restricted committees, with a CHU [public hospital] problematic, by center, in fact. So there, we did it more on request in a way to show them examples of what works and what doesn't, and how we could help them. And I think it was beneficial because we can see that for some university hospitals, there were many requests that had been made and that have been abandoned."*
>
> *Interview with the operational manager of Platform A, March 10, 2021*

In this case, the care pathway of the PFMG was not already embedded in the hospital organization and the physician was supposed to accomplish all the logistical steps by himself. This situation explains why nothing happened after he validated of the prescription by the MTB.

On the two platforms, the implementation of the prescription pathway requires presentations of the software and its associated steps so that physicians in each hospital can appropriate it. These training sessions are also provided in structures that could support physicians in addressing these issues, such as the Regional Health Agencies (ARS)—the institutions responsible for implementing the State's health policy in the regions -, existing cancer networks, etc.:

> *"I do a little less [presentations] but here, for example, next week I have an appointment with the ARS [Agence Régionale de Santé] [...] next to Tours, where we have not succeeded in setting up the MTB. To try to stimulate this kind of things, to speed up the operation. When there is a problem in the regions, as soon as there are questions [...] I do coordination work. [...] Last year, in June, I even went to make a presentation of the Plan. It was at the [regional cancer network bringing together several hospitals]. I also made a presentation in the North of France. [...] Afterwards, my name is still around because at the beginning, I was the only one to train everyone on [E-PRES]."*
>
> *Interview with an oncologist, head of a molecular tumor board (MTB's) for the PFMG, January 12, 2022.*

This assistance to digitalization through trainings or presentations is carried out either by clinicians involved in the development of the PFMG or by people with positions of responsibility in the platforms or in hospitals. Yet, these measures (webinars, training, presentation) are not sufficient to overcome the clinician reluctance to use E-PRES. Using the software is also time-consuming. A new division of labor has been set, that involves the recruitment of new professionals in charge of all extra tasks associated with the e-prescription.

5.2. The emergence of new prescription support professions based on the clinical research model

While the use of HTS technologies by the PFMG is new in the healthcare setting, several hospitals have already integrated in-house molecular screening programs based on restricted forms of genetic analyses, i.e., own gene panels, into their clinical routine. Thus, E-PRES is not only an addition to existing softwares, but it also fits into existing genomic medicine practices. In this context, E-PRES participates in the appropriation of new genomic technologies for care, which are supposed to allow a particularly fine analysis of the patient's genome. Moreover, the software centralizes the follow-up of the different steps of the genomic test and is thus supposed to simplify the monitoring of the results.

In some cases, however, the implementation of E-PRES has been hampered by these internal processes, which are considered more efficient than the prescription chain provided by the PFMG. Indeed, at the time of the survey, the HTS on the national platform was carried out in longer delays—3 months in the best of cases—than in some health care institutions, where the HTS pathway took about 2 weeks. For some physicians HTS precision level and its associated delay could thus be deemed inefficient for the patient care, as one of them explained in an interview:

> *"Because if you look at it, the hospital administration tells you at the same time: send your samples to [platform B] and don't do your research here [within the hospital]. So, they don't understand that we do a targeted search and we have the result in 15 days. So, we can give the result right away. [Platform B]*

> *currently takes between 3 and 4 months. So, for a disease that has a median survival of one and a half years. [...] So there are a lot of problems at that level."*
>
> *Interview with a neuro-oncologist, prescription with E-Pres, June 17, 2021*

For the cancer with a life expectancy does not exceeding a few months, the sequencing times erquired by the PFMG platforms are not compatible with clinical needs. Some patients die before the results of the Plan's genomic tests:

> *"For now, there is an observation phase to see how it works. And then after that, what happened to the delivery of the results. Now I think we have the results for four or five patients. Unfortunately, I know that the results were returned... because at least two of my patients had died when we got the results. So, I didn't have the opportunity to give them back the results [of their test]."*
>
> *Interview with a professor of neurology, prescription with E-Pres, June 10, 2021*

The match between the temporality of the platforms and the temporality of care is crucial for genomic pathway to succeed (Beaudevin et al., 2019), and the question of delay is thus a major improvement issue to satisfy clinical needs. The shortening of the latter relies both on the recruitment of more bioinformaticians and biologists available for the analysis of an increasingly large quantity of data (Cambrosio et al., 2021) but also on an increased monitoring and optimization of the sequencing process.

In this context, most of the clinicians who are familiar with genomic medicine, and already involved in clinical research activities, intend to reproduce their work methods in this scientific framework. Indeed, the proper organization of clinical research trials relies on Clinical Research Associates (CRAs) whose job is to ensure the monitoring of protocols and the quality of data collected from the investigating physicians, i.e., those responsible for the trials (Petit, 2018). Similarly, the role of "little hands" appears essential here, not only to carry out tasks considered as time-consuming by clinicians but also to optimize processing times between each stage, validations, negotiations. Clinicians have gradually imposed the idea of using positions similar to CRAs to ensure the prescription of a genomic test in E-PRES:

> *"And that's where we felt the need for the prescription assistance. Because they [oncologists] are not used to do that. They are used to work with the CRAs [Clinical research associates], with clinical research technicians. In fact, oncologists, when they include, [...] we prescribe. Because here we prescribe diagnosis and therapy. So, we are in the context of care. And it's true that it's complicated because we're in the context of care, so we don't need the resources for clinical research to support it. But the problem is that we face physicians [...] who don't know how to fill out this type of document because they don't usually do it. Because usually the CRA takes care of that. So that's why we've created positions called prescription assistants that can help physicians. But the validation remains the responsibility of the physician. Because it is under his responsibility, his prescription must be made. So, it's true that these prescription supports, I felt this need. But we didn't have the fundings, it wasn't foreseen in [the platform project]. In the case of the rare diseases, they found the solution: they have it financed by the Rare Diseases Plan. We did not have this, because there is no such plan for cancer. So that's why in the CLCCs [centers] or the university hospitals they now send some CRA staff to help the doctors."*
>
> *Interview with the operational manager of platform A, March 10, 2021*

However, the funding of these prescription support positions was not anticipated by the PFMG2025. Consequently, as the operational manager of one of the platforms explains, some CRAs had part of their position re-assigned to support prescription physicians on E-PRES. In some hospitals, genetic counselors provided this prescription support. Ultimately, thanks to a supplementary financial envelope released by the Plan FMG, dedicated prescription assistance positions have been created in several hospitals. This heterogeneity of professionals accomplishes an invisible but necessary work for the prescription process to run correctly.

5.3. The invisible "little hands" of genomic medicine

One of the unexpected effects of the digitalization of prescription is, in particular in the case of the genomic tests provided for in the PFMG, the need for greater technical supervision (Carricaburu, 1994), in the sense that prescription now includes various obligatory steps that did not exist until then.

> *Interviewer: "Can you tell me exactly what are all the extra steps?*
>
> *Doctor: Entering consent. Print the prescription for the blood draw. Call the transporter to have the blood*
>
> *samples sent [to the platform]. Notify the anaphylactic physician that he must send the samples. . . [. . .]*
>
> *Well, It's... it's heavy. It's very, very burdensome, in fact."*
>
> *Interview with a physician oncologist in charge of one of the MTB including patients in the PFMG, January*

12, 2022

This higher complexity of the prescription chain increases the technical supervision needed, particularly for the validation of the different steps in the monitoring software, for which the prescription physicians are originally responsible. Moreover, the work of entering the patient's clinical information into the software does not always end at this point. The clinicians may be recontacted if an error or inconsistency is detected during the following stages of the test, at the sequencing platform or by the biologists. During an interview, the manager of Platform A mentions a discrepancy in the sex of the patient between the data in EPRES and the biological sample analysis on the platform:

Lab Manager: "In fact, it's not an F [female], it's an M [male]. [Laughs] Here again, there is a mismatch between what was entered by the referring physician and what we see behind it. And well, we have to inform the physician. Well, it's not up to us to modify the prescription data.

Interviewer: And for that, very concretely… You make a phone call?

Lab Manager: Yes, I mean, I make a phone call and send an e-mail, saying: "Well, we see that we have this, so would you..."

Interviewer: And you do that?

Lab Manager: No, not me directly. The biologist or the intern who actually does all this correspondence, saying: "Well, we saw that. So, can you modify...?" Because as a result, it's under the prescription that you have to modify the gender to regenerate the right data. And then, the bio-info will say: "ah well, it's a male and we can see a male, so everything is fine."

Interview with Platform A Lab Manager, March 30, 2021

This excerpt reveals the decisive role of the "invisible technician" in laboratory work (Shapin, 1989) and, more recently, the cognitive work required to update medical databases (Pontille, 2010). However, faced with the diversification of administrative tasks assigned to clinicians, the digitalization of prescription imposes, alongside laboratory technicians, the arrival of new professionals who support clinicians, thus participating in the process of stratification of the health professionals (Freidson, 1988). Essentially composed of women, these new professions, often considered to require less technical training, are at the bottom of the chain of delegation of medical tasks, representing a division of medical work that gives pride of place to the most qualified tasks, and therefore the most prestigious (Arborio, 2012). Indeed, the implementation of e-prescribing software reinforces gender biases that the literature has already well identified in several countries. As such, Elianne Riska and Katarina Wegar's sociological survey of health care systems in India, Great Britain, the United States and Finland shows the segregation in the division of labor where the work done by women is devalued, while the work done by men is highly valued because the professions define it as work with measurable skills (Riska and Wegar, 1993).

On the one hand, the prescription assistants, who will be employed by the reference centers for the prescription of the genomic test provided in the PFMG, are more often called upon for administrative tasks directly linked to the process of digitalizing the prescription. On the other hand, other professions, also dominated by women, support doctors during certain stages of the prescription process. This is the case of genetic counselors who intervene, in our case, at the stage of signing consent by patients. On the model of the clinical research assistants solicited in the framework of therapeutic trials as logistical support, the genetic counselors find themselves between care and research, having to master certain technical knowledge in order to explain it to the patients and to support the doctors in their administrative tasks, as one of them explains:

"I work with three doctors. So, I'm under their delegation, legally speaking. So, I prepare everyone's consultations. Mine and the doctor's. So that means getting the medical records. Sometimes asking for tests beforehand so that we can move forward. Asking the patient for information on his family... also preparing his family tree in advance. Then there is the whole consultation part which is the biggest part of the work where we receive the patients in consultation. We establish their family tree. We list all the personal history. [...] So once we have explained all this, if the patient wishes to launch this genetic testing process, we sign a consent form. So, we explain to him the interest of the test. And what he will be legally obliged to do, including the obligation to the family. If he agrees with all that, he signs the consent."

Interview with a genetic counselor, January 7, 2022

Despite the centralization and digitalization of the monitoring of the prescription chain via e-prescription software, this supervision is largely based on the work of "little hands" (Denis and Pontille, 2012), which are invisible and not very highly valued by the health professionals institutionally responsible for validating prescriptions. This is a form of "dirty work," not very prestigious because it is highly administrative, and because it is delegated to new professions located at the bottom of the delegation hierarchy (Hughes, 1997). The links between dirty work and gender have tended to focus in the literature on nurses and care assistants, who perform tasks that are considered less rewarding than those performed by doctors (Bolton, 2005). In our case, women occupy positions as administrative assistants in order to run the software. Nevertheless, both prescription assistants and genetic counselors are overqualified ("master's degree") for the "dirty work" they perform. However, they do not have the skills to perform all the work assigned to the physician. They do not have the medical expertise required for the diagnostic work, they are consequently relegated to the less qualified tasks of prescription work, such as administrative tasks. In fact, this

work requires little technical training, no interaction with patients and, finally, little recognition by the institution itself. Some of their tasks on the software require them to use the clinicians' identifiers and passwords. Despite their daily involvement in the digital tool, they have only a restricted official access to it, despite its importance to the proper execution of the job. This contributes to the lack of consideration for their status and the invisibility of the indispensable nature of their work. Indeed, since access to some of the software's functionalities is restricted, they often have to borrow the login of a doctor or a manager to be able to perform follow-up or reporting tasks. As a result, their name does not appear in the tracking of activities performed. Using someone else's login and password strongly echoes the tasks that lead individuals to the rank of "non-persons" (Star and Strauss, 1999), especially since they do not appear in the reports they have written.

This invisibilization can also be explained by a restricted conception of prescription time made necessary by the digitalization of its processing. Clinicians have only partial visibility of the stages of e-prescription, whereas behind the scenes, the extended time of prescription must be considered. The digital version of prescription requires a multiplicity of administrative procedures, both upstream and downstream of the molecular tumor board. Indeed, prescription assistants must ensure that all the information necessary for the discussion of the patient's case appears clearly in the software form. During a day of observation of the work of a prescription assistant, we were able to record in our notebook all of these information gathering tasks:

> *In the case of patient 1, the prescription assistant shows us that an information is missing in order to calculate the patient's RMH score, which is essential to determine whether or not the patient is eligible for the genomic test. The file remains on stand-by until she can fill this gap, by contacting the referring physician to ask for more informations or his medical secretary to get new documents from the patient file.*

> *Excerpt from the observation notebook of a day's work by a prescription assistant in a health care institution in Paris, conducted on 22 March 2022.*

The work of prescription assistants can also consist in providing guidance to the physicians and checking that all the information is present. This means entering all of the new prescriptions into the software, requesting the removal of biopsy samples which may be in remote institutions, organizing the safe transport of blood samples and finally launching the analysis. It is also a matter of notifying the DNA extraction centers and the anatomopathologists of the new samples in progress. Finally, the bulk of the work is done around the tracking and the execution of tasks that are supposed to be done by the prescribers (physicians): creating a patient number in the software, retrieving the signed consents, filing the necessary documents, and validating the prescription in the software. A prescription assistant told us, "*Physicians don't go to [E-PRES] to look up information: where the sample is and so on. It is not at all practical for them*"[7]. It is therefore a question of doing "what remains to be done" (Avril and Vacca, 2020; p. 89) and what the doctors have not done themselves, covering both the failings of other professional groups and those of the software itself, which is supposed to ensure the monitoring and the centralization of data.

Prescription assistants are in charge of monitoring and, above all, of registering the e-prescription. They carry out a whole range of invisible tasks, which go beyond the physical framework of their office and which only become visible when they are not carried out, such as reminders of appointments (Avril and Vacca, 2020) with the doctors who prescribe for the signing of consent. Their work is made invisible by the very tool of the e-prescription software, which is supposed to carry out all these tasks by itself, which ultimately becomes the responsibility of the prescription assistants. On the other hand, if this work is not carried out, it is made visible insofar as the implementation of the software has revealed the need to recruit people to make it operational.

6. Discussion

The Plan FGM2025 embodies the centralized vision of the French State in supporting the implementation of HTS technologies in healthcare. To be effective at the entire national scale, this vision a radical increase in the standardization and digitalization of prescriptions. Consequently, E-PRES appears as a central tool in the PFMG2025 large-scale implementation of genomic in healthcare. The software has a decisive organizational role in the design of new care pathways and in the work division between professionals to integrate the HTS genomic technology into their practices.

In addition to collecting and digitalizing information, E-PRES help monitoring the care process, linking and guiding each stage of the genomic test. Digitalizing the prescription by means of software should allow any physician to refer a patient and guarantee the principles of equity for patients.

Nevertheless, this desire of health system regulators to impose a new organization of care at a national scale is confronted with logistical and technical difficulties as well as with pre-existing local practices within hospitals. The time required to perform the genomic test proposed by the PFMG is longer than those routinely performed in hospitals. Further, while the software is taking on a central organizational importance in the care pathway, it also requires much more specific work.

The PFMG's attempt to involve clinicians in this procedure of long-distance prescription encountered resistances directly linked to the hospital division of labor. In the end, the implementation of genomic medicine pathways turned to be in line with the pre-existing practices of the medical profession, namely the use of "small hands." Thus, far from dematerializing care, E-PRES has largely intensified the "dirty work," most often assigned to women, who are poorly recognized, in precarious positions (fixed-term contracts, part-time work, etc.) and often overqualified. This work is also largely invisible because it is integrated, without leaving any

7 Excerpt from the observation notebook of a workday of a prescription assistant in a health care facility in Parisian region, conducted on March 22, 2022.

trace, into the routine usage of the software. Yet, this work is crucial for the proper running of these pathways and particularly for the respect of deadlines. Ensuring that the software procedure are completed is essential if the HTS genomic analyses should improve care for patients who are often in precarious therapeutic situations.

7. Conclusion

This article analyzes how the digitalization of prescribtion and the organization of health professionals associated with precision medicine are transforming medical work. Far from avoiding any human intervention in the process, e-prescription requires the use of digital tools whose manipulation relies on learning and adaptation, but also on inputting, translating and sorting information. The automation and ddematerialization brought by software such as E-PRES, also increases the burden of work done by small hands, very largely feminized.

Largely made invisible, these tasks could qualify as dirty work. Yet, given the specificities of the clinical context and the operations of translation from paper to digital (or from one software to another) that are required, they should imply a certain form of expertise. We have described the centrality of small hands in the functioning of E-PRES but many of them do not have a formal nominal authorization to access it. Further, the software does not keep track of the data entry and formatting work and. Consequently, our enquiry did not allow us to observe the expert work of the little hands in the making. To further describe the effects of digitalization on the work of prescription, additional fieldwork with longer observations of the little hands daily work will be required, with more systematic observations of each task carried out, from data entry to bioinformatics, sorting work and monitoring of the prescription process. This would allow a more specific analysis of this prescription work nature, from the diagnostic work to the announcement of the results to the patient. We would be able to question the relational dimension of diagnostic work (Seim, 2022) not only between the different health professionals, but also between human work and that of the algorithms for labeling clinical data, in the particular case of the little hands and the prescription software whose operation they are responsible for.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by CEEI/IRB Comité d'Evaluation Ethique de l'Inserm: The ethics évaluation committee of Inserm, the Institutional Review Board (IRB00003888, IORG0003254, FWA00005831) of the French Institute of medical research and Health, has reviewed and approved the research project. The patients/participants provided their written informed consent to participate in this study.

Author contributions

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

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Conflict of interest

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

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Thalassemia, biobanking infrastructures, and personalized stem cell therapies in Chennai

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Thalassemia and leukemia and related blood disorders are approved for blood stem cell transplants in India, for a stem cell transplant to be successful, the human leukocyte antigen (HLA) complex located on the arm of chromosome six must be a match between the cord blood donor and the recipient. In the quest to find an exact blood stem cell match for an individual, the HLA becomes the node at the center of community genetics where the HLA match is sought (not necessarily successful) in the extended family, the same caste, language, and ethnic (both national and the diaspora) groups. By considering thalassemia as a case study, how do we understand personalized stem cell therapies within biobanking infrastructures in Chennai? How do social categories get entwined with biological materials like cord blood?

KEYWORDS

biobanks, Chennai, cord blood, ethnicity, HLA, personalized therapy, thalassemia, stem cells

Introduction

Biobanks come in various types (a) to cater to public needs (Gottweis and Lauss, 2011; Beltrame and Hauskeller, 2016, 2018), (b) for private or family use (Santoro, 2011), or (c) for community use. Tissue samples with respect to stem cells include blood (Starr, 2002), cord blood (Wagner and Gluckman, 2010), menstrual blood (Fannin, 2013), peripheral blood, and dental pulp (Collart-Dutilleul et al., 2015). Cord blood stored in biobanks is a potential source for hematopoietic (blood-producing) stem cells. These cells can regenerate the entire blood system (Cooper and Waldby, 2014) in severe cases of blood disorders such as thalassemia (a genetic blood disorder) and leukemia (blood cancer). Cord blood becomes significant because blood stem cells extracted for a stem cell transplant are important for categorizing HLA, thereby finding a match for a stem cell transplant.

Each cell in the human body consists of threadlike structures called chromosomes[1], which consist of intertwined strands of DNA (deoxyribonucleic acid: the repository of genetic information). The HLA complex is located on the short arm of chromosome six. HLA antigens are glycoproteins that reside on the surface of almost every cell in the body. The primary function of these antigens is to serve as recognition molecules in the initiation of an immune response (Scaradavou, 2013). HLA is a critical component in establishing a match between a donor and a recipient. Once a match is established, a (stem) cell transplant can take place. Cord blood stem cells are preferred because they are "young" (Alvarez-Palomo et al., 2019)

[1] "What is a chromosome?" (Medline Plus, 2019).

"raw, new and adapt easily (from personal interaction with a cord blood bank stakeholder at a conference in New Delhi, January 2017)." If a perfect match is not found among the parents and siblings (or anyone related), an unrelated donor is sought, making public storage of cord blood units a preferred choice among transplant physicians and the biobanks.

Considering HLA as data stored against categories of individuals understood as belonging to a family, caste, language, or race, I use Pinel and Svendsen's (2021) definition of personalized medicine. Personalized medicine is seen as a flow of data from the "personal" (data representing individuals) to the "collective" (common resources representing the population) and then to the "personalized," i.e., representing populations but stored for individual benefits (p. 2), therapy, and recovery. I build this article as follows: The first part explores thalassemia as a case study where the cord blood unit can be seen at the center of both the social and biological. Given the high incidence of thalassemia in South India, how do biobanking infrastructures help in finding an exact HLA match for stem cell therapy and treatment? Over time, HLA matches have been likened to the "collective" representation of populations where cord blood samples are stored for certain social categories of populations. Therefore, caste, race, and language become seen as communities catering to making therapy "personal." Therefore, in this article, I investigate, how do cord blood banking infrastructures help in finding personalized HLA match to treat blood disorders like thalassemia. How do social categories get entwined with biological materials like cord blood?

Materials and methods

I was a Research Assistant in India with a project titled "The Red Revolution: Emergence of Stem Cell Biotechnologies in India" based at the Geneva Graduate Institute, Switzerland and funded by the European Research Council (ERC) from 2014 to 2015. My fieldwork was supported by this project from 2015 to 2017. The study involved researching and archiving media reports, managing data and documenting, identifying available gray literature, writing reports, collecting and annotating relevant publications, and scoping the field for stem cell facilities in India. By stem cell facilities, I mean transplant and research centers, banks and their subsidiaries, and governing bodies in India. Among these, stem cell facilities were numerous private cord blood banks and a number of public cord blood banks. In India, umbilical cord blood stem cells are used to treat thalassemia, leukemia, and related blood disorders, whereas cord blood stem cell treatment for all other disorders is classified under research and requires registration of a clinical trial with the governing body in India.

Once I compiled a list of facilities in India, it was clear that the largest public cord blood bank was in Chennai. Chennai is also the headquarters to major private cord blood banks and home to the largest blood stem cell registry in India. Most of these banks are networked with the blood and marrow transplantation center, Apollo Hospitals in Chennai, which has performed over 1,500 stem cell transplants (as of September 2022) with a high success rate. I conducted 20 interviews with stem cell bank owners, scientists, doctors, technicians, marketing agents, and counselors with limited and difficult access given the secrecy surrounding the stem cell industry in India—15 involved semi-structured open-ended interviews and limited observation at cord blood banks. I also interviewed 60 people at a maternity clinic in Chennai, including pregnant women and their respective families, initially with a semi-structured open-ended interview questionnaire, but later switched to having conversations with them in the waiting room. Through the prewritten interview questions, my intention was to survey the number of women and their families opting for cord blood banking, be it public, private, or community banking (Panwar, 2023). I established contact via email with LifeCell (a private cord blood bank), Jeevan (a public cord blood bank), and W, a blood stem cell registry in Chennai. LifeCell is one of the largest operational private cord blood banks in India. It began operations in 2004. It has about 375,000 units of cord blood units banked (as of July 2023), having started as a technological partner with Cryo-Cell International, the world's first private stem cell bank based in the USA. With over 200 centers spread across India, LifeCell is headquartered in Chennai and has a fully functional cord blood processing facility in the suburbs of Chennai and Gurgaon in the National Capital Region of Delhi.

Jeevan cord blood bank began as a blood bank initially. Later as a a public stem cell bank (encouraging voluntary donations of stem cells), it started operations on principles like the blood bank with the help of corporate sponsors, philanthropists, and community support. I first met Dr. Srinivasan in the summer of 2015 in his office located in a building that housed a blood stem cell laboratory and bank. He has published widely with his colleague and co-founder of Jeevan, Dr. Saranya Narayan, on the need for cord blood storage facilities in India, voluntary donations, and the necessity of HLA-matched donors for a diverse country like India. Dr. Narayan introduced me to Dr. X at Apollo Hospitals in Chennai, a leading pediatric oncologist in Chennai. To work with Dr. X, ethics approval was required from the Ethics Committee at Apollo Hospitals in Chennai, the largest private hospital in South India. Having obtained the clearance from the Committee, I was invited by Dr. X to the hospital's children's wing. Dr. X made it clear that I would not be allowed to interact with the patients saying that it would not be right to ask the parents anything as they were not in a state of mind to respond. I agreed to observe and interact with junior doctors about stem cell transplants and related procedures. Similarly, none of the biobanks allowed interaction with patients, clients, donors, and recipients citing confidentiality as a reason. At Jeevan cord blood bank, I observed sorting, labeling, and processing of seven cord blood units with the help of laboratory staff. While at LifeCell, I was only allowed interviews with the scientific director and the marketing office; the processing of cord blood units happened behind closed doors.

This research has largely been multi-sited (Marcus, 1995; treating multi-sited ethnography as a conceptual topology requiring different methodological strategies, access to a different range of sources, and different narrative strategies), considering

different sites of observation in Chennai and New Delhi between 2015 and 2017. All interviews were recorded with permission and a signed consent form (signed by myself and the interviewee at the end of the interview). Most of my interlocutors' names in this article are anonymized, and in cases where they are identified, it is with permission on a signed consent form. I performed all Hindi-to-English language translations. Patient anonymity has been maintained, and data, documents, and information arising out of this research are confidential, i.e., only subject to my research and analysis. The study has been conducted as per the prevailing ethical guidelines of the Geneva Graduate Institute and ethical committee approvals obtained with concerned hospitals and biobanks in India. Data collection, analysis, and writing have been performed simultaneously to prevent any loss of substantial information and to draw valuable insights and inferences continuously throughout the course of the research.

Thalassemia, cord blood, and stem cell matches

Across from me on the operating table at Apollo Hospitals in Chennai (2015) was a boy, aged 6. Dr. X walked in, as was routine, continued expertly to turn the boy onto his stomach and enquired about the right dosage of anesthesia. I watched as she injected a thick needle into the boy's hip. The needle did not pierce the flesh easily. She winced a bit, tightened her grip, and turned the needle a little to the left and a little to the right, almost drilling through the flesh. The boy moaned a little. She continued this process until the needle touched his hip bone. Her assistant immediately brought the collection bag and placed it on a steel table near the feet of the boy. The plastic sheet around the boy's hip collected the blood dripping from the fresh wound and the rest was transferred to the collection bag, continuously shaken to prevent clotting.

She turned to me as the child was turned onto his back, and the wound was cleaned and closed with white gauze. "This boy is saving his brother (aged seven-and-a-half) today. His brother is a thalassemic, and his sibling was found to be an exact match." In this case, the sibling could be the donor, but in other cases, the quest for finding an exact match for a blood stem cell transplant sometimes took months or years (Panwar, 2020). This search for an exact stem cell match involves hospitals, banks, and registries—both national and international. This cocktail was essential as stem cells used for transplant need to match the patient's weight, and the ones collected separately by banks may not have had enough blood stem cells. Dr. X later added that in some instances the team injects a cocktail of stem cells sourced from various banks and registries—Jeevan (the public bank); LifeCell (the private bank); and W, a blood stem cell registry based in Chennai. This cocktail, she emphasized, was essential as stem cells used for transplant need to match the patient's weight, and the ones collected separately by banks may not have had enough blood stem cells. But blood, as we know, acquires meanings in its myriad states—fluid, solid, and viscous—and "becomes" (Copeman, 2009; Bennett, 2010) in every association it makes. Weston considered blood as having a "meta-materiality" (Weston, 2013; p. 35) blood's different evocations and imagery exist beyond its materiality and can still comment on each other (Copeman, 2014; cited in Carsten, 2019). Taylor (1992) explored blood as a liquid gift, a concept made popular by Copeman (2009) in his detailed ethnography about blood donation as a sacrifice and gathering merit (or *punya,* in Sanskrit). Therefore, how do we understand cord blood in relation to disease and biobanks? In movement and practice, how does the cord blood unit entangle social lives and biological material (Nading, 2017), thereby defining present-day biobanking infrastructures in Chennai?

Thalassemia is the most common inherited blood disorder across the world. It is estimated that about 100,000 children are born every year with blood-transfusion-dependent thalassemia and 1.1 percent of couples are at risk of having an affected child (Black et al., 2010; Bandyopadhyay et al., 2013; Panja et al., 2017). Previously known as the "Mediterranean disease," the first recorded case of thalassemia East of the Suez was reported in 1938 (Mukherji, 1938; Verma et al., 2011). The word thalassemia, or sea in the blood, was coined by Nobel-prize-winning pathologist George Whipple and William Bradford: *thalassa* in Greek means "the sea" (like the Mediterranean Sea) + *-emia* means "in the blood."[2] Chattopadhyay (2006; p. 2662) showed that most of the studies on thalassemia have focused on "immigrant populations living in Europe or in the Mediterranean region" with others focusing on prevention, counseling, and screening in Iran (Samavat and Modell, 2004; Strauss, 2009), Thailand (Hartwell et al., 2004), Saudi Arabia (Al- Hamdan, 2007), Jordan (Hamamy et al., 2007), Iraq (Al-Allawi and Al-Dousky, 2010), Bahrain (Al-Arrayed, 2005), Turkey (Mendilcioglu et al., 2011), and Pakistan (Ahmed et al., 2002; Ishaq et al., 2012). Most of these studies have focused on pre-marital counseling and prevention given the high incidences of cross-cousin marriages. Populations of North Africa, West Asia, and South India prefer consanguineous marriages or the "coming together of blood" (Clarke and Parsons, 1997; p. 7) with 20–50% of these marriages being culturally and socially preferred and 33% of which are first-cousin unions (Tadmouri et al., 2009; Bittles, 2011; Hamamy, 2012). Proctor and Smith (in Clarke and Parsons, 1997; p. 98) suggest that birth outcomes are affected by behavioral factors (e.g., diet), environmental factors (e.g., poverty), healthcare services (e.g., equity of access), and finally genetic, consanguinity factors, and geography (Akinyanju in Clarke and Parsons, 1997; p. 133).

Medically, cross-cousin marriages in South India have led to various cases of genetic conditions, especially where the birth of the male child is deemed more important than aborting a child with thalassemia. Therefore, lifelong transfusions of red blood cells are considered better than not having a male child at all (from personal interaction with a transplant physician at Apollo Hospitals, 2015). The prevalence of cross-cousin marriages in South India has led to inherited blood disorders like thalassemia, the cure for which is a blood stem cell transplant sourced from banked cord blood. By introducing and discussing consanguineous marriages while counseling parents opting for cord blood banking,

2 Medical definition of Mediterranean anemia (MedicineNet, 2022).

the natural fact of procreation is combined with the social fact of marriage and property and becomes part of a scientific discourse where kinship is medicalized (Strathern, 1992; Atkinson et al., 2001; Finkler, 2001). Linking genetics to disease rests on the premise of the medicalization of family and kinship. Genetic diagnostics is based on charting the family medical history and includes questions on inheritable diseases, marriage patterns, and working on finding the exact HLA match for a stem cell transplant. Both Schneider (1980) and Trawick (1992) have suggested that biogenetic kinship relations are bound by love, marriage, and choice. But biobanks take it a step further. It expands this circle of kinship and connects individuals and families via banking and voluntary donor networks through a community.

Understanding biobanking infrastructures: *community* in personalized therapy

How does one find an exact HLA match for a blood stem cell transplant in cases of blood disorders? Over many conversations with the various stakeholders, both public and private, it was clear that the first criterion that a transplant physician will look for is an almost-exact HLA match. In a conversation with Mr. Y at W, the blood stem cell registry in Chennai:

> […] there is less than 25 percent chance of finding an exact match within the family. We don't say it, but we find members within the same caste. The markers are the same. For example, Rajalakshmi in London died this morning. We organized a drive for her but couldn't find a match. But you know it is necessary that you find an exact match within the same community. Of course, there are people who have got an Italian match. The donor is Italian, but the patient is Telugu speaking… Andhra… but the first preference is to look for matches within the community. So, Raji, for example, didn't find a match within the community.

As Rajalakshmi (name changed) was from Andhra Pradesh in South India, the search for a match began with her family and moved outwards to the joint family, her caste members (details were not shared with me keeping in mind client confidentiality), and finally, the search was expanded to the World Marrow Donor Registry.[3] In addition, caste and community are being used interchangeably in this conversation with Mr. Y. Although searches for a stem cell transplant involve creating a fully functional registry where any person in need (in India) can find a match, the word "community" has been used as an umbrella term for members of the same caste, ethnicity, race, and related family members. A member of the marketing team at LifeCell stressed that community means family for the time being:

> "So when the child's stem cells come into the community, father also gets access to the entire community. Father, mother, and future siblings are the community, these four people can access the stem cells from the community. I think in a few years, even cousins can get access. So you can mix samples from the community and use them if the quantity is not enough."

Brown and Kraft (2006; p. 321–323) highlight that even though the banked blood might not be an exact immunological match within the family, it is presented as a "family asset" and these become "communities of promise." Santoro (2011; p. 86), following Brown and Kraft, explains that "the familial body is projected in new ways toward the future and the past: toward an act of responsibility over expectations of biotechnological futures, and toward a past of familial "genetic" diseases—real or imagined—that is often behind the decision to bank the cord of one's child."

Moreover, since my first meeting with Dr. Srinivasan and Dr. Narayan at Jeevan in 2015, they were clear about the benefits of voluntary donation of cord blood and emphasized HLA matches being ethnicity specific. In a 2018 article, matches being ethnicity dependent was clarified further: "HLAs are ethnicity dependent. With the poor representation of the potential donors of Asian origin in the database of over 32 million donors listed by the World Marrow Donor Association (WMDA), the chances of an Asian finding a 10 out of 10 HLA match for HSC (Hematopoietic Stem Cell) transplantation are very low. Consequently, hope for [sic]potential cure through transplantation is far lower for Asian patients compared to Caucasian patients" (Periathiruvadi, 2018; p. 5). In March 2017, Jeevan released a short movie on YouTube highlighting the need for voluntary blood stem cell donations for public use (see Figure 1).

These two images are screenshots taken from the short movie made and advertised by Jeevan to create awareness about donating cord blood and creating a registry. "For Indians and By Indians." I was struck by the change of photographs from different races to photographs with people who visibly looked Indian in the second image. In advertising ethnicity as the source of finding an exact HLA match, science also calls for an affinity and similarity (Bärnreuther, 2018) among blood relatives (Street, 2009). It also suggests that genetics provides a language of kinship and affinity, creating communities of individuals banking on genetic advancements, risk, and research (Silverman, 2008). "Folk notions of [sic]family as a biogenetic entity allow for an effortless embrace of the scientific and biomedical notion of genetic determinism *precisely because it mimics cultural conceptualizations of the biogenetic foundations of kinship*" (Finkler, 2001; p. 247). By projecting cord blood as a unit capable of treating members

3 The World Marrow Donor Association (WMDA) was set up in 1988, and by 2007, it was established as a worldwide network of blood and marrow transplantation (WBMT). The WBMT is a non-profit scientific organization established to promote stem cell transplantation, donation, and cellular therapy. The WMDA provides a list of guidelines for establishing cord blood banks and registries. Through the stem cell donor registry, the association aims to provide and promote access to stem cells for donors in need across the world (WMDA, 2019).

of a family upon a complete or partial HLA match for a stem cell transplant, cord blood banks rely on the popular cultural notion of "parental responsibility, family ties, and private property" (Brown and Kraft, 2006; p. 325), thereby extending the circle of non-related donors to create a community of parents banking cord blood. In this case, the concept of community cord blood banking depends on the family as a biogenetic entity and draws on the concept of kinship with its basis in family and blood ties. Therefore, the first beneficiary of the cord blood unit is the child whose blood is banked. The cord blood unit then belongs to family members if an exact match is established and, finally, to the community of people who have come together to invest in the processing and storage of the cord blood unit.

Mauss' (1990) concept of the gift relation, that voluntary giving and receiving will promote reciprocity and promote a collective/community understanding, holds true in this context. The concept of voluntary blood donation having qualities of civil inclusion and social justice was first introduced by Titmuss (1997). In an era of neoliberalism and globalization, where the collective (i.e., community) seems bleak (Waldby, 2006), Jeevan is working toward the opposite, i.e., establishing a community of people who donate voluntarily. Instead of "wasting precious cord blood," why not donate (reads the flyer promoting public cord blood banking at Jeevan, March 2017)? Moreover, the updated National Stem Cell Guidelines in India 2017 states:

> Public cord blood banks across the world, for several decades, are playing an important role as a source of HSCs for transplant in selected hematological conditions. Hence, parents should be encouraged for voluntary donation to public cord blood banks for allogeneic use based on HLA matching and for research purposes. Obstetricians must educate parents to be, about the options available, especially donating cord blood to a public bank (National Guidelines for Stem Cell Research (NGSCRT), 2017, p. 37).

Waldby further states that voluntary donations (of cord blood) can be treated as a "compromise position between the social generosity of the gift and the exploitative utilitarianism of tissue markets. It involves neither a generous donation nor an exploitative acquisition, but rather uses the individual's body as its own resource, potentiated by prosthetic or ex-vivo intervention" (Waldby, 2006; p. 59). But are voluntary donations of cord blood easy in a country like India where blood (read cord blood) is seen as a marker of social categories like caste and family as a biogenetic unit?

Understanding biobanking infrastructures: *South Asian* in personalized therapy

A conversation with Mr. Z, area head of sales at LifeCell, presented clarity to the case at hand. Mr. Z has been in the cord blood industry for over a decade. I asked him whether people have problems donating cord blood. My curiosity stems from the fact that blood donation is often associated with the blurring of caste and religious boundaries in India (Copeman, 2009).

> I … you know when parents find out that you cannot use it for your own child… then they won't agree…. You know it's like their own possession. So first they say yes (referring to cord blood donation/public banking) and then *no no humko karne do…* (no no let us do it) referring to private banking this is what we have seen plus the criteria (referring to the checklist for a cord blood unit to be banked) for banking in public banking is high and that's the reason only 50-50 samples are in the public bank. …. India… it is a HLA diverse country… getting a match is so difficult… there are castes, creed, and [also] marriages within the community (referring to consanguineous marriages) […] Here, we have Asian but in community banking… you get an ethnic match…

The need for Asian donors or the claim that the Asian genetic makeup has its roots in the study of populations for biomedical research, as Tupasela points out, draws on historico-cultural narratives of national genetic heterogeneity to brand themselves as ideal targeted populations for medical research (Tupasela and Tarkkala, 2018; p. 741). The branding of genetic uniqueness for population research has been seen in various studies based in Iceland (Rose, 2001; Pálsson, 2007; Fortun, 2008), India (Sunder Rajan, 2006), Israel (Prainsack, 2007), Mexico (Kent et al., 2015), Brazil (Gibbon, 2013), Singapore (Ong, 2016), and Estonia (Fletcher, 2004). This is also linked to the marketability and advertisement content of biobanking practices, thereby addressing questions of inclusion and identity (Tupasela and Tarkkala, 2018; p. 741–743). This embodiment of a need (e.g., being healthy) in the other/the outside gives rise to what he calls the "social imaginary," the individual projection of one's hope, fear, and anticipation (Bennett, 1976; p. 848) in a larger moral domain of biobanking practices and stem cell transplant. Therefore, when a family decides to bank their child's cord blood, be it in private banks, or donated to public banks, the decision is built on the anticipation of disease and fear of ill health combined with the hope of being cured.

The need for Asian donors in registries across the world was brought to the fore when Nalini Ambady, Professor of Psychology at Stanford University lost her life to leukemia in 2013 after a year-long battle. This case was cited by most of my interlocutors at LifeCell as the turning point for investing in Asian- and India-specific donor registries, thereby investing in community banking. Experts had suggested a bone marrow transplant and a perfect 10/10 HLA match for a transplant to save her life as both her children were not a perfect match. A campaign was launched by her daughter to find a perfect match; 12 donors were found, of which six were ruled out as the HLA match was not perfect. Once the 6/6 match was obtained, doctors proceeded to the 10/10 HLA match; six of the 12 potential donors were a match. All but one backed out,

FIGURE 1
An initiative to encourage Indians to donate stem cells with the aim of building a national registry.[4]

and he was from Professor Ambady's home state in Kerala, South India. Unfortunately, the final donor was talked out of the procedure by his parents. The conflation of race (i.e., Asian)[5], ethnicity, and community is further complicated by introducing the very recent "Indian cells" and language-specific registries (both launched by Jeevan 2017, see Figure 1 for one such media initiative). While "Indian cells" has a nationalistic fervor in its establishment (with colors of the national flag in its logo, see

4 Screenshots from "Jeevan Be the Cure Thalassemia" (2017)—A short movie made by Be the Cure registry at Jeevan enabling quick, affordable, and free access to matching stem cells from donated cord blood and bone marrow donors to Indians with blood cancers and thalassemia. Available on YouTube: https://www.youtube.com/watch?app=desktop&v=tw_VcPnBiOE&feature=youtu.be.

5 However, an article by Yang et al. (2006) proved that "Asian" is not a definitive or exclusive category (Robertson, 2012) instead it is mixed, varied (due to migration), and complex. This problematizes the aim of managing a registry based on "Asian" donors.

FIGURE 2
This figure of "Indian cells" has colors from the Indian national flag: saffron, green, and white. It represents Jeevan's campaign to have a "million cells" (stem cells) for Indian patients in need. (Source: https://www.indiancells.in/).

Figure 2), the need is also scientifically valid as the case of Professor Ambady shows.

In an interview with *The Hindu*, a leading national daily, Dr. Srinivasan said, "Our goal is to have 30,000 donated cord blood units and 1,00,000 bone marrow donors registered by 2022. This will enable 70 per cent of Indians with blood cancers to find a match and hope for a cure" (Hamid, 2017). While Dr. Narayan, the co-founder of Jeevan added, "This is truly a Make in India[6] project." Be the Cure registry, run by Jeevan Stem Cell Foundation, is the largest repository of stem cells obtained from donated cord blood in South Asia and a fully functioning adult marrow donor registry.[7] Dr. Srinivasan, in conversation with *The Hindu,* mentioned the grant given by the government of Tamil Nadu.

> Every year, 10,000 children are born with thalassemia and every year over a lakh people are identified with leukemia. If they were to look for an HLA match for treatment, there is no inventory of any great size in India yet. An HLA match is ethnicity dependent. When an Indian is looking for a match, there is a greater likelihood of finding a match within an Indian inventory. In 2013,[8]Tamil Nadu Government was the first government to realize the importance of this programme and has given us funding to the tune of INR nine crores (∼USD 140,000) spread across three years (Hamid, 2017).

The aim as Dr. Srinivasan suggests is to establish the largest registry for Indian stem cell matches in South Asia. Health is a state subject[8] in India, and Tamil Nadu has outperformed all other states in India on specific social development indicators, such as primary education and health. The state government, therefore, supports subsidies and has adopted a social spending approach in matters concerning health (Menabde, 2015). *The Hindustan Times*, another leading daily, reported that a consortium of blood stem cell registries is required in India to make a national donor registry and in turn, maintain uniform standards and cost of treatment (Kaul, 2019). The term "national stem cell registry[9]," as we have seen, is being touted as a consortium of state and language-specific registries, which will combine to make the national stem cell donor registry.

Understanding biobanking infrastructures: *Tamil* in personalized therapy

Dr. Srinivasan: "[…] The first thing (for a stem cell transplant) is the HLA match, [sic]the second is the blood group. Nobody looks at religion, caste, or language. But it does come from the point of view of [sic]registry. India has twelve major languages…from the HLA point of it and the haplo point of it, nine major linguistic groups have their own minor variation. In fact, we have submitted the publication[10]… for Tamil speaking population and the next is Urdu, Hindi, and Malayalam. This is the basis on[sic] the govt of Tamil Nadu's grant to us for the 3,000 samples.… They said we need it for the Tamil speaking population. And we collected [the samples] with the money provided and it will be added to the registry. This is science-based, not the politics of Tamil Nadu or Tamil story […] And if you do that for every state, then you have created a national registry in no time."[11]

6 The *Make in India* initiative was launched by Prime Minister, Narendra Modi, in September 2014 as part of a wider set of nation-building initiatives. Devised to transform India into a global design and manufacturing hub, *Make in India* was both a timely response and opportunistic deflection from a critical situation: by 2013, the much-hyped emerging markets bubble had burst, and India's growth rate had fallen to its lowest level in a decade. The promise of the BRICS Nations (Brazil, Russia, India, China, and South Africa) had faded, and India was tagged as one of the so-called "Fragile Five". Global investors debated whether the world's largest democracy was a risk or an opportunity. India's 1.2 billion citizens questioned whether India was too big to succeed or too big to fail. India was on the brink of severe economic failure (Make in India, 2019).

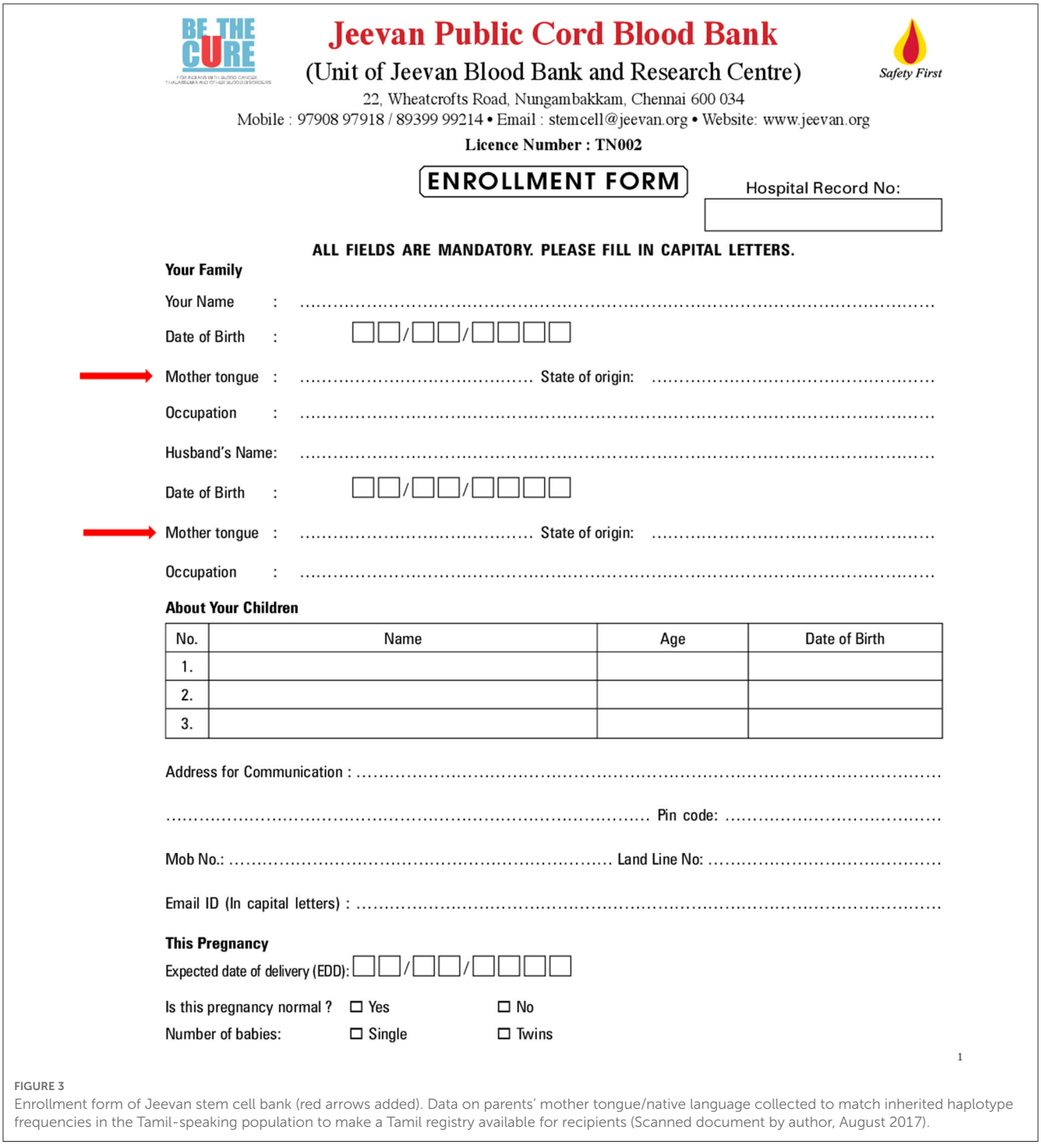
7 About Indian Cells (Indian Cells, 2019).

8 The Constitution of India under the Seventh Schedule prescribes the Union, State, and Concurrent lists for a division of powers between the Central and State governments. The Union list included subjects such as defense and foreign affairs and laws regarding these are passed by the Parliament. Public health and sanitation, hospitals, and dispensaries fall under the State list, and laws regarding these are passed by the respective state legislatures. Powers to both state and the center are provided in the Concurrent List and include subjects such as education, population control, and family planning. The complete list is available at: The Constitution of India, Ministry of External Affairs (2019).

9 Writing on blood and nationalism, Robertson (2012) presents evidence that "pure Japaneseness" is qualified and circumscribed by blood. In other words, blood is seen as an active agent of Japanese nationalism and the Japanese started identifying themselves as one national community based on blood types (p. 107).

10 Referring to Narayan, 2018, human leukocyte antigen (HLA)-A, -B, -C, -DRB1, and -DQB1 haplotype frequencies from 2,491 cord blood units from Tamil-speaking population from Tamil Nadu, India.

11 Maharashtra is located in central India along the Western coast of India and Marathi is the most commonly spoken language. The government of Maharashtra and the Tata Trust launched a campaign in September 2017 called *Jeev Rakshak Sena* (from Hindi as Life Saving Army) with the aim of creating awareness and opening a bone marrow registry at the Government Medical College and Hospital, Nagpur (The Indian Express, 2017). Maharashtra is part of the sickle cell belt, a point that was stressed upon the launch of the campaign. There is, however, no mention of it being a language-based stem cell donor registry (i.e., Marathi based).



Jeevan Public Cord Blood Bank

(Unit of Jeevan Blood Bank and Research Centre)

22, Wheatcrofts Road, Nungambakkam, Chennai 600 034

Mobile : 97908 97918 / 89399 99214 • Email : stemcell@jeevan.org • Website: www.jeevan.org

Licence Number : TN002

ENROLLMENT FORM

Hospital Record No:

ALL FIELDS ARE MANDATORY. PLEASE FILL IN CAPITAL LETTERS.

Your Family

Your Name :

Date of Birth : ☐☐/☐☐/☐☐☐☐

Mother tongue : ..... State of origin: .....

Occupation : .....

Husband's Name: .....

Date of Birth : ☐☐/☐☐/☐☐☐☐

Mother tongue : ..... State of origin: .....

Occupation : .....

About Your Children

No.	Name	Age	Date of Birth
1.			
2.			
3.			

Address for Communication : .....

..... Pin code: .....

Mob No.: ..... Land Line No: .....

Email ID (In capital letters) : .....

This Pregnancy

Expected date of delivery (EDD): ☐☐/☐☐/☐☐☐☐

Is this pregnancy normal ? ☐ Yes ☐ No

Number of babies: ☐ Single ☐ Twins

1

FIGURE 3
Enrollment form of Jeevan stem cell bank (red arrows added). Data on parents' mother tongue/native language collected to match inherited haplotype frequencies in the Tamil-speaking population to make a Tamil registry available for recipients (Scanned document by author, August 2017).

The politics of Tamil Nadu is worth mentioning as it is intrinsically linked to being Tamil and identifying as one. The Dravidian movement recognized the linguistic divide between the Indo-Aryan languages (North Indian, West Indian, and East Indian) and the Dravidian languages (South Indian). Sanskrit was considered a sacred language of the Aryan group, and the Brahmins who belonged to the upper caste had access to this language in practice. The divide was set in a manner that made the Dravidian language inferior, and the divide was made more prominent given the political dominance of the Brahmins under the Madras Presidency. As Venkatraman (2017) notes, anti-Hindi agitations lasted three years until 1940 till the move was repealed and rose again in 1950 when the Constitution of India was being framed. The opposition against Hindi being made the official language of the country by the national government continues even today and was also a matter of concern in the 2014 general elections. This need for

difference, being separate from the "Hindi speaking North India,"[12] has a regional nationalistic fervor to it and has been so for a very long time in Tamil Nadu.

In 2015, When I sat in the office of Jeevan in Chennai listening to Dr. Srinivasan narrate his story, he suddenly stopped and asked, "you tell me, how can I include the diaspora in expanding this bank? [pause] You know I have to create a Tamil repository" (field notes, July 2015). The statement had a flavor of pride in it and is stated rather nonchalantly. Tamil is a language, an identity, and a political tool used to build an ethnic community separate from the rest of India. Tamils have lived in the Southern portion of peninsular India for over 3,000 years, and today, most of them live in Tamil Nadu. Tamil belongs to the Dravidian family of languages along with Telugu, Kannada, and Malayalam. It is significant to note that "Tamils alone have remained culturally and linguistically least influenced by the Sanskritic civilization of North India" (Pandian, 1998; p. 546).

The mother tongue or one's native language is therefore used as a marker against the donors' sample, making a language-specific registry possible (see Figure 3). A 2018 study with data obtained from donated cord blood units at Jeevan identifies certain inherited haplotypes (set of genetic determinants inherited from both parents)[13] frequencies in the Tamil-speaking population (Narayan, 2018). A recent study proposes a link between South Indian language groups (Malayalam, Urdu, Kannada, Telugu, and Tamil) and finding donors for patients based in Sri Lanka (Seshasubramanian et al., 2021). Hegde mathematically posits the link between HLA and language and proves the relationship using Nei's genetic distance formula. Laboratory work for this thesis was carried out at *Jeenomics*, the HLA laboratory at Jeevan. The aim of Hegde's work was to build a first-of-a-kind (in India) population-based genetic model for four native language groups: Tamil, Telugu, Hindi, and Urdu. HLA data for this were obtained from the UCB registry at Jeevan.

A study by Chen et al. (1995; p. 607) placed geographic distance as a major confounding factor in the correlation between genetics and linguistics. Their study is based on the fact that languages change over geographic space, possess numerous characteristics, and have a phylogenetic (the evolution of a genetically related group of organisms as distinguished from the development of the individual organism[14]) history. Another study by Cavalli-Sforza et al. (1992; p. 5621) found that populations speaking languages from the same family tend to be genetically related. For example, the Indian population is grouped under the Indo-European language group, and the Southeast Indian population is grouped under the Dravidian language group. Nei explains genetic distance as a "statistical method for estimating the number of codon differences per gene and the divergence time between closely related species. This method utilizes electrophoretic data on protein identity between different species (Nei, 1972; p. 283). Thus, the average number of codon or nucleotide differences per gene is a measure of genetic distance [. . .] when two species to be compared are distantly related, data on amino acid or nucleotide sequences are used" (Nei and Kumar, 2000; p. 828). Hegde calculated pairwise Nei's genetic distance on each of the four native language subgroups (Tamil, Telugu, Urdu, and Hindi) and arrived at the following:

TABLE 1 The proximity of languages in South India based on genetic distance (Source: Hegde, 2018).

Native language	Tamil	Telugu	Urdu	Hindi
Tamil	0.0000	0.0361	0.0522	0.1700
Telugu	0.0361	0.0000	0.0563	0.1582
Urdu	0.0522	0.0563	0.0000	0.1494
Hindi	0.1700	0.1582	0.1494	0.0000

The results state "lesser the Nei's genetic distance value, [sic]greater is the population related to each other." Table 1 clearly shows that the population with Tamil as their native language is most related to the population with Telugu as their native language, and vice versa. The population with Urdu as their native language is most related to the population with Hindi and Tamil as their native language (Hegde, 2018).

The point Dr. Srinivasan and Hegde make is that finding HLA matches within a certain language subgroup is higher and India needs to build a registry for each of these language subgroups. Lupton (1994) would have drawn our attention toward the "geneticization" of race or what Callon et al. (2005) have termed an "economy of qualities" where banks are deemed as repositories of a certain community of people. Only that in India and Chennai, we are not dealing with race but with ethnic groups deemed as language-specific communities. Today, much of the public cord blood sector is aimed at collecting cord blood of rare immunological types—particularly ethnic minorities for whom it is difficult to find a conventional donor (Brown and Kraft, 2006). Rabinow and Rose (2006) have introduced concepts, such as biosociality, where individuals and communities manage life by considering genetic risk and prevention. Ong (2016) provides an atlas of genetic mapping of cancers and their intervention in her study of Asian populations in Singapore. She explains that diagnosing cancers today focuses on genetic and protein markers in certain populations that are termed biomarkers. These biomarkers are acquired both epigenetically and genetically—the latter is where characteristics are acquired somatically, and the former is a result of living in a certain cultural lifeworld.

As Dr. Srinivasan said, "chances of finding my haplotype is[sic] higher among Indian donors and the success rate is likely to be higher from my own lineage: Tamil population." Lineage is descent traced from either of the parents—either matrilineal (from mother) or patrilineal (from father). As Ong suggests, finding a genotypically similar match is closely linked to the "ethnicity heuristic" and is a more "sophisticated way of marketing science" (Ong, 2016; p. 30–31). In the case of cord blood banks and

12 The attempt to consecrate Hindi as the national language was stirred again when a draft of the National Education Policy 2019 by the Modi-led government proposed teaching Hindi and English mandatorily alongside the respective regional language in non-Hindi-speaking states. This draft was later revised to make learning Hindi non-mandatory (Dutta, 2018 & Firstpost, 2018).

13 Haplotype (National Human Genome Research Institute, 2019).

14 Phylogeny (n.d.). *Online Merriam-Webster Dictionary*. Retrieved from: https://www.merriam-webster.com/dictionary/phylogeny.

unrelated donors in Chennai, the biomarker is being termed as the language, Tamil. By analyzing the HLA frequencies of parents (who donate their child's cord blood and mark Tamil as their mother tongue), the final aim, as Dr. Srinivasan suggests, is establishing the national stem cell donor registry. By locating Tamil as a biomarker, Jeevan stem cell bank establishes the first step to finding a match, and this, as most of my interlocutors suggest, is based on finding positive matches within the same ethnic community.

Conclusion

Banking on the cord blood community, therefore, becomes a "life strategy" where genetic endowment (Novas and Rose, 2010; p. 488) is considered as both the diagnostic and the cure.

> "[And] by deploying ethnicity as a code for identifying specific genetic risks and mutations, [...] the goal is to customize the right cocktail of drugs for a particular patient so that the disease can be managed as a chronic condition. Nevertheless, *by zeroing in on ethnic, family, and individual genetic targets, the new research milieu is also productive of affects of fear, hope, and pride in a novel form of scientific self-knowledge, one that frames "personalized medicine" as situated within a diagnosis and affective formation of collective bodies"* (Ong, 2016; p. 77, emphasis mine).

Given that HLA is being touted as an identity antigen representative of a certain "community" of people, one can say that the social lives and biological materials (Nading, 2017) are conflated in finding an exact match. The risk to health will always remain uncertain (Bharadwaj, 2002), therefore allowing the possibility to capitalize and make a "cultivated cure" (Bharadwaj, 2017) imaginable. Cord blood and genetics are closely linked and redefine personalized therapy for a "community" and the individual. The chance occurrence of falling ill and hoping for a cure in the future in modern healthcare practice gives people the choice of storing their child's cord blood privately, in a community bank or donating it voluntarily.

Biobanking infrastructures can be seen as repositories of information, data, and insurance against stored biosamples. The cord blood unit is processed (personal to the collective in practice) and stored in biobanks for the treatment of blood disorders such as thalassemia. In India, these biobanks holding cord blood are being used to determine stem cell matches where personalized stem cell therapies are sought within social categories. HLA-based stem cell matches in practice include varied definitions of community; in some cases, matches are sought within the family or the extended family, in other cases, caste or race. To complicate the definition of community, matches are sought within the South Asian diaspora or the Tamil-speaking population (collective to the personal in practice), thereby "personalizing" stem cell therapies in Chennai.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by the Graduate Institute of International and Development Studies, Geneva. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

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

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The illusion of immediacy: on the need for human synchronization in data-intensive medicine

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Medical practice is increasingly shaped by big data sets and less by patient narratives. Data-intensive medicine promises to directly connect the patients with the clinic. Instead of medical examinations taking place at bedside and discrete moments, sensor-based technologies continuously monitor a certain body parameter and automatically transfer the data via a telemedical system. Based on a qualitative study of remote cardiac monitoring, I explore how the uncoupling of processes that used to happen in one place, changes the way diagnosis is made. Using ethnographic observations and semi-structured interviews with patients and tele-nurses of two university hospitals in Switzerland, I describe remote cardiac monitoring as a data network. The perception of being constantly connected to the hospital resulted in a reassuring effect among patients and healthcare professionals. Moreover, the notion of an automatically synchronized data network led patients to expect immediate feedback from the hospital as soon as an irregularity was detected. However, it obscured the fact that although the inserted sensor monitors the heart around the clock, the data is transmitted only once a day, and the tele-nurses only work during office hours, from Monday to Friday. I call this misperception "illusion of immediacy". It takes time to accurately correlate and interpret a recorded episode with other types of data, such as the last hospital visit, comorbidities, and/or the actual situation in which the recording was made. Accordingly, tele-nurses and cardiologists play a central and privileged role in the data network. The findings highlight the importance of synchronizing the different temporalities that coexist in the patient remote monitoring data network in order to generate meaningful knowledge that ultimately leads to a diagnosis.

KEYWORDS

personalized medicine, data-intensive medicine, patient remote monitoring, telecare, temporalities, synchronization, immediacy, Switzerland

Introduction

The heart beats about 60–100 times per minute in a healthy human. Blood rich in oxygen and nutrients circulates through the body with every heartbeat. The heart rhythm, or its palpable effect, the pulse, are easy to detect vital signs. However, the human body does not always work like a clock, and the heartbeat can get out of sync. Strong feelings or physical exercise might be the cause for short-term changes in the heart rhythm. Such experiences are captured by idioms like "losing one's heart to someone" or the heart "racing a mile a minute". Most heart arrhythmias do not represent an immediate danger to life. Nevertheless, experiencing a heart out of sync or the associated symptoms, for example fainting, can be scary, especially if there is no obvious cause. Quite like earthquakes, heart arrhythmias can occur at indefinite intervals of varying duration, and sometimes even without noticeable

symptoms (Jones, 2013). As a result, they are almost impossible to detect during regular office or hospital visits. This is where my story begins (Moers, 2008).

To detect such an elusive but potentially life-threatening condition, the heart must be monitored continuously. In countries like Switzerland, where telecare is covered by basic health insurance, cardiologists may recommend the insertion of a small, remotely connected device called a cardiac monitor. Instead of data snapshots of a given patient, at a given time and place, inherent in traditional calendar-based follow-up, long-term remote cardiac monitoring creates a continuous flow of data. Using several algorithms to analyze the electrical signals detected by the two sensors of the cardiac monitor, the continuous monitoring reports any event that deviates from the programmed thresholds. Thus, measurements that are within the norm will no longer appear in the patients' medical records, because the algorithms will only report what is outside the norm. This is a major difference from calendar-based measurements, which are based on a specific point in time (e.g., every 3 months) determined by evidence-based medical standards or the cardiologists' experience. Therefore, continuous monitoring delivers unprecedented big data sets for long-term intrapersonal data comparison (Sysling, 2020), thereby inducing a shift in how, when and where patient data are collected, analyzed and interpreted.

This kind of data-intensive medical practice has profound implications for how, when, and where a diagnosis is made. In a traditional medical appointment, the patient and his or her narrative, the cardiologist and his or her expertise, the device, and likely the recordings, are all in one place. This configuration allows the patient and cardiologist to immediately comment and discuss possible findings or agree on the next steps (e.g., call the patient as soon as the test results are available). In a remote monitoring system, the device follows the patient wherever he or she goes, the cardiologist works his or her usual shifts at the hospital, and the recordings are simultaneously with the patient, in the data cloud, and at the hospital. The processes of data collection, analysis, and interpretation that used to be part of the traditional doctor-patient appointment, become uncoupled.

Previous studies mostly focused on the obvious spatial uncoupling of healthcare induced by surveillance medicine (Armstrong, 1995) or telecare (Oudshoorn, 2011; Pols, 2012). However, in addition to the important questions related to the spatial distribution of the different actors, who were previously reunited in a medical site according to a calendar-based schedule, the remote monitoring of patients raises another problem that has not yet received much scientific attention: the temporal uncoupling.

Data-intensive technologies are often promoted with the promise to deliver timely diagnosis through continuous data monitoring thereby anticipating bad outcomes. From the cardiac monitor to biobanks or wearables—not only medical practice, but health in general is increasingly shaped by big data sets (Ruckenstein and Schull, 2017). These sets are getting bigger on the one hand because measurement tools are multiplying, starting in the mid-nineteenth century with acoustic, visual, chemical, and eventually sensor-based technologies aimed at ever more detailed and comprehensive measurements. On the other hand, they are getting bigger because measurement intervals are getting shorter or even disappearing altogether, as is the case with patient remote monitoring. The implicit promise is that the larger and more comprehensive the data sets, the better and more personalized the healthcare (Rosenberg, 2002). With the proliferation of such data-intensive biomedical technologies, the concepts of "personalized," "stratified," and "precision" medicine have emerged in the scientific and policy landscape over the past 20 years (Mackintosh and Armstrong, 2020; Cesario et al., 2021). The most commonly used term, "personalized medicine", adopts the above vision and promises to use large integrated datasets to deliver the right treatment to the right patient at the right time (Petersen, 2018; Erikainen and Chan, 2019). However, contrary to what the term suggests, the main feature of "personalized medicine" is not the person, but the big data sets (Prainsack, 2017; Hoeyer, 2019). Today, the vision of "personalized medicine" is based on a *technoscientific holism* consisting of an integrative aggregate of all quantifiable units of human life (Vogt et al., 2016). However, in order to construct and connect all these different types of data, they must be easily transferable from one context to another. Just as mathematics has become the universal language in public and scientific discourse, datafication is the answer to a medical practice that increasingly resembles a data network (Porter, 1995). Such a network-like character is made possible by prioritizing digital, quantified, and computable evidence while downgrading unstructured data, narratives, and embodied experience (Prainsack, 2017; Hoeyer, 2019). Contrary to unstructured information, quantified evidence is easier to collect, process, and share remotely. Therefore, Theodore (1995) called quantification a technology of distance fostering global networks rather than local communities. Thinking of medical practice as a data network is not only about the fact that data travels easily. It's also about data being not just in one physical place, but in multiple places at once. Even if remote cardiac monitoring data are stored by the biomedical companies in the Netherlands, France, or Germany, it can be accessed from other places if access rights are granted (Maillard et al., 2014). In this way, digital data and the knowledge it contains are no longer tied to one place, but are a property of the network (Weinberger, 2011).

Already by the mid-twentieth century, biophysicist Norman "Jeff" Holter dreamt of a system continuously collecting, transmitting, and analyzing all types of physiological data to detect potentially hidden diseases in the seemingly normal measurement variations (Greene, 2022). Enthusiastic about emerging transmission technologies, he developed the first portable cardiac monitor in 1949 that could record an electrocardiogram "on the go" (Kalahasty et al., 2013). Initially worn as a bulky backpack, the device soon became smaller, and his dreams of continuous monitoring became more realistic. Today's "Holter" monitors consist of three leads attached to the skin of the chest and a recording box, usually attached to a necklace or belt, that monitors for 24 h, 48 h, or 7–14 days. Patients wear such a device for the desired period, then return the recorder box to the hospital, where the data are analyzed, and the results are reported to the patients. Other conventional tests include x-rays, echocardiography, or an electrophysiology study (Deftereos et al., 2016; Schweizerische Herzstiftung, 2022). If these examinations or short-term cardiac monitoring do not yield results, long-term

remote cardiac monitoring offers a possibility of detecting the suspected arrhythmia.

Current cardiac monitors are barely the size of a triple-A battery, weigh about 4 grams, and are made of titanium, sapphire, parylene, silicone, or iridium components that protect the electronics and make them compatible with human tissue. In Switzerland, the insertion (and later removal) of the cardiac monitor and remote monitoring are covered by basic health insurance. Once inserted, it is not possible for patients to interrupt or stop the continuous monitoring. Usually, the cardiac monitor is connected to a telemedical system automatically transmitting the recorded data once a day. The battery life of the cardiac monitor lasts between 3 and 5 years. The cardiac monitor typically gets removed once a diagnosis is established or when the battery life ends.

The number of patients having cardiac monitor in Switzerland is not tracked separately to other cardiac implants. Most devices under telemedical monitoring serve therapeutic purposes, which is for example the case for defibrillators. Based on the interviews done for this study, the two studied hospitals monitor about 1,000 patients for diagnostic reasons.

Remote cardiac monitoring differs from conventional methods in that the measurements are no longer bound to a specific space and timeframe. Hence, examining the temporal uncoupling of data collection, analysis, and interpretation is at the core of this article. Different time frames and data types must be in sync to render them meaningful for cardiologists and patients. A condition which is no longer given when these processes do not happen in the same place as it was the case for traditional follow-ups. Hence, the aim of this article is to illustrate how patient remote monitoring is reconfiguring the way diagnosis is made, based on a qualitative study of remote cardiac monitoring conducted in Switzerland. To highlight the challenges of synchronizing what has become uncoupled by remote monitoring, the analysis will frame remote cardiac monitoring as a data network. Although the imaginary of a data network conveys the idea of constant synchronicity, I will show that data transmission, processing, and medical interpretation introduce time lags that lead to misunderstandings between patients and healthcare professionals.

Materials and methods

The qualitative study was conducted at two university hospitals in different linguistic regions of Switzerland from October 2020 to July 2022. Ethnographic observations were conducted in the telemedical unit and during the ambulatory insertion procedures. The latter served also to recruit patients for interviews. Semi-structured interviews were conducted with patients (women = 12, men = 16), nurses specialized in remote cardiac monitoring (n = 7), cardiologists (n = 9), and industry representatives (n = 4). The median age of the patients was 62 years, with the youngest being 21 years and the oldest being 85 years. Their socioeconomic backgrounds varied from truck driver to secretary to director of a retirement home. Of the 28 patients interviewed, 15 were included in a longitudinal follow-up consisting of two interviews. The first interview took place 3–8 weeks after device insertion. A second interview was conducted 6–8 months after insertion. Patients were asked to provide an additional update on their experience by letter in the summer of 2022. Three patients dropped out after the first interview. The other 10 patients participated in a retrospective interview after the cardiac monitor was removed, either when a diagnosis was made or when the battery was exhausted. Partners of the patients were present in three interview situations. The researcher was unable to recruit a patient who had refused to have a cardiac monitor implanted. This article focuses on the data collected during the ethnographic observations and interviews with patients and nurses.

Data collection was affected by the COVID-19 pandemic, which significantly prolonged fieldwork. Correspondingly, the opportunities for ethnographic observations were limited by the regulated access to hospitals for non-medical staff. Although originally planned as face-to-face conversations, all of the first wave interviews were conducted remotely (by telephone or videoconference), with the exception of one person who insisted on being interviewed at her home. Once vaccination was available to all adults in Switzerland, it was up to the participants to decide whether they preferred a face-to-face interview or a remote form of communication. Most opted for a face-to-face interview.

Interviews were transcribed verbatim. Ethnographic notes were taken by hand and then transcribed on the computer. Data were coded using Atlas.ti software and applying reflexive thematic analysis (Braun and Clarke, 2021). Some codes were derived from the interview guide. Others were created while listening to the first wave of patient interviews. Several codes indicating the various forms of absence within the data network of remote cardiac monitoring (e.g., feedback, data access, cardiologists) were combined under the theme "illusion of immediacy" as perceived by patients. This theme was the starting point for this article.

The study was reviewed and approved by the "Commission cantonale d'éthique de la recherche sur l'être humain" (Cantonal commission on ethics in human research of the canton Vaud) in September 2020. Patients and healthcare professionals provided their written informed consent to participate in this study.

Results

The following subsection headings are deliberately chosen to resemble a manual that could belong to any other digital device connected to a data network, such as a smartwatch. The cardiac monitor represents the sensor that is integrated into a data network, connecting it to the company's servers and to healthcare providers. By describing remote cardiac monitoring as a data network, I will illustrate the modus operandi of the data network, focusing on how different temporalities and data types external to the monitoring system must be synchronized to make the remotely collected data useful for diagnosis. Furthermore, I will show how the imaginary of remote cardiac monitoring as an automatically synchronized data network does not match with everyday data practices. The difference between the patients' perception of continuous care and the uncoupling of data collection, processing, and interpretation creates an illusion. Instead of the traditional medical appointment reuniting the patients' narratives, the cardiologists' expertise, and measured evidence, remote cardiac monitoring will disrupt the usual feedback loop between patients and doctors. Drawing on the

analytical framework of temporalities, I conceptualize this as the illusion of immediacy.

General instructions

Cardiologists in Switzerland may recommend remote cardiac monitoring to patients who are experiencing symptoms they suspect are related to a heartbeat that is too slow, too fast or irregular. Another important group are patients who have suffered a stroke of unknown cause. When conventional examinations fail to detect the suspected arrhythmia, long-term remote cardiac monitoring is the last possibility to eventually detect it. A cardiologist told me that it serves to identify a potentially "hazardous seed", while the market-leading biomedical company promotes remote cardiac monitoring as the possibility to "unlock the answer". Although it is possible to have a cardiac monitor inserted without being connected to remote monitoring, cardiologists and companies strongly encourage adherence. Algorithms become more accurate as they are trained on large amounts of data, so medical and commercial stakeholders are interested in accumulating data and, therefore, in patients who adhere to remote monitoring. Patients sign a general consent for data sharing. Doubts about privacy are very rare among them, and when they do, they express them in the form of jokes, for example by comparing it to a cat microchip. Overall, the hope of finally finding out what was wrong with them outweighed privacy concerns. Specifically, the telemedical follow-up is promoted by healthcare professionals to patients by pointing out the possibility of immediate feedback compared to a manual download at the hospital during a calendar-based follow-up that would take place every 3 or 6 months. Nurses and cardiologists explained to patients that the remote monitoring system would regularly transmit any relevant episode of irregular heartbeat. As a result, potential treatment could be implemented in a timely manner. Another argument made by nurses and cardiologists is the time saved by patients not having to come to the cardiology department every 3 or 6 months.

Assemblage

The insertion of the cardiac monitor requires a minor surgical procedure and is usually performed at the bedside by cardiologists or specially trained nurses. Compared to other heart surgeries, it is a minimally invasive procedure because the device is placed just under the skin without a direct connection to the heart. The procedure itself takes only a few minutes, but preparation can take up to an hour. Because of the cardiologists' busy and unpredictable schedule, patients may have to wait a few hours before he or she is available to perform the insertion. Specially trained nurses who can perform the insertion can reduce the patients' waiting time. Before the insertion, the spot on the chest is sensed by touch, shaved, if necessary, marked with a drawn arrow, and disinfected. The patients are then covered with a sterile fenestrated drape. Patients receive local anesthesia. Nurses and cardiologists typically describe the anesthetic injection as similar to a dentist's to prepare the patients for the burning pain that local anesthesia initially causes. The local anesthetic takes longer to take effect than the actual insertion of the cardiac monitor. First, the nurses or cardiologists use a cutting tool to make a small incision of about 1 cm. The applicator is then carefully inserted under the skin to serve as a placeholder for the cardiac monitor, which is then placed under the skin by manipulating the applicator. Finally, the applicator is removed, and the wound is sutured or glued. Most patients are surprised at how little time it takes to insert the monitor.

Setup

After insertion, the patients and the cardiac monitor are connected to the remote monitoring system. It was this moment that stuck with me from the beginning of the ethnographic observations, and which also gave me the idea for this article. The nurses or cardiologists placed a company-specific "device reader" on the dressed wound of the freshly inserted cardiac monitor. They then used a company-specific computer or tablet to connect the implant, the patients' personal information, and the remote monitoring system. They would usually comment on this action by saying that they were now "programming" it. Inevitably, the image of a cyborg came to mind. But instead of just looking at the patients, I decided to look at the system as a whole. From that perspective, this scene represented the moment when the patients and the cardiac monitor were connected to a data network. It was simply like adding another data-collecting sensor to a pre-existing data network, centralized by corporate servers and accessible by healthcare providers. This image reminded me of other data networks in our everyday lives, where devices are constantly being added to or removed from other devices or data networks, such as connecting a speaker to a friend's smartphone.

Patients then receive final instructions before leaving the hospital. They receive the transmitter, which is responsible for automatic data transfer. Again, the cardiac monitor must be manually connected to the transmitter. The nurses or cardiologists guide this process step-by-step. Once the devices are successfully connected, they explain remote monitoring in detail. They focus on the easy handling, the automatic data transfer and that the transmitter must be plugged in near the bed, ideally at the bedside table. Often nurses or cardiologists give them the simple advice: "Just plug it in and forget about it" (fieldnotes, both hospitals). This is intended to reassure patients, especially if they do not feel comfortable using a technological device correctly. The patients are then discharged with the cardiac monitor placed under the skin and the transmitter packed in a cardboard box. In general, and if the patients have no follow-up due to other comorbidities, remote reading works on the principle of "no news is good news. Nurses and cardiologists told patients that they would be contacted as soon as something was found (field notes, both hospitals). This means that patients will only hear from the hospital if the cardiac monitor detects an arrhythmia that the tele-nurses or cardiologists deems clinically relevant. One of the two hospitals I visited has adopted the practice of calling the patients the day after the insertion to inform them that everything is working as is it should.

Operation mode

Before I present the perspectives of the nurses who handle the data and the patients, I will illustrate the automated processes of data collection and transmission by tracing the path from the moment the heart beats irregularly to the moment this irregular beat is taken into consideration at the hospital.

Let's imagine a patient, named Sandra. She had received a cardiac monitor 10 months ago following a stroke of unknown cause. The cardiologists suspect atrial fibrillation as the cause. After the stroke, she continued to work with a reduced workload. Today, she had lunch with her co-workers as usual. Now she is sitting comfortably at a table, having coffee with them before going back to work. The room is filled with laughter. She feels a little tired. Unnoticed by her, the upper and lower chambers of her heart are beating out of sync for a few minutes. But the algorithms in the cardiac monitor detect the irregular electrical signals by comparing them to the millions of heart rhythm sequences with which they have been trained. As a result, this sequence of atrial fibrillation is recorded and stored in the cardiac monitor. Sandra finishes her workday, goes home, and does not stay up too late because she still feels a little tired, not thinking of any potential harm. After midnight, the transmitter next to her bed automatically connects via radio frequency or Bluetooth to her inserted cardiac monitor. The recording is then transmitted to a company-provided online server via a landline telephone or wireless cellular network. The next day, tele-nurses log into a software program provided by the company and reviews the recordings. Recordings from cardiac monitors are considered the least important compared to other connected devices such as defibrillators or resynchronization therapy devices. Consequently, and depending on the total daily number of alerts sent, the recordings coming from cardiac monitors will be checked only in the afternoon. If considered relevant by the tele-nurses, the recording is forwarded and/or discussed with the attending cardiologist, who makes the final decision on whether or not to act on it.

Data processing

Every time the algorithms detect an irregular heartbeat, or a series of signals interpreted as such, an alert is sent via the transmitter to the remote monitoring system. Yet, data do not speak for themselves. It is only in the specific context of a patient that it may or may not make sense. It is the task of specialized tele-nurses to correlate the recorded data with the patient's case. The telemedical follow-up takes place during office hours, Monday through Friday. In the morning, a tele-nurse enters the office and starts her computer. With her personal login she has access to the telemedical platforms provided by the different biomedical companies. The platforms are similar to an email inbox, displaying the latest alerts from the cardiac monitors and other cardiac devices. Some of them can be color-coded, like a traffic light, to indicate the level of importance. The thresholds for the different types of arrhythmias, which are set by default by the companies, can be reprogrammed by the healthcare professionals. The number of data recordings to be processed varies from day to day. Currently, they have to check about a hundred alerts daily including therapeutic and diagnostic devices (usually a bit more on Mondays as data accumulates over the weekend). Moreover, the high sensitivity of the cardiac monitor generates a significant number of false-positive alerts (Afzal et al., 2020). This is not the only time-consuming part of the data review process.

At first glance, the tele-nurses use detailed knowledge of the patients' health status and often also of the patients' everyday life and hobbies to contextualize a recorded heart rhythm episode. In this case, knowledge means recognizing the name and/or type of arrhythmia transmitted by a connected cardiac device. Over time, they acquire a detailed knowledge of the connected patients and the frequency with which their cardiac device sends an alert. As a result, they will learn which patients are prone to false-positive alerts and adjust the processing of these data accordingly.

One ethnographic observation provides an illustrative example. Once, when I was sitting in the telemedical unit, a tele-nurse showed me an episode of palpitations. The episode indicated 180 beats per minute. Recognizing this patient by its name, the tele-nurse told me that in this specific case, the arrhythmia episode was nothing serious. I asked her how she could be sure about that. She drew my attention to the time the episode was recorded and said:

> "Look, here he was cycling again. At this time of day, he always uses his stationary bicycle. We know that. It's normal if you are doing sports" (tele-nurse, 53 years old).

Nevertheless, the algorithm of the cardiac monitor systematically marked this episode as potentially relevant, because of the fast heartbeat. The tele-nurse told me that this is typically an alert to be discarded. She went on in her explanation, telling me that this is the main challenge of her everyday work: distinguishing between relevant and irrelevant episodes, contextualizing them with the patients' background knowledge, and not missing any important indication.

If the tele-nurses are unsure about a recording, they will still click on it to see the recorded heart rhythm in detail. They will look closely at the graph representing the heartbeat to see if the algorithm has missed or overidentified a particular moment in the heart contraction. Sometimes, they will use a calculator to manually calculate the heartbeats per minute. If they need further clarification, they can ask their colleagues or the cardiologists in charge to examine the recorded episode more closely. The responsibility for correctly interpreting the recorded data makes their job exciting, but it also positions them as a critical node in the remote monitoring data network. One tele-nurse explained this ambivalence in the interview as follows:

> "It's really never boring. Every day there is the suspense: What will I find today? Amongst us we say: What will I catch today? (...) But if you don't see it, it will be lost" (tele-nurse, 55 years old).

Even though patients are made aware that remote cardiac monitoring is for monitoring only, not for emergency intervention, tele-nurses play a central role in establishing a diagnosis. If they miss a decisive alert, there will be a delay in diagnosing a potentially life-threatening condition. Accordingly, one nurse referred to the

task of reassembling, linking, and interpreting different types of data to understand the transmitted episode as "detective work." The fine knowledge of how to examine recorded episodes or learning which cardiac monitors regularly recorded false positives was acquired over time. Consequently, they would directly discard an alert according to a name and/or a type of arrhythmia without further investigation if they recognized it as a repeated artifact.

Sometimes the tele-nurses would call a patient to verify the situation in which the episode was recorded. They would first ask if the patients were feeling well or if they had noticed anything unusual the day before the episode was recorded. Together with the patients and the time the episode was recorded, they reconstruct what they were doing at that moment the day before. Thereby, the automatically recorded data was connected to the patients' sensations and/or actions. This additional information helped the tele-nurses to either discard the alert or make a note for further discussion with the cardiologists.

However, the tele-nurses did not contact the patients unless it was necessary or asked for by the cardiologists. The sovereignty of data interpretation, knowledge production, and the decision to communicate it to the patients remained clearly in the hands of the tele-nurses and the cardiologists. They justify this approach by saying that they want to prevent patients from becoming anxious. In one hospital, a one-page written report is sent to patients every 3 months. However, the healthcare professionals refrain from communicating every arrhythmia recorded, as this tele-nurse explained:

> "For example, we have many ventricular tachycardias, but they are self-limiting. Or we see many, frequent ventricular extrasystoles. We don't write the supraventricular stuff in the report. So, if it's not atrial fibrillation, it worries patients when you write that they had supraventricular tachycardia" (tele-nurse, 55 years old).

She told me, that she had once mentioned the recording of a "supraventricular tachycardia" in a report. The patient had immediately called the telemedical unit immediately after receiving the report and asked for clarification. It took a lot of time to explain to the patient that this episode was part of the non-dangerous arrhythmias. Hence, they keep these events confidential and communicate only if they judge it appropriate from a clinical point of view. However, not all tele-nurses do fully agree with this practice, but they have to follow the rules set by the cardiologists. This illustrates that the main source of frustration was not the data produced as such (Pols, 2012), but the different views on how to deal with them.

User satisfaction

Overall, patients and healthcare professionals perceived the inserted cardiac monitor as reassuring. The fact that the patients' heart rhythm was continuously monitored, regularly transmitted, and reviewed by healthcare professionals by healthcare professionals was reassuring to all users. For all involved actors remote cardiac monitoring is a way of taking seriously the unexplained symptoms and the uncertainty associated with their possible recurrence (Nettleton et al., 2004).

This effect was particularly strong for potential arrhythmias that patients are unlikely to notice, such as atrial fibrillation, which is a risk for recurrent stroke. Patients and healthcare professionals alike were convinced that these irregularities would be detected by the cardiac monitor and could subsequently be taken into adequate consideration. I call this phenomenon the "reassuring effect" of remote monitoring. On the one hand, this effect resulted from the perception of constantly being cared for by a healthcare professional. On the other hand, it was related to a reduction in the feeling of uncertainty about unexplained symptoms. Although the cardiac monitor could not intervene to prevent another symptomatic episode of major (e.g., stroke) or minor (e.g., fainting) impact on their lives, patients appreciated the feeling of being in control, while cardiologists appreciated the feeling of having at least some control over the situation. One cardiologist described remote cardiac monitoring as a kind of digital ties reassuring her in a situation of diagnostic uncertainty:

> "It is reassuring for the doctor to say, 'I've set up everything I could. I keep these ties.' Personally, I consider them as ties, like protections for the patients. To reassure the patients but also to reassure yourself, so that we do not lose the patients in the "wilderness." So, the patients are still being monitored. It is a kind of double psychological effect, but especially for the doctor" (cardiologist, 43 years old).

Her description of digital ties fits well with the imaginary of a data network. However, tele-nurses and cardiologists had a privileged access to the data compared to the patients who could not see whether their cardiac monitor had detected and transmitted an heart rhythm recording or not. Consequently, they depended on the feedback from the healthcare professionals to know about potential data transmissions. Nevertheless, a reassuring effect was established just by the imaginary of being permanently connected to the hospital. Adding up to the previous findings of Pols (2012), the reassuring effect persisted even if there was not much contact between patients and tele-nurses or cardiologists. A patient who has had a cardiac monitor for two and a half years after having two unexplained ischemic attacks said about the implant:

> "I would like to say that I have been really happy about this thing. This gave me some kind of certainty for at least two and a half years. That was actually true. Being monitored made me feel safe. There is someone in the hospital who is looking after me. Even if there wasn't much direct contact" (woman, 66 years old).

For patients like this woman, the digital connection was enough to provide a sense of reassurance. Interestingly, this effect was sometimes even more present among patients' family members who were worried about their loved ones, as this example shows:

> "My sons and my husband said: Be happy, if there is something, they will immediately sound the alarm. Even if you would not notice it" (woman, 82 years old).

The reassuring effect of being cared for was particularly strong in the first few months after insertion. However, the persistence of this reassurance depended on the system working as promised. Patients expected to receive a call from the hospital within a short time if their cardiac monitor recorded an event, as they were told by nurses and cardiologists during the instruction after the insertion. Several patients expressed disappointment when a recorded episode was not handled as expected. In the following quote, a patient told me how he complained when he was not informed immediately, and how the second time it went as expected:

> "The first episode was recorded on October 11, but I did not receive the [written] report until October 21, when I was asked to see my cardiologist. I had already called my cardiologist to report the incident. Then she apologized. The next time, my cardiologist called me directly about an episode that had happened the day before. That was the confirmation for me, 'Okay, it can work right away if needed.' The first episode probably got stuck somehow. (...) It was probably a unique situation. I work in healthcare myself and I know how it works with accounts and reports. It falls on the staff, who then have to deal with all of that" (man, 65 years old).

His experience illustrates the expectations patients have toward remote cardiac monitoring. Moreover, it shows that a bad experience can be compensated by a later one which meets this patient's expectations. Contrary to what he believed, receiving "delayed" feedback or no feedback at all was not his unique experience. It was a recurrent topic among the interviewed patients.

However, to be disappointed or reassured by remote cardiac monitoring, patients needed to know that an event had been transmitted. Typically, heart rhythms are monitored using trained and self-learning algorithms that automatically record abnormal heart rhythms. The bedside transmitter shows only an "ok" sign and the date of the last successful transmission, which usually happens automatically once a day. Because no other information is provided, some patients were concerned in the first weeks or months after insertion whether the telemonitoring system was really working. Some of them regularly checked the screen to see if the data transmission had occurred. If the displayed date had not been updated, they performed a manual data transmission using the "device reader", as shown in the example of this patient:

> "I think recently I had to do it manually three times in a row. It did not do it at night. I don't know why. I don't sleep so well anymore. Or haven't slept so well now with the last chemotherapy. When I wake up at night, I press the button to check it briefly, and then it connects. Then it does [the transmission]. The last three times, I had to hold [the reader] onto [the insertion spot]. [The transmission] is kind of set somehow between 12 and 5 in the morning. I woke up too late and did it manually. But that's not a problem" (man, 60 years old).

This patient, like some of the other interviewees, wanted to make sure that the recordings were transmitted, especially during the first few months after insertion. This woman described in the interview how her behavior changed after a first arrhythmia was diagnosed and treated with ablation:

> "Somehow, I had this feeling in the beginning: It's mega important that I check if it's really been sent and all that. Afterwards, after the first ablation, I felt like: Well, well, it's all right. (...) I checked maybe every three months to see if it had really been sent. And most of the time it had been sent. However, in the first year, I had checked it almost every day or at least every second or third day" (woman, 23 years old).

Like other study participants, she initially wanted to make sure that data was being transmitted regularly. This does not correspond to the "just plug it in and forget about it" advice given to patients by nurses or cardiologists during instructions after the insertion. These patients' experiences also illustrate the importance of the materiality of the transmitter, which, unlike the cardiac monitor, is a visible device in their bedroom that allows them to check (at least in a very simple way) whether the system is working or not (Weiner and Will, 2018).

Additionally, some patients were given a third device looking like a remote control with which they could actively force their implant to record an episode. The idea behind this device is to generate a link between an embodied experience and a potential heart arrhythmia. This allows patients to mark a heart rhythm episode in a moment in which he or she experiences symptoms of unease for example. However, the possibility of deliberately forcing and transmitting a recording during a moment of discomfort raised high hopes for receiving feedback. The experience of this patient who regularly felt disturbed in her everyday life by the sensation of extrasystoles shows her disappointment about the lack of feedback:

> "So, I would set off alerts precisely because of [the extrasystoles]. And then, well, what annoyed me was that I never got any feedback. In fact, yes, later [the cardiologist] reassured me by telling me that it wasn't serious. Still, it would have been reassuring for me to be contacted when I launch an alert. Not within an hour, because it's true, it has happened quite often over the weekend. After I had been in contact with the other doctor, I often set it off to show how frequently it happened. He had told me to do so every time I feel something. So, I did it, but then I didn't get any answer to that. I would have liked someone to call and tell me that there was nothing, nothing to report, nothing serious, you know. Just to reassure me. So, afterwards, I asked myself: well, what's the point of having this, if, when setting off an alert, I have no news, no follow-up. So, then they said, in fact if there's no problem, we won't call you" (woman, 58 years old).

To avoid frightening patients and to be cost effective, patients are contacted only when the nurses or cardiologists choose to do so. Thus, there is no follow-up for manually recorded episodes that show no irregularities. However, my qualitative interview data underscores the importance of feedback for monitored patients. They often felt cut off from the feedback loop.

Moreover, the reassuring effect generally diminished over time. Most patients were less reassured by the remote cardiac monitoring system when I met them for the second interview. This is well illustrated by the example of this patient, whom I asked during the second interview if the reassuring feeling was still as present

as during our first interview:

> "Yes, that is a good question. I was thinking about that today. I thought you would ask me that (both laugh). It is true I have said in the beginning, "Now, I am totally monitored." It also gives me a good feeling. Yes, it is still a bit there in the sense of which I have talked about before. If I had [another stroke] now, maybe I'd see it differently. Or maybe there is something [like an arrhythmia] that I do not know about. In fact, that is probably what is preventing me from having [the cardiac monitor] taken out" (woman, 68 years old).

This quote, as well as the one above, shows how important it is for patients to continue to feel well cared for. When a cardiac monitor is placed, there is great hope that the cause of unexplained symptoms will be found. If the cardiac monitor fails to detect arrhythmias for several months, these hopes are dashed. Similarly, patients who did not receive feedback on episodes they deliberately marked to show the cardiologists when they felt unwell began to question the usefulness of remote cardiac monitoring.

Discussion

In this article, I have illustrated how data-intensive medicine changes the way a diagnosis is made. Thinking of medical practice as a data network illustrates how the spatial and temporal uncoupling of processes that used to happen in one place creates an "illusion of immediacy". Instead of being automatically in sync as one would expect it from other data networks, the simultaneity or closeness (Pols, 2012) of the elements constituting a diagnosis need to be put into sync by a human. This article explores the coexistence of multiple temporal dimensions in data-intensive medicine by examining the experiences of patients, tele-nurses, and cardiologists with remote cardiac monitoring in Switzerland. In the following paragraphs, I will discuss the four main findings based on ethnographic observations during the insertion procedure and in the telemedical unit of two university hospital, as well as longitudinal and retrospective interview data.

First, the tele-nurses have a central position within the data network of remote cardiac monitoring. Her role is crucial, because data do not speak for themselves, but must be interpreted in relation to the patient's lifeworld (Grew and Svendsen, 2017). Although the data recorded by the monitor is automatically transmitted and synchronized through the telemedical system provided by the company, they need to be further synchronized with other data types, such as the last hospital visits, co-morbidities, and/or the actual situation in which the recording has been produced. Hence, this article suggests that the use of data-intensive technologies for diagnosis increases the need for human synchronization (Elias, 1992). Contrary to the traditional follow-up during which simultaneity is given by a shared space, the network-like character of data-intensive medicine can only produce meaningful knowledge if the links between the different types of data are correctly put into sync by a human (Weinberger, 2011). This requires "detective work" as the interviewed tele-nurses called it. But it did not just involve consulting the right documents to gather the relevant information. Over time, the tele-nurses acquired a fine knowledge about the patients' habits which helped them to faster process false-positive alerts (Piras and Miele, 2019). For example, they knew that a certain patient always uses his stationary bicycle at a certain time of the day which resulted in an alert of an abnormally high pulse. Consequently, they always dismissed this alert without further examination. This suggests that a certain form of intimate knowledge is indispensable for medical decision-making. However, the way remote cardiac monitoring is uncoupling the processes of data collection, analysis, and interpretation shifts the balance of power in favor of medical professionals, thus calling into question the promise of the participatory dimension of "personalized medicine."

Second, the setup of data-intensive technologies such as the cardiac monitor resembles that of any other connected devices, for example smartwatches. Consequently, receiving a cardiac monitor conveys the imaginary of being in sync with the hospital and therefore the clinician. Even though most patients know that remote monitoring does not work like an emergency system, they were reassured by the idea of being constantly connected to the clinic. This article shows how remote cardiac monitoring has a subjective reassuring effect on both patients and healthcare professionals. While patients felt that they were being "continuously cared for," healthcare professionals perceived it as "caring well" for their patients. This reassuring effect resulted from the imaginary of the digital ties provided by remote cardiac monitoring. For patients, however, it was precisely this reassuring effect that disappeared over time or was even a source of disappointment when the technology did not live up to the imaginary of a synchronized data network (Petersen, 2015).

Third, this gap between the reassuring effect based on the imaginary of a data network in snyc allowing for prompt feedback after an alert of an arrhythmia, and the above-described human synchronization work, which takes time, led to what I call an "illusion of immediacy". Although the inserted sensor monitors the heart round the clock, data transmission only happens once a day, and the tele-nurses work only during office hours from Monday to Friday. Consequently, if the heartbeat stops for a few seconds on a Saturday morning, the recorded episode will not be seen until Monday morning at the earliest. Some patients have expressed disappointment in not receiving immediate feedback or no feedback at all. Similar to the introduction of the telephone into the doctor's office, data-intensive medicine conveys the notion of a doctor-patient connection that is available 24/7 (Greene, 2022). Although technically feasible via the data network, healthcare professionals need time to accurately link and interpret the recorded data to produce meaningful knowledge. This reconfiguration of the temporal dimension of diagnostic work through patient remote monitoring may also affect the role and value of the gut feeling in everyday clinical practice (Kristensen et al., 2021).

Fourth, data-intensive technologies like the cardiac monitor uncouple the traditional diagnostic procedure of anamnesis, examination, and discussion of the results between the cardiologists and the patients. My article shows that the setup of remote cardiac monitoring fosters healthcare professionals to hold back on patient feedback. As it is precisely the role of the doctors or cardiologists to come up with a conclusive diagnosis (Groopman, 2008), they do not communicate every arrhythmia episode with

the patients to prevent them from becoming anxious. Moreover, they neither comment on episodes recorded and sent deliberately by patients while having symptoms if they do not show any abnormal rhythms according to clinical standards. This illustrates how the spatial and temporal uncoupling of data collection, its processing and interpretation in remote cardiac monitoring leads to a privileged data access for healthcare professionals making them the main users of the data network (Oudshoorn and Pinch, 2003). However, this may lead to disappointment among patients in the long run, especially if they make efforts to control and ensure data transmission, thereby becoming "diagnostic agents" (Oudshoorn, 2011). The sovereignty of data interpretation, knowledge production, and the decision to communicate with the patients remains within the walls of the clinic, thus devaluing patient work and participation (Oudshoorn, 2008). This is in line with the vision of "personalized medicine" focusing on data first, and on patients second (Vogt et al., 2016; Prainsack, 2017; Hoeyer, 2019). Future studies should aim to carefully disentangle how different types of big data sets are combined and who has the power to collect, process, and interpret them (Canali and Leonelli, 2022).

Looking at data-intensive medicine from the angle of a data network (Weinberger, 2011), instead of a classic care infrastructure (Weiner and Will, 2018), was useful to disentangle the multiple temporal dimensions co-existing in patient remote monitoring. In general, the temporal aspects of data-intensive medicine are not yet well-understood. While the patients and their embodied experience are always in sync, maybe except for sleep, this is not the case for the clinical examination. The promise of data-intensive technologies like the cardiac monitor is to put the patients and the clinic in one data network. But simply connecting the two is not enough. There is a need to put different types of data and different time frames into sync to render the endeavor meaningful for patients and doctors.

Limitations

The patient profiles of the participants were very different in terms of their clinical history (congenital heart disease, unexplained arrhythmias, stroke, comorbidities, etc.), which influenced the importance they attached to the cardiac monitor in their lives. However, it was the observation during this fieldwork that all these clinically very different patients share similar concerns, especially the lack of regular feedback. Although I tried several times to recruit a patient who had refused the insertion of a cardiac monitor, I was not successful. According to the cardiologists interviewed, very few patients completely refuse remote cardiac monitoring.

Conclusion

Data-intensive medicine privileging easily quantifiable information over unstructured patient narratives promises to improve healthcare through bigger and more comprehensive data sets. However, the production of these types of data sets uncouples the processes of data collection, analysis, and interpretation which previously took place within a single medical site. However, to make these data sets meaningful and useful, human synchronization of the multiple data types and time frames involved is required. This article on remote cardiac monitoring in Switzerland illustrates how the diagnostic process changes when the data is no longer collected in discrete moments in the cabinet or the clinic but continuously and remotely. The network-like character of patient remote monitoring conveys the perception of continuously "being cared for" among patients, and constantly "caring for patients" among healthcare professionals. On the one hand, this results in a reassuring effect among for patients and healthcare professionals alike. On the other hand, patients lose this reassurance over time or especially if their expectation of a prompt feedback is not met. I call this phenomenon the "illusion of immediacy". Although medical practice increasingly relies on data, the data only makes sense if it is properly linked to other information, such as the situation in which it was recorded. Tele-nurses play a central role in doing the "detective work" to make the data meaningful to the cardiologists and, ultimately, to the patients. The knowledge generated by these networked data is the decisive element for data-intensive medicine to generate a diagnosis which might not be made as immediately as promised, but—with a bit of a chance—sooner than with conventional discrete measurements.

Data availability statement

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

Ethics statement

The studies involving human participants were reviewed and approved by Commission cantonale d'éthique de la recherche sur l'être humain (Cantonal commission on ethics in human research of the canton Vaud). The patients and healthcare professionals provided their written informed consent to participate in this study.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

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

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What rare cancers have in common. The making of lists of (very) rare cancers and the coordination of medical work

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This article aims to understand why medical actors recently published lists of rare and very rare cancers. It studies four lists of rare and very rare cancers based on interviews with the main actors on these lists and an analysis of medical articles in which these lists were published. It argues that these lists constitute boundary objects whose aim is to deal with the organizational challenges raised by precision medicine, which imply increasing the coordination work between various types of actors. Our work therefore allows a better understanding of the functioning of the recursive standardization process of a boundary object and, by analyzing how the category of rarity is built at the intersection of both professional and nosographic principles, shows the intertwining of the biomedical, organizational, and political aspects on which rests the practice of contemporary precision medicine.

KEYWORDS

rare cancers, oncology, precision medicine, lists, coordination, rarity, boundary objects

Introduction

Advances in precision medicine have produced an increasing subdivision of cancers, thus generating a disaggregation of the "cancer" object in favor of a multiplication of new medical entities now qualified as rare (Bourret, 2005; Castel et al., 2019), and the need for new classifications (Navon, 2019). Classifications are a classic issue in the epistemology of medicine, as they directly question the ontology of medical categories (Fagot-Largeault, 1989; Plutynski, 2018). Recent works have shown how precision medicine, also called "personalized medicine, renews the way of considering these classifications (Keating et al., 2016). These works show how genomics represent a turn to a "molecular gaze" in a Foucauldian sense (Rose and Miller, 1992; Rabinow and Rose, 2006; Rose, 2007; Navon, 2011). Some of the analyses also show how precision medicine, by producing a proliferation of new medical entities, engendered a need for "finer grained and more dynamic taxonomies" (Green et al., 2022)," and renews the way of considering rarity and of classifying tumors (Wadmann, 2023). However, the organizational dimensions of this proliferation of new medical entities in terms of the coordination of medical work, of the production and circulation of expertise, of the organization of—more and more individualized—healthcare pathways, and of the regulation of the production of new drugs has not been completely explored yet. In order to analyze how medical actors try dealing with the organizational challenges raised by the proliferation of new entities related to the emergence of precision medicine, this article analyzes the making of lists of rare and very rare cancers by these actors, since the beginning of the 2000s. The article argues that, facing this proliferation of new entities, medical actors feel the need to group the latter again following their incidence rate, thus building a "rare" category. It shows that the appropriation of rarity by medical actors in the field of oncology is therefore a response to the difficulties raised by the necessity of building more dynamic taxonomies, which questions the possibility of coordination between these actors.

These lists of rare and very rare cancer, which reference what there authors consider as rare entities, their coding in the International Classification of Diseases and their incidence or prevalence rate, do not renew existing nosological categories. They do not aim at drawing disease categories relevant for diagnosis. They aim to label certain types of cancers as rare, thus imposing rarity as a relevant medical criterion for identifying certain cancers and grouping them into a comparable category. The objective of this article is to explain why these lists have appeared and show the fundamental role they play in the coordination of medical work on new entities that are part of uncertain and dynamic categories: they aim to build a governable object (Lascoumes, 1996), to organize specific healthcare pathways, to facilitate the circulation of expertise and to coordinate action with the medicine agencies. This article shows that rarity does not constitute a medical category in itself, but both a nosographic and organizational category whose construction aims to coordinate different actors confronted to an increased complexity related to the multiplication of medical entities. It is inspired by different works that demonstrate how organizational, political and epistemic dimensions are deeply intertwined in the making of the categories that have emerged from precision medicine (Cambrosio et al., 2006; Green et al., 2022). They also show how these classifications constitute a material basis for creating and regulating the production of new medicines (Navon and Eyal, 2016), but also how they can create new types of identities for patients (Jutel and Nettleton, 2011) and potentially engender new types of inequalities and discriminations. By doing so, this article adds to this literature by showing how this collective appropriation of the notion of rarity at very different scales is a response of medical actors to the organizational aspects raised by the proliferation of new entities, which implies the production of categories that rest on an increased intertwining of biomedical, organizational and political dimensions.

The issue of rare diseases is, however, not new in the field of healthcare. This category of diseases was put on French and then European political agendas under the impetus of patient associations (Huyard, 2009a,b; Rabeharisoa et al., 2014) who joined together in a common European movement, Eurordis. The political work done by patients' associations contributed to put forward rarity as a relevant criterion for public health policy. This led to the establishement of a standardized European rarity threshold based on prevalence (1 person per 2,000), linked to the European regulation on orphan drugs. Caroline Huyard uses the concept of boundary object to characterize rare diseases and shows that the construction of this category of rarity derives both from the specific experience of the disease put forward by patients' associations and from the desire of the European Union to achieve an alignment of regulations with the European common market. But Huyard points out that at the time of her survey, the category of rarity had little resonance among health professionals.

However, the making of lists of rare diseases by health professionals challenges this idea, from the foundation of Orphanet, a database on rare diseases launched by a French geneticist in the 1970s, to the recent proliferation of lists of rare and very rare cancers. This article raises the question of the appropriation of the notion of rarity by medical actors. It shows how lists of rare cancers have been constituted as boundary objects in order to coordinate medical work. The notion of boundary object, initially developed by Star and Griesemer (1989) and used by Huyard, describes entities that are both abstract and material, around which different communities organize and structure themselves. This article shows that lists of rare cancers constitute boundary objects, in the way that they are a material object making reference to an abstract category, and which is used by different medical actors to coordinate with each other. The interpretive flexibility of the boundary object is a key element in this process, in the sense that it allows the object to be reappropriated by different communities according to various local issues, and therefore allows these communities to work together. This aspect has been already analyzed through the prism of the coordination of medical work by using a ≪ shared space ≫. But another dimension of the boundary-object remains quite unexplored, which is the recursive dimension of the boundary object: indeed, Susan Leigh Star explains how ≪ boundary objects are constantly caught up in a ≪ back and-forth between the ill-structured and wellstructured use of the arrangements ≫. The construction of a boundary object thus constantly oscillates between attempts at standardization, never completely achieved since the process of abstraction cannot capture the plurality of complexity of the multiple arrangements, and constant work to redefine this object to make it more tailored to local uses, thus working at new standardization attempts. Star shows that this constant restandardization movement is related to the fact that standards create ≪ residual categories ≫, which caracterize categories at the margins of standards and left apart by the standardization process (Star, 2010). Rare categories, because they are numerous, heterogeneous, and difficultly caught up in this standardization process, can be considered as residual categories.

This article focuses on the work done by medical actors concerned by these "residual categories" to understand how they build arrangements to allow themselves to achieve some sort of consensus on what is rare and what is not rare. The demarcation of rarity oscillates between, on the one hand, attempts at standardization, never completely stabilized, which emanate from different types of actors and that aim to establish epidemiological thresholds, and, on the other hand, more specific circumstances where the concept of rarity is mobilized and can push certain actors to free themselves from these standards and produce new definitions of rarity.

In order to better characterize the constant back-and-forth between wellstructured and ill-structured uses of the concept of rarity, aiming to trace how different medical actors effectuate a boundary work to conceptualize, circumscribe and define rarity, this article proposes the notion of jurisdiction (Abbott, 1988). Jurisdictions characterize, for Abbott, the link between a profession and its work: that is to say, the way in which some actors claim an expertise about specific areas or entities. This article will thus show how professionals use the notion of rarity to define, maintain or expand their domain of expertise over specific medical entities. As Abbott claims, "jurisdictional boundaries are perpetually in dispute, both in local practice and in national claims." By understanding how different medical actors circumscribe their areas of expertise by defining rare entities, this article will thus show how the study of these jurisdictional struggles helps understand the recursive standardization of rarity as a boundary object.

This article is also inspired by more recent works that use or criticize Abbott's concept of jurisdiction. Firstly, this article

is inspired by the analyses of Timmermans, who shows how "professions gain jurisdiction when they control their skills through abstract knowledge and technique" (Timmermans, 2002), how they attempt to sway legislation, and how this leads to a "politics of expertise," since professionals seek to maintain the boundaries of their expertise by monopolizing abstract knowledge and technique. This will help us to understand how medical actors, by effectuating a boundary work around the notion of rarity, seek to create their own jurisdiction, characterized by rare entities. Secondly, this article is inspired by the work of Eyal, which criticizes Abbott's analysis by explaining that expertise should be understood with much more fluidity, showing how actors do not always seek to maintain a jurisdiction, aiming at keeping a monopoly of expertise, but sometimes at the opposite aim to make knowledge and expertise circulate (Eyal, 2013).

Drawing on these studies, this article will first analyze the creation of lists of rare cancers to understand why medical actors effectuate a boundary work around rarity, showing how they publish such lists to make these residual categories visible for public actors and to claim funding for their research, and to claim specific healthcare pathways for these patients. By so doing, they seek to create and maintain a jurisdiction on these residual categories, thus contributing to the standardization of the boundary object, which allows them to stabilize the contours of this jurisdiction.

Then, the article focuses on the making of lists of very rare cancers, residual categories left apart by the standardization of rarity. It shows how medical actors concerned by very rare cancers aim to coordinate biomedical work about them, and to communicate with actors from the regulation agencies about the specificities of these entities. This ill-structured work around a new boundary object aims at the contrary to make expertise circulate rather than monopolize control over a jurisdiction.

Methods

This article is based on the study of four lists of rare cancers that were published between 2007 and 2020. It is part on a broader research program on the Europeanization of healthcare for rare cancers. The first list, Orphanet, is the first list of rare disease that has been made in Europe in the 1990's. This list, which includes a list of rare cancers, is important because it is a reference in Europe concerning rare diseases, and a basis for European policies on rare diseases.

The second one, RareCare, is the result from a research program on rare cancers funded in 2007 by the European Union. This list has been chosen because it is the most important list of rare cancers at the European level, used by both medical actors and European authorities to create reference networks for these cancers. The two other lists that have been chosen are specific to sarcomas and childhood cancers and reference ≪ ultra ≫ or ≪ very ≫ rare tumors and were published in medical journals in 2019 and 2021. They have been chosen because they are the only lists published in oncology journals that reference ultra-rare and very rare tumors. Indeed, both sarcomas and childhood cancers are two specific fields in oncology that deal mostly with rare entities, and medical actors from these areas feel the need to distinguish between rare and ultra rare entities. The analysis of these three lists makes it possible to consider rarity at different granularity levels, thus helping us understand the constant standardization and destandardization of the boundary object.

A study of six medical articles that got published around these lists has also been conducted. These articles have been chosen because they are the ones in which the lists have been published, or articles that give comments on these lists or use them. The study of these articles help specify both the reasons for the making of the lists and the way they have been made.

A difficulty in studying lists of rare and very rare cancers consists in the diversity of actors involved in their construction and their use, considering the fact that they aim to coordinate these actors. The article issued from the RareCare study is signed by 22 co-authors, mostly epidemiologists and people in charge of cancer registries in different European countries, but also oncologists and molecular biologists (Gatta et al., 2011). Three of them have been interviewed.

The article presenting the list of ultra-rare sarcomas is signed by 60 co-authors involving epidemiologists, clinicians, researchers and hospital directors from all over the western world (Stacchiotti et al., 2021). Eight of them have been interviewed. The article presenting the list of very rare childhood cancers is co-signed by 18 authors, oncopediatricians and epidemiologists (Ferrari et al., 2019), eight of whom have been interviewed. One epidemiologist, Annalisa Trama, is central, as we will see, in the making of these lists is present in these three articles.

Semi-directive interviews with these actors lasted between 1 and 2 h and were based on an interview guide which aimed to understand which place the actors occupied in the making of the lists, why they participated to this process and why they find these lists useful. Another part of the questions aimed to understand from which type of network these actors were part of and the link they have with the European institutions, and especially expert committees of the European Commission.

From rare diseases to rare cancers

The first official classification of diseases dates to 1893 when a French physician, Jacques Bertillon, was commissioned by the International Statistical Institute to establish a classification of causes of death at a congress in Vienna in 1891 (Bowker, 1996). This classification was subsequently revised five times in 10 years until 1938. At its creation in 1945, the World Health Organization (WHO) was entrusted with the evolution and update of this classification. In 1948, the sixth revision became the "International Statistical Classification of Diseases, Injuries and Causes of Death" (ICD), which moved away from listing only causes of death to broaden its focus on morbidity in general. In 1967, the WHO stipulated that Member States should use the latest revision for their health statistics on morbidity and mortality. In addition, the classification of cancers was separated from the ICD in 1976. From this time, cancers have been classified in a separate list, the ICD-O (International Classification of Diseases for Oncology). This separation is explained by the need of oncologists to have lists both on the topography and morphology of tumors: that is, the location

of cancer cells (breast, lung, uterus) and their form (carcinoma, mesothelioma, sarcoma).

To understand the emergence of lists of rare cancers, it is necessary to start with the history of lists of rare diseases, which emerged earlier. The history of the making of lists of rare diseases is linked to the realization of certain physicians, confronted with difficulties related to the diagnosis of certain diseases, of the shortcomings of the ICD, which they thought did not reference well enough the rarest diseases. Until this point, rare diseases thus constituted ≪ residual categories ≫, only referenced in classifications in categories such as ≪ Not elsewhere categorized ≫, or ≪ None of the above ≫, In order to better characterize these residual categories, a French geneticist and physician, Ségolène Aymé, who had also studied epidemiology and bioinformatics, was confronted in her clinical practice with patients having rare diseases that she did not hear about before and that were not referenced in the ICD. In the 1970s, she set up a database on rare diseases, initially for her own use. This database became Orphanet in 1997.[1] This database does not only reference rare diseases better than what was the case in the ICD, it also compiles information on the epidemiological indicators of rare diseases via a systematic collection procedure in medical journals and registries.

Orphanet quickly took on a European institutional dimension. The European Commission started to use the list as a model to trace and codify rare diseases in the European Union. This process of recognizing rare diseases as a category asking for a specific public response has led to a standardization of rarity at the European level, under the aegis of the European Commission, based on a prevalence threshold, following an important mobilization of patient associations (Huyard, 2009a). The creation of this list thus characterizes the material process by which Ségolène Aymé created a boundary object, aiming to seek cooperation between scientific actors working on these residual categories and political actors within the European Commission. The creation of this database has also contributed to making the creator of Orphanet a central and unavoidable figure of the cause of rare diseases, present in most commissions at both the French and European levels. The making of this boundary object therefore allowed her to create her own jurisdiction over these residual categories, by establishing control over a new public problem and its government, hereby establishing herself as the main interlocutor of the European Commission concerning rare diseases. For example, Ségolène Aymé was appointed as president of the ≪ Rare Disease Task Force ≫ in 2004, the first committee of experts on rare diseases that was created by the European Commission. This appropriation of this public problem was only made possible by the construction of a boundary object that allowed her to translate a medical expertise into the political field.

Specific lists of rare cancers emerged later, in the mid 2000s, following the making of rare diseases as a boundary object between the medical and the political fields. Indeed, several actors from the oncology field wanted to stress out the specificities of rare cancers, which cumulate both the specificities of rare diseases and of cancers. Indeed, the idea that these rare cancers present common specific difficulties compared to rare diseases regarding care and management emerged in the mid-2000s. Some clinicians emphasized the difficulties common to the treatment of all rare cancers, which nevertheless group very heterogeneous entities: diagnostic difficulties, lack of standardized protocols, and the difficulties of patients to find people who share the same conditions (Raghavan, 2013). As this oncopediatrician, member of the ExPERT group emphasizes it, precision medicine was at the origin of this multiplication of rare tumors:

> The recurrent molecular anomalies found in a certain number of patient groups are synonymous with a certain prognosis, a certain treatment and so on. What is very complicated is that at the time we had 3 groups of treatments, today we must have 15 because we are segmenting more and more. And so, diseases that were relatively frequent... when you have a disease that is frequent and you make 10 groups, it doesn't become 10 frequent diseases, it becomes 10 rare diseases. It makes things more complex.

This excerpt shows well how medical actors perceive the multiplication of rare entities engendered by the emergence of genomic medicine and the related complexity of managing care and research about them. This subdivision of disease categories into multiple subtypes has already been well shown (Bourret, 2005; Green et al., 2022), as well as the renewing of their relationship with diagnosis and of the characterization of illnesses (Navon, 2011).

But if the way in which precision medicine has renewed existing classifications has been well analyzed, it is not the case for the apparition of a ≪ rare ≫ category, which is not about subdividing existing entities, but about thinking of how to deal with this proliferation of new entities by defining, labeling and grouping them into new categories in order to organize expertise and care about them.

The first list of rare cancers was published within the framework of the RareCare project, funded by the European Union in 2007, bringing together oncologists, epidemiologists and geneticists from the main countries of Western Europe and which was the first European funding program specifically dedicated to rare cancers, mostly aiming at identifying and quantifying them. Thus emerged a progressive standardization process of a new category inside the standardized rare disease boundary object.

In order to build the first list of rare cancers, members of the RareCare project used the ICD-O-3 (3 means the third version) classification and identified rare cancers according to their incidence rate defined as <6 per 100,000 per year. From this list, different groups and subgroups were formed. The RareCare list also references the topography and morphology codes from the ICO-3 and the incidence rate of these cancers:

The recursive standardization of the object ≪ rare diseases ≫ did not stop, however, with the making of the ≪ rare cancers ≫ boundary object apart from the ≪ rare disease object ≫. More recently, a list of very rare cancers has been developed for childhood cancers. It has been published by a European network of pediatric oncologists, which groups together clinicians who struggle to treat these diseases. These oncopediatricians started to build national networks from 2000, in order to share expertise. In Poland, the Rare Pediatric Tumor Study Group (PPRSTG) was launched in 2002, in Germany the STEP (Seltene Tumoren in der Pädiatrie) in 2006,

1 On Orphanet, see the work of Dagiral and Peerbaye (2012, 2013, 2016).

in France the FRaCTurE group (Groupe FRAnCais Des TUmeurs Rares de l'Enfant) in 2007. Projects financed by the European Commission have helped to structure these networks. In 2008, these networks grouped together and built the European ExPERT group, specialized in very rare childhood tumors. This list is based on the ICD-O-3, cross-referenced with data on incidence rates taken from the RareCare study. The making of this list has been, as for the RareCare list, accompanied by the standardization of the category by the definition of a threshold. Indeed, members of the ExPERT group have defined the threshold for very rare as an incidence rate of <2 in 1,000,000 per year. According to this list, 11% of pediatric cancers are very rare. These very heterogeneous tumors include both cancers that are common in adults but rare in children, and rare cancers that are specifically pediatric (hepatoblastoma, pleuropulmonary blastoma, pancreatoblastoma, etc.).

At the same time, another network of experts started to build another category of ≪ very rare tumors ≫, also identifying specific entities from the RareCare list. The Connective Tissue Oncology Society (CTOS) brings together sarcoma specialists from around the world, and has commissioned a panel of experts in 2019 to develop a list of ultra-rare sarcomas. The committee brings together specialists from Europe, North America, Asia and Australia, covering all disciplines involved in sarcoma research and care (epidemiology, pathology, molecular biology, surgery, radiotherapy, medical oncology). As with pediatric cancers, these experts took the ICD-O classification of soft tissue and bone tumors and cross-referenced it with epidemiological data from the RareCare studies to extract those classified as ultra rare. The CTOS-appointed expert committee set the threshold for ultra-rare at an incidence of <1 case per 1,000,000 per year. As we see, this threshold this resulted in 18% of sarcomas being considered as ultra-rare. The resulting list was updated as new versions of the ICD-O emerged.

This multiplication of lists of rare and then very rare diseases and cancers across time testimonies for an increased need of medical actors to better define, label, count and circumscribe these residual categories. This need gave raise to a recursive and progressive standardization of imbricated boundary objects at very different scales and for different usages: firstly rare diseases, then rare cancers, then very rare cancers. We thus have to wonder how and to what extent is the appropriation of the category of rarity the response to the organizational challenges raised by the proliferation of new entities by imposing a new criterion for grouping them.

Why do medical actors publish lists of rare cancers?

Indeed, defining some cancers as rare not only means better referencing them as individual entities but also thinking about what they have in common that requires grouping them into a specific category, which is not anymore referenced as ≪ Not elsewhere categorized ≫ or ≪ None of the above ≫ anymore, but as ≪ Rare ≫. In other words, it means admitting that rarity is a relevant characterization for constructing a space of comparability between entities that would otherwise be completely heterogeneous.

Medical actors decided to characterize and to group these residual categories into a ≪ rare ≫ category for two reasons. The first one, epidemiological, aims at defining and counting rare cancers in order to create a boundary object that allows medical actors to represent the important number of these residual categories in order to build a significant public problem for which public authorities should find solutions. As such, grouping rare tumors is a strategy to make visible residual categories that were left apart by previous European politics on cancer: these lists deeply intertwine epistemological and political dimensions.

The second is based on the need to organize specific healthcare pathways for these rare entities to ensure that patients have access to clinical expertise that might be scarcer than for other cancers. But of course, the creation of a new boundary object which is ≪ rare cancers ≫ raises important power relationships between medical actors who aim to circumscribe and establish control over the new jurisdictions created by the emergence of these new categories.

Publishing rare cancers lists to build a governable object

The making of lists of rare cancers in the mid-2000s consisted for these medical actors in constructing a boundary object that allowed them to translate their difficulties to make them both perceptible and governable by public authorities. Epidemiological issues played an important role in the construction of such categories, since they made it possible to construct and circumscribe a rare category and to evaluate its importance in numerical terms. This epidemiological work is thus directly in line with what Vololona Rabeharisoa and her colleagues have described as a logic of numbers and a logic of singularization (Rabeharisoa et al., 2014). Indeed, the latter emphasizes not only the heterogeneity of entities, but also what these entities have in common by aggregating them in order to release a logic of number and make it worthy of attention.

Researchers participating in the European RareCare study, having circumscribed the category of rare cancers, have shown that they represent about 20% of all cancers (Gatta et al., 2011). The title of the article is "Rare cancers are not so rare." By this oxymoron, the authors imply that, by a logic of aggregation, rare cancers taken in isolation are no longer rare if the whole category is considered. The construction of this category is thus part of a logic of numbers that might seem paradoxical at first sight. This is what the epidemiologist in charge of the RareCare program financed by the European Union, and the main actor in charge of the RareCare list, mentioned in an interview:

> So, I'm an epidemiologist and basically since the last eleven years I've been studying mainly rare cancers because we initiated a European project during which we proposed a definition and a list of rare cancers. In the framework of this research I started of course to get in contact with most experienced oncologists, pathologists, radiologists, you know, surgeons of rare cancers and once we defined this list, we also decided that it was important to have data showing that rare cancers, because they are rare, so their frequency is low, are better treated in expert centers. So, we basically used data to

> provide evidence that rare cancers are not so rare. That together they're a lot. Calling for, you know, for priority, to give priority to rare cancers at national and European levels.

This grouping work allows the authors of the RareCare study to stress the numerical importance of the category of rare cancer, thus calling for specific European politics specifically directed toward them. The emphasis on the numerical importance of this category then contributed to put the issue of rare cancers on the European agenda and also to highlight the issue of quality of care for this type of disease. In this sense, rarity is not a purely medical concept, but the very idea of grouping residual categories into this category is in itself political: rare cancers are grouped to make them worthy of political attention. The construction of the "rare cancer" boundary object, based on a standardization process of epidemiological thresholds, then makes it possible to call for a specific treatment in terms of organization of care. As the same epidemiologist explains:

> So, basically with the first project we identified the list of rare cancers, we showed there were differences in survival across member states. And we started reasoning about possible reasons for differences we thought that they had to do with the different healthcare organizations, which would imply the type of quality of care, because…we had to understand to what extent rare cancers patients are referred to the appropriate centers of expertise. So, we thought that one of the possible reasons for these differences was also the different quality of care provided in the member states.

The actors involved in RareCare, by constructing lists of rare cancers, thus constitute the material support of a boundary object and make the latter of attention for the European Commission, which no longer has to deal with a multiplicity of heterogeneous entities that are more complex to manage. The production of this boundary object also allows them to construct a governable public problem by highlighting its numerical importance and to call for a specific treatment. The translation of these issues into the political field, allowed by the making of a boundary object, is facilitated by the fact that some actors from the medical field have been recruited in expert groups of the European Commission in order to implement a specific organization of care. For example, Annalisa Trama has been attributed a place in the EUCERD (European Committee of Experts on Rare Diseases), the expert group which replaced the Rare Disease Task Force in 2009. In this expert group, Annalisa Trama represented the community of rare cancers and advocated for putting specific healthcare pathways for rare cancers into place, alongside with Ségolène Aymé.

Publishing rare cancers lists to better organize healthcare pathways

Some studies have shown how the renewing of classifications related to genomic medicine did not only have epistemological implications, but also political and organizational ones (Green et al., 2022). In this way, rare cancers are a response to the organizational challenges raised by the profiferation of new medical entities engendered by the emergence of precision medicine: if medical actors group rare cancers into a category to seek political attention, it is in order to claim a specific and common organization for rare cancers.

Since the beginning of the 2000s, under the impetus of patients associations, the treatment of rare diseases has tend to be increasingly centralized in expert hospitals that are concentrating cases around a specific disease. This organization is the result of several national plans for rare diseases in various European countries. Initiatives have also been taken to set up this type of organization at the European level, by creating European rare disease networks (ERN) organized around centers of reference. Four of these networks are dedicated to rare cancers: pediatric cancers are covered by the PaedCan network, sarcomas by the EuraCan network dedicated to rare solid cancers, the EuroBloodNet network is dedicated to hematological cancers and the Genturis ERN to tumors with genetic risks. The delimitation of the scope of action of these networks derives directly from the construction of lists of rare cancers.

Both medical and political actors have to deal with the tension between the heterogeneity of residual categories and the standardization process required by the construction of the rare cancers' boundary object. Indeed, each cancer cannot have a completely individualized care pathway so it implies to group them. Lists have to become classifications that can aggregate residual categories into groups, a need expressed here by a French physician, specialized in sarcomas:

> Now the challenge will also be to use these classifications and to know how to group things together. Because [...] what I'm saying seems to be aberrant when I've just said that it's important to dismantle, but it's also good to know how to reorganize groupings because we don't necessarily have 150 therapeutic strategies and so there are also subtypes that can cross from a diagnostic point of view and from a treatment point of view. And so today the effort to be made is that we have seen what is different, we must also see what is common. Identifying common vulnerabilities for therapeutic strategies that can be identified for different subtypes is important.

This excerpt shows the organizational challenges that have been raised by the emergence of precision medicine and the subdivision of tumors into multiple rare entities, which requires grouping heterogeneous entities into different "categories" to be able to build specific healthcare pathways. However, this process of grouping raises tensions between political and medical actors. The way of grouping rare cancers in order to build the European reference networks has raised a debate between the members of the European Commission, who wanted to limit the number of networks in order to facilitate their management, and the actors of RareCare, who wished a greater of networks were created as explained by Annalisa Trama:

> And there was another output of Rarecare, we gave a list of twelve groups of rare cancers. Because we said that rare cancers are approximately 2000 different types of tumors but this is really difficult to perceive…so because for us it was

> really key to address the big families of tumors for which are specific referral pathways. . . which basically implies referent centers where expertise would be needed. We basically grouped these 2000 types of rare cancers in 12 families, which basically includes all childhood cancers, because they are all rare, and there is an ERN for childhood cancers, Paedcan. And there was an ERN dedicated to the rare hematological tumors, EuroBloodNet. Our original idea was to have other ten ERNs for what we call rare adult solid cancers. But the European Commission was against the fragmentation of cancers, as well as for rare diseases, so they asked the rare cancers and the rare diseases to try to combine the efforts. And so we ended up developing one ERN for the ten families of rare adult solid cancers which is Euracan. So, basically from the epidemiological data one of the big outputs for me to get involved in designing a bit the ERN was because of this concept of families that we discussed together.

The actors of RareCare finally decided to organize the grouping at two levels. Firstly, they created categories which constitute relevant entities for patient care pathways organized around expert hospitals. Next, these categories have themselves been grouped into twelve families of rare cancers (e.g., nervous system cancers, digestive system cancers, sarcomas, pediatric cancers). These tensions around the grouping of heterogeneous rare entities reveals the tensions of rarity as a boundary object between political and medical actors.

This process of grouping has quickly led to a rethinking of the notion of rarity, which no longer applies only to clinical entities but also to families of rare cancers. Indeed, epidemiologists and clinicians no longer consider only clinical entities, but which groups of entities are rare. Indeed, several rare cancers can be grouped together in a family that is not rare from an epidemiological point of view:

> There is a big difference between a rare "family" of cancers and a rare cancer "entity" belonging to a common family of tumours. For example, metaplastic cancers of the breast are a rare cancer entity, with the same incidence as, say, pleomorphic liposarcoma. However, while it may well be equally problematic to do any clinical research exclusively focusing on both, the expertise needed to approach appropriately a metaplastic breast cancer will be relatively easy to find in the community. This does not apply to pleomorphic liposarcoma, for which referral centres, or networks, will inevitably be more difficult to find in the community.[2]

These tensions around the making of lists of rare cancers between medical actors and the European Commission have led to the transformation of the boundary object from a list into a classification. This transformation shows how the organizational questions raised by the emergence of rarity as a specific category around which organizing healthcare pathways led to reconsidering rarity as a whole, which is here not only defined by the establishment of an epidemiological threshold but also by a lack of ≪ expertise ≫, that is to say of knowledge about how to treat these tumors. This evolution in the way of considering rarity, embodied into the materiality of a list, which is getting transformed by the usages that different actors make of it, is typical of the plasticity of the boundary object. It also shows the deep intertwining of both epistemological and organizational dimensions in the grouping of these rare tumors.

A conflict of jurisdiction between rare cancers experts and rare diseases experts

Of course, as for every categorization process, the emergence of rarity as a boundary object raised important power plays, characterized by the willingness of certain actors to establish control over this new jurisdiction. The medical actors who tried establishing a jurisdiction over rare cancers ended up being confronted with Ségolène Aymé, who, as we have seen, was also trying to establish a jurisdiction over rare diseases, and thus about rare cancers. As Ségolène Aymé explains, she had troubles communicating with these new actors in the field of rare diseases, who were trying to assert a jurisdiction on a field that she perceived as her own:

> So rare cancers are rare diseases... All childhood cancers are rare... And the cancer community has had a hard time accepting to join the rare disease community. I was welcomed like a cat amongst the pigeons. It's not easy... Well, that's normal, all communities have their culture. While finally they are in exactly the same type of galleys. . . they continue not to want to consider themselves completely on the side of rare diseases... and yet, Annalisa Trama, all that, we made efforts to get them into the Eucerd, into the working groups of the European Commission, but they continue to want to play their game... while basically, for orphan drugs, they are in the same boat.

These conflicts of jurisdiction that take place within the European expert groups of rare diseases are also reflected in discussions around the making of lists of cancers. Indeed, the list created by Ségolène Aymé, Orphanet, also references rare cancers. But if Orphanet contains, as a list of rare diseases, a list of rare cancers, they are not referenced in the same way as in RareCare. Indeed, Orphanet's list uses the standardized definition of rarity accepted at the European level in 1999, according to the incidence rate, while the RareCare study qualifies rarity based on the incidence rate as explain in this article:

> We used a new incidence-based criterion for defining rare cancers. In Europe rare cancers are often defined according to the prevalence criterion of <50/100,000, in the same way as rare diseases in general. However, prevalence has shortcomings as a measure of cancer rarity since some cancers with low incidence but good survival will fall into the common category as good survival pushes up prevalence; examples are squamous cell carcinoma of the uterine cervix and thyroid carcinoma. Similarly, some commonly-occurring diseases for which survival is poor are considered rare because poor survival pushes prevalence down. Examples are adenocarcinoma of stomach and lung and squamous cell carcinoma of lung. These considerations suggest that incidence

2 Casali and Trama (2020).

> is better for defining rare cancers, and is also in harmony with the sub-acute clinical course of most rare cancers; whereas most rare non-neoplastic diseases have a chronic course so prevalence is a better measure.[3]

Researchers argue that this definition corresponds better to remission phenomena. Basing rarity on the prevalence threshold has resulted in the bad prognosis cancers being removed from the so-called rare cancers since their prevalence rate is higher. This definition was rapidly adopted, particularly by European epidemiological studies. It has also been adopted beyond Europe in various studies in Asia and the United States (Tamaki et al., 2014; DeSantis, 2017; Matsuda et al., 2019). This imposition of a new definition of rarity that fits more the specificities of rare cancers is thus representative of the recursive standardization process that affects boundary objects (Star, 2010) and the constant reappropriation by local actors who build other objects more tailored for their own use. This gave rise to different definitions of rarity and various establishments of epidemiological thresholds depending on the scope of the boundary objects. What is interesting to consider is that this multiplication of definitions of rarity is related to the willingness of certain medical actors to impose a jurisdiction on a field, thus extending or at the opposite restricting these definitions to more or less specific uses. This encourages to consider the important power plays that are at stake in this progressive emergence of rarity as a specific category in response to the organizational challenges raised by precision medicine.

Very rare cancers: a new boundary object in construction

We have analyzed why medical actors decided to make lists of rare cancers, in order to build visible and governable objects for the European Commission and to implement specific healthcare pathways for these diseases. This work of grouping medical entities lead actors to question the very notion of rarity, going beyond the setting of an epidemiological threshold.

More recent initiatives aim to establish lists of very rare cancers. The study of the emergence of this new category shows that the proliferation of medical entities related to precision medicine implies for the medical actors involved to group rare entities into categories at different scales, These processes concern in particular rare oncology fields that are particularly confronted with a lot of rare tumors, whether they are not that rare ("common rare," as medical actors sometimes say) or "very" rare. Here, on an even finer scale, an intertwining of nosographic and organizational dimensions is at play in the making of these new categories that aim at coordinating actors of biomedical innovation and political actors. However, contrary to rare cancers, the category of very rare cancers is not standardized at the European scale yet. This new boundary object is just starting getting used by medical actors for quite different reasons than the rare cancers' category, and reveals different types of coordination between the actors at stake.

3 Gatta et al. (2011).

Lists of very rare cancers: a new boundary object aiming at the circulation of expertise

At the beginning of the 2000's, some national and then international networks, among which the ExPERT group on very rare pediatric tumors, started to get interested in what they began to call ≪ very rare tumors ≫ as a specific category. The interest of medical actors in these residual categories raised with the realization among certain physicians-researchers that extreme rarity raises specific difficulties that are different from rarity. The creation of lists of very rare cancers is thus characteristic of the recursive back-and forth of the boundary object between wellstructured and ill-structured uses of the concept. Indeed, by standardizing rarity by imposing rarity threshold, the actors we studied before left again apart residual categories, very rare tumors, which are obviously part of rare tumors but also raise specific difficulties for clinicians. For example, very rare cancers may be confused by specialists with non-cancerous diseases, even in an expert hospital, as explained by a German pediatric oncologist specialized in very rare childhood tumors:

> It's more difficult because these cancers are often primarily misdiagnosed for other types of cancers, or even other diseases, because with certain symptoms in certain age groups, you don't necessarily think about cancer diagnosis. So, for example, lung carcinoma in children is something which is very rare. And if a child presents with cough, and breathlessness and hemoptysis, or something like that, you don't necessarily think about the tumor first, but rather think about infection or something like that.≫

These difficulties were not raised by clinicians who dealt with "common" rare tumors. The boundary object "rare cancer" was then not able to completely cover the specificities of these entities and to respond to the specific organizational challenges that they raised in terms of coordination of expertise and care. Very rare entities are therefore characterized by the uncertainty that surrounds them clinically. These are residual categories that clinicians face difficulties to identify and for which there are no clear treatments guidelines, as explains a French specialist of sarcomas:

> I became interested in this pathology for several reasons. The first reason is the clinical situations I was confronted with. So, it was a semester that was particularly striking for me considering the situations I saw, with many young adults, people who were my age, I was 25 at the time. They were teenagers, young adults with cancer who had clearly had major difficulties in terms of diagnosis. That's what struck me, that there were diagnostic errors that lasted for some time, and even when the patients were taken in charge in a reference center, the diagnosis was not always that simple. And I was quite struck by the variety of subtypes of sarcoma, and on the contrary by the fact that they were all treated in the same way, which seemed to me to be completely appalling, since there was a variety of pathologies that were clearly very different from a pathological point of view, from a biological point of view, from a molecular point of view, and yet we had very few drugs and always the same drugs that were used in these young people.

The notion of extreme rarity is rooted in the experience of clinicians who had specific difficulties treating some patients because of a lack of expertise. These difficulties encouraged them to reflect on how to make the available expertise better circulate and to create specific scientific networks, such as the ExPERT group, in order to improve the coordination of medical actors from different European countries. By doing so, these new networks created a new boundary object, "very rare cancers," to characterize these residual categories.

The fact that extreme rarity is linked to a lack of expertise on specific medical entities characterized by certain mutations influenced the way these new networks of experts took it into consideration. What is interesting to consider is the fact that extreme rarity is not defined by these networks in terms of epidemiological thresholds, but by the fact that no network has already a specific expertise on most of these tumors. For example, in this excerpt of an article in which the ExPERT group published a list of very rare childhood tumors, is explicitly mentioned the lack of expertise as a specific criterion to characterize very rare tumors:

> This means that all types of cancer occurring in childhood are rare: so how do pediatric oncologists define 'rare tumors?' Rather than by their low incidence, rare pediatric tumors are generally identified by the fact that they are 'orphan diseases,' in the sense that most pediatricians might encounter them only once in their working lives, there are few or no published reports on clinical experiences, it is difficult to establish shared treatment guidelines (and there are no evidence- based therapeutic recommendations available), and few or no cooperative groups have dedicated and structured projects, and financial support for studies on these tumors.[4]

Both the idea that there are no guidelines for these tumors and that no research group is interested in them is important to define extreme rarity. The previous excerpt therefore defines extreme rarity by the absence of medical actors who have developed a specific expertise on these tumors. In this situation of uncertainty about the very identity of the clinical entities at stake and about therapeutic choices, medical actors have therefore developed their own lists in order to identify entities that suffer the most from a lack of expertise. This shows how the very rare cancers' category is not a very stabilized boundary object yet, but is still in construction and is the object of negotiation between medical actors concerned with these residual categories. This constant and recursive work aiming to group medical entities into different categories of rarity shows the difficulty of medical actors to restructure the expertise and its circulation to adapt to the specificities of the new medical entities produced by precision medicine.

Publishing very rare cancers lists to coordinate biomedical work

Lists of very rare tumors then constitute a tool to organize the division of medical research and the production of expertise, in a context where the entities studied are particularly uncertain and the expertise concerning these cancers is disseminated in different research teams located in different countries, as explained in the following interview excerpt with an oncopediatrician who is part of the ExPERT group and who is a co-author of the article in which the list of very rare childhood cancers is presented:

> Me: And what's the point of having such lists of very rare cancers?
>
> It's useful not to get angry with your friends... The difficulty in our job is to manage to make projects while remaining diplomatic. Well, it's true that it allows us to be sure that we're actually within the frameworks, that we're not making mistakes, to be sure that... it's true, so I'm saying that, but it's true that in order to be sure that we're not encroaching on other people's groups by saying: we've decided to take care of that. So that's it. But it allows us to say to ourselves, ok, it seems logical to take care of it, and then to identify, above all if there are diseases that we would not have identified and that deserve it.

Contrary to what has been observed for rare tumors for which jurisdiction struggles were very strong between rare cancers experts and rare diseases experts, here it is more a question of cooperation and coordination between medical actors. Lists of very rare childhood cancer are therefore a means of controlling the heterogeneity of entities and of coordinating research work about them within different and heterogeneous medical actors. Lists are therefore made as boundary objects aiming to coordinate research work between specialists in order to distribute the production of knowledge as well as possible, by identifying entities for which there is no available expertise. In this sense, the aim of these actors is not so much about controlling a jurisdiction than about allowing the circulation of expertise among different actors and group of actors. As expressed by another French pediatric oncologist who is also a member of the ExPERT group and a co-author of the article where the list is presented:

> It is absolutely essential to have this information in order to know who will take care of it. If you don't have this definition, I, who deal with rare tumors, who is part of... who is the president of the rare tumors committee, I will tell you that I will deal with hepatoblastomas, I will deal with sarcomas, these are rare diseases. These are very rare diseases and they can correspond to the definition of very rare diseases because we have been... we have worked in particular with the Italians, we have said that less than 2 cases per million inhabitants per year is a rare cancer. And so hepatoblastomas fit into that definition, retinoblastomas fit into that definition, most sarcomas fit into that definition. And so if I take this definition, I will be able to take care of all that. Except that I'm not a specialist and I'm going to be bad at it, so it's no use. There is a sarcoma group, there is a sarcoma group that will take care of these diseases and these sarcomas very well, and so if... it is important to identify which group will take care of them so that we don't step on each other's toes and so that people are actually specialized and work on their specialty, and get better little by little. So, it's really essential, if you don't define things in advance, first of all it's going to create tensions, tensions, completely sterile

4 Ferrari et al. (2017).

> competition, and then you're going to dilute things and have people who will take care of everything and nothing and that's not going to advance, that's not going to help patients.

The making of lists of very rare cancers thus constitute a boundary object for new scientific networks to create an agreement on what are the specific entities at stake and to make the expertise circulate, and then to make sure that every one of these entities is part of the area of expertise of at least one research team. This aim to distribute well expertise is favored by the strategies of certain medical actors who have chosen these cancers for strategic reasons. Some physicians involved in these communities have also seeked for a niche encompassing themes where competition is less important, as expressed here by a German pediatric oncologist in the ExPERT group:

> I think that most of the pediatric oncologists have first focused on the more frequent tumors because they saw more hum... more sustainable effect by improving the therapies for very... rare... hum for frequent tumors. And after, for most tumors, their concepts have improved a lot and the prognosis have improved, they... everybody has been looking for those where... who have been problematic. And so... in the first years of pediatric oncology, rare tumors have just been forgotten. They happened. But hum... but they were just treated, and nobody was caring. The other thing is... and this is more a hum... misanthropic interpretation, is that people like me were searching for their ecologic-... hum ecological niche, where they could find something, where they could do research without other people disturbing.
>
> (Laughs) And to be honest for me it has been quite of both. And it's also been very pleasant to work in a niche where not one thousand pediatric oncologists wanted to work too.

Lists of very rare cancers thus constitute a boundary object aiming to improve the internal organization of international medical networks. What is more, this boundary object is useful for these networks to distribute a scarce expertise in the best way. In this sense, the creation of the category of "very rare tumors" consists in imposing a new way of managing the activity of medical actors that aim to take the best advantage of the competition between the latter.

Publishing very rare cancers lists to coordinate the relations with medicine agencies

Lists of very rare cancers can therefore be considered as a boundary object in the way that they constitute a common basis for discussion between medical actors who do not belong to the same field. But these lists also constitute a boundary object that aims to coordinate medical and political actors. Indeed, lists of very rare cancers are also intended to provide a basis for discussion with drug regulatory agencies. Concerning very rare cancers, there is very often no drugs authorized by national and European regulation agencies for these diseases. Drugs are therefore often used by clinicians off-label since randomized clinical trials are almost impossible to conduct because there are not enough cases. According to all the physicians-researchers interviewed, this is a clear dividing line between rare and very rare tumors, which is mentioned in the article that presents the list of very rare childhood cancer:

> In fact, although all childhood cancers are rare, designing randomised controlled clinical trials is feasible for most paediatric tumours thanks to the well-established international cooperative networks, but it is unrealistic for many of the very rare paediatric tumours (it would take years to conclude a clinical trial).[5]

Lists of very rare cancers therefore make it possible to identify diseases for which it would be relevant to regulate the use of drugs in a context where randomized clinical trials are not feasible. They therefore serve as a boundary object between medical actors and the regulatory agencies at the European level with the aim of imagining a common and specific mode of regulation for the very rare clinical entities that are identified in the list and thus optimizing the production of new drugs for them.

> Currently, there is no mechanism for bidirectional communication between clinicians, researchers, and regulatory bodies. We suggest that this could be achieved through regular mutual updates between the ultra-rare disease communities and regulators. In ultra-rare sarcomas, large studies are only possible with either long study durations and/or the involvement of a very large number of study sites (with corresponding quality-control issues).[6]

Aiming at producing new drugs, and with a logic of equity between all patients, whether they have very rare, rare or non-rare cancers, medical actors are using these lists as boundary object to call for new regulations to address the uncertainty that surrounds the conduct of clinical trials and the production of new drugs for very rare cancers:

> In the area of ultra-rare sarcomas, disease-based discussions with regulatory agencies need to be planned on a regular basis, before embarking on the assessment of specific agents, including the incorporation of expert scientific advice, which affects the type of study protocol proposed for development. If an internal control arm is not feasible, optimizing the collection of external high-quality data by clinical registries should be encouraged. In the European Union, an opportunity not to miss is the involvement of the European reference networks: i.e., networks of cancer centers appointed by their governments to treat and research rare cancers. When label extension is not feasible, centralizing the use of selected off-label agents in sarcoma networks would be a way to guarantee appropriateness (…) while a higher degree of uncertainty should be tolerated; shared clinical decision making should be resorted to in order to manage such uncertainty.[7]

5 Ferrari et al. (2019).

6 Stacchiotti et al. (2021).

7 *Ibid.*

The creation of lists of ultra-rare cancers obeys logics that are different from those that animated lists of rare cancers. Very rare cancers constitute a boundary object created by medical actors that aim, internally, to divide up the work and the production of knowledge on heterogeneous clinical entities characterized by particularly significant clinical uncertainty. These lists also ambition to circumscribe the clinical entities for which it would be relevant to organize the regulation of drug production outside the gold standard of the randomized clinical trial. In this sense, the construction of "very rare entities" as a new boundary object is also a way, although at a different scale, to try to deal with the difficulties raised by the proliferation of new medical entities in terms of the production of new drugs. Indeed, this category might be useful to medical actors to question the traditional structures of expertise and care related to evidence-based medicine.

Conclusion

The notion of rarity is taking an increasingly important place in the field of oncology due to the development of genomic technologies and precision medicine which tends to subdivide types of cancer into more and more entities (Bourret, 2005). This work shows the consequences of the development of precision medicine on the reappropriation of rarity by medical actors, and how the notion of rarity, born in the field of rare diseases under the impetus of patient's associations (Huyard, 2009a,b), has been reappropriated and adapted to the specific field of oncology.

To understand the reasons and consequences of this reappropriation, this article has focused on the lists of rare cancers, which constitute material objects aiming to circumscribe rare tumoral entities. It has shown that these lists constitute boundary objects that have been drawn up by health professionals, with the aim of coordinating medical work and responding to the specific challenges raised by these diseases: structuring networks of experts, identifying lack of knowledge, and giving access to new treatments. However, since the notion of rarity has been reappropriated by different medical and political communities, working on very different scales, these communities constantly produce new definitions of rarity. The notion of rare cancer is thus caught up, like every boundary object, in a recursive movement of standardization—establishment of thresholds from which a cancer can be considered rare—and adaptation to specific subfields of activity—sarcomas, pediatric oncology—which engender a multiplicity of ways of defining rarity. This recursive tension generates difficulties between the different medical networks at stake, which produce specific definitions of rarity and standards. In the end, far from being fixed, the notion of rarity is constantly evolving in the face of transformations in cancer care as shown by the case of ultra-rare cancers.

This study allowed us to better understand this recursive tension by characterizing the relationship between the different residual communities that are caught into it as a conflict of jurisdiction. This concept helped us to show that these lists allow medical actors to both circumscribe and extend their jurisdiction, in order to coordinate medical research activity, to build a visible and governable object, to organize care pathways and the relationship with the regulation agencies.

This article thus allows to understand how rarity, after having been claimed as a new identity basis by patients' organizations in the 1990s (Huyard, 2009a,b; Rabeharisoa et al., 2014) for a diversity of syndroms, has now been constituted as a relevant medical and organizational category aiming to coordinate various medical actors in oncology, as a response to the proliferation of new entities engendered by the emergence of precision medicine. Previous works on precision medicine have shown how the challenges raised by new diagnostic tools engendered a constant need for the revision of classifications (Green et al., 2022) as well as a constant recursive work between diagnosis and classifications (Navon and Eyal, 2016). They have also analyzed how precision medicine gave rise to an increased intertwining between organizational, political in the making of these categories (Wadmann, 2023). Instead of focusing on the constant revision of disease categories by the addition of new subdivisions (Bourret, 2005), this article analyzes how medical actors find a way to deal with the organizational challenges raised by the proliferation of new entities by appropriating the category of rarity. It shows not only how rarity is built on epidemiological thresholds, but is constituted as a performative organizational tool, which justifies to put specific regulations into place and to organize healthcare pathways for these particular types of diseases. By showing how this appropriation of rarity as a new category in oncology lies at the intersection of both professional and nosographic principles, this article shows how precision medicine requires the production of new categories, which rest on an increased intertwining of biomedical, organizational and political aspects, thus requiring analyzing them as "boundary objects" in order to better understand their plasticity and characterize these new entanglements. Further analysis should wonder what are the implications of this multiplication of rare medical entities, which at some point will make rare conditions a common thing, by analyzing its political implications, such as the questioning of the traditional structures of evidence-based medicine, and showing how it can create new boundaries between patients, new identities, and potentially new inequalities.

Data availability statement

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

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication

of any potentially identifiable images or data included in this article.

Author contributions

HP: problematization, fieldwork, and writing. SB: coordination, editing, and reviewing. Both authors contributed to the article and approved the submitted version.

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Conflict of interest

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

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Precision public health in the making: examining the becoming of the "social" in a Swiss environmental health population-based cohort

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Expanding the concept of "precision" or "personalized" medicine, personalized health and precision public health designate the use of various kinds of data—genomic, other omics, clinical, or those produced by individuals themselves through self-tracking—to optimize health interventions benefiting the whole population. This paper draws on an ethnography of the implementation of a population-based environmental health cohort to shed light on the reconfigurations brought about by the "personalization" of public health in Switzerland. Combining human biomonitoring and molecular epidemiology, this cohort aims to advance the science of the exposome, a notion referring to the totality of exposures to which individuals are subjected over their lifecourse. Addressing the tension between holism and reductionism, this paper points to the important gap between the promissory horizon of the exposome and the realities of practices. Situations of reductionism are defined as moments of friction and negotiation between different rationales and values, exposing what makes the science of the exposome, including its material, economic, institutional, and methodological constraints, as well as its imaginaries and values. Rather than opposing holism and reductionism, I emphasize that they constitute two sides of the same coin, as they both pragmatically enable action and produce situated versions of the social. This empirical case shows how reductionism operates at the chemical, biological, and populational levels to produce public health scientific and social values. It thus contributes to contextualizing the pragmatic and strategic choices made by scientists, as well as the values they favor, in a research environment marked by the predominance of biomedicine over public health. It shows how the reductionism of the "social environment" was made for a better social integration of the cohort into the Swiss political and scientific landscape of public health. Bringing together actors involved in public health and questions of environmental exposures, this cohort can be interpreted as a biomedicalization of public health research, as well as an attempt to socialize it through the broad category of the exposome.

KEYWORDS

precision public health, exposome, biomedicalization, reductionism, holism, environment, cohort

1 Introduction

"*We need to measure exposure throughout the lifecourse, and exposure does not just mean if I smoke or I do not smoke, it also means where I live, what's my income, what are my social interactions, how do I feel, how polluted is it, what do I eat, can I do physical activity, do I have a bike path near my home, what is my mental health, what is my ability to resist stress at work, my financial room for maneuver? It's all this that influences health and we are interested in all of this. It's true that we have this holistic vision of the determinants of health, including socio-cultural determinants.*" Bright-eyed, this molecular epidemiologist is explaining to me what a framework of the exposome can bring to epidemiological research and public health. As she enthusiastically enumerates different kinds of "exposures" or "health determinants," I can feel the promissory potential of the exposome's holistic ambition. Not only to produce a more comprehensive understanding of what influences health over the lifecourse, but also to include what I, as an anthropologist, consider to be often overlooked: people's socio-cultural living environments. This paper draws on an ethnography of the implementation of a population cohort aiming to study the exposome, to ask how this holistic understanding of the "social" is translated into research practice.

The concept of the exposome emerged in the field of molecular epidemiology two decades ago, in the aftermath of the Human Genome Project (HGP) (Wild, 2005). Building on the limits of genomic approaches, it promises to "complement the genome" by integrating environmental, or non-genetic exposures, to understand the complex etiology of chronic diseases and causal pathways leading to ill-health. Transferring approaches from life and health sciences—especially sequencing techniques, biomarkers research, and exposure science (Canali, 2020)—it aims to go beyond the current limits of epidemiology and toxicology (Giroux et al., 2021). Unlike genetic material, which is stable and transmitted vertically over generations, the exposome is apprehended as dynamic, context-dependent, and evolving over an individual's lifetime. Three kinds of "environment" are distinguished in this field: the general external, the specific (individual) external, and the internal (Wild, 2012). The general external environment comprises health determinants as varied as the climate, socio-economic status, or urban surroundings. It has a systemic and global dimension, which makes it hardly modifiable, whereas the specific external one is more behavior-related and assumed to be modifiable by individuals (Sillé et al., 2020). In exposomics, the internal environment is supposed to reflect the imprinting of the external environment on an individual's biology. Facing the challenges of making low-dose multiple chronic forms of exposure visible, this field promises to reveal how the global environment "out there" is actually "within" us (Washburn, 2013; Creager, 2018). In this way, it becomes a "biosocial trace" (Müller et al., 2017; Chiapperino and Panese, 2021) or a "mediator between the naturalized worlds of the genome and the social world of illness and inequality," operating as an "open signifier, an object shaped by its relationship to the genome, which then gives the genome new life as significant to the social world of public health" (Whitmarsh, 2013, p. 490).

The exposome is part of a broader shift, called the postgenomic (Richardson and Stevens, 2015) or the biosocial turn (Meloni et al., 2018), observed in other fields of life, health, and population sciences. This includes, for example, epigenetics, microbiome research, and other studies investigating gene–environment interactions (Ackerman et al., 2016). Departing from gene-centrism, this field renews how body-environment relations are understood. Reconfiguring the knowledge of how the environment permeates human bodies, it gives rise to new technoscientific imaginaries of public health science and politics (Shostak, 2013). Notably, the prospect of a better understanding of environmental exposures generates new possibilities for interventions in public health. For example, "precision public health" (Khoury et al., 2016)—or, in Switzerland, "personalized health" (Meier-Abt, 2016)—aims to use technoscientific advances in sequencing techniques and data sciences to intervene at the population level and reinforce public health. Expanding the clinical and disease-oriented focus of genomic or precision medicine, their ambition is to "provid[e] the right intervention to the right population at the right time" (Khoury et al., 2016, p. 398), "to promote health, prevent diseases and reduce health disparities by focusing on modifiable morbidity and mortality" (Khoury et al., 2016, p. 398).

While it generates the hype of a new paradigm (Canali, 2020), the value of postgenomics for public health is also understood more critically. Reacting to the declaration that 2016 would be the "year of precision public health" by the head of the US Office of Genomics and Public Health and Center for Disease Control and Prevention (CDC), critical voices have pointed to the techno-optimistic hype surrounding big data and postgenomics, and recalled the fundamental differences between public health approaches—which focus on structural vulnerabilities and favor prevention and health promotion—and precision medicine—which focuses on diseases and prioritizes treatment for individual patients. They highlight the risk of conveying a biological-molecular understanding of vulnerabilities, molecularizing "complex social phenomena, reducing the social experiences that condition population-level variations in exposure to individual-level molecular-level differences" (Senier et al., 2017, p. 107), emphasizing especially the risks of promoting interventions targeting individuals, and diverting precious resources away from the wider public (Chowkwanyun et al., 2018).

The social sciences have also both welcomed these developments as an opportunity, and taken a critical stance. On the one hand, they see it as an acknowledgement that structural forces shaping health are directly linked to the genome, providing scientific "proof" that politics and socio-economics are embodied, and that "biologies" have always been "local" and "situated" (Landecker and Panofsky, 2013; Lock, 2018; Niewöhner and Lock, 2018; Gibbon and Pentecost, 2019). This environmental recognition also opens up new possibilities for innovative interdisciplinary engagements (Niewöhner, 2015; Canali and Leonelli, 2022). On the other hand, valorizing the permeability of the postgenomic body might obscure other forms of violence (Roberts, 2017), and the future-oriented dimension of datafying public health could be used to postpone action and avoid addressing the uncomfortable realities of the present (Hoeyer, 2019). More specifically, the exposomic approach is seen as promoting a technicist and individualized vision of health, leaving out critical social and political questioning about social inequalities (Guchet, 2019).

Pointing to the tension between the reductionism and holism at stake in exposomics, Giroux shows that the objective of finding biomarkers, even though they reflect the external environment, remains caught in a causalist and mechanistic model of health and disease (Giroux et al., 2021). In addition, whereas exposomics create interesting opportunities to recognize the impact of environment on

health, the main focus remains on the biological component of embodiment (Krieger, 1999), rather than the social. Giroux shows how, in fact, exposomics renews the historical tension between molecular and social epidemiology (Giroux, 2023), focusing, respectively, on how the internal environment of individual bodies react to exposures (Rappaport, 2011), and on the external environment's biomarkers of health, for example the allostatic load[1]—a biomarker of chronic stress exposure (Serviant-Fine et al., 2023) — and their role in chronic conditions' causal pathways, or, in other words, on "the biology of inequalities in health" (Senier et al., 2017; Vineis et al., 2020). In addition, Louvel and Soulier's (2022) review of literature on the social production of inequalities, using the concepts of "biological embedding" and "embodiment of social experiences," shows the important different meanings of the "social" in both approaches. Furthermore, the extent to which these are reconcilable is still debated (Yates-Doerr, 2020). If the exposome has holistic ambitions and aims to capture complexity, it also conveys a specific "technoscientific" form of holism and not a humanistic or experiential one, leading to what can be called "holistic medicalization," which assumes that "each person's whole dynamic life process is defined in biomedical, technoscientific terms as controllable and underlain a regime of control in terms of monitoring, quantification, prediction, risk profiling, early diagnosis, therapy, prevention and optimization that is all-encompassing" (Vogt et al., 2016, p. 310). In this way, these debates revive long-standing social sciences critiques of reductionism, essentialism, biologism, determinism and individualization, which have been present in technoscience and medicine since the early 1970s (Zola, 1972; Conrad, 1975). These critical insights are crucial in unfolding the promissory regime of exposomics and not taking its goals and assumptions for granted.

Still, the double-edged dimension of these critiques sheds light on the limits of critical narratives that have "run out of steam" (Latour, 2004), on the need to refine historical and epistemic genealogies of the "revival" of the environment in life, biomedical, and population sciences, and to examine how biological and social entanglements are produced in practice. What does the holistic "social" of the environment become in exposomics? To what extent is its complexity molecularized or reduced? Through which processes does reductionism operate, and with what effects? The need for a stable single referent is needed, for example, in mash-up studies bringing together data from different kinds and sources (Leonelli and Tempini, 2021). In other words, some situated forms of reductionism—or shrinking (Stengers and Isabelle, 2021)—are needed to grasp environmental exposures (Leonelli and Tempini, 2021). It is thus relevant to observe how, as data travel across levels, disciplinary cultures, and infrastructures, they retain some aspects of the social contexts they stem from Bauer (2008). Reductionism is not only produced through epistemic assumptions, scientific tools, and methods, but also through the politics and economics of scientific research. Accounting for how reductionism is made in practice, Pinel sheds light on the constraining logics of the entrepreneurial university, characterized by a market-driven institutional environment favoring a type of epigenetic research which is individualized and clinically centered (Pinel, 2022). In a similar way, Ackerman et al. (2016) show how the politics and moral economy of quantification lead to a shrinking of the environment in the interests of data standardization and harmonization. They especially highlight the pragmatic dimension of the scientists' choices, as they are "compelled to make trade-offs or exchanges between competing priorities and commitments" (Ackerman et al., 2016, p. 197) in the name of objectivity, to make epidemiology more robust scientifically. Penkler et al. also soundly document the discomfort of Developmental Origins of Health and Disease (DOHaD) researchers, who attempt to capture how environmental factors such as deprivation, nutrition, and stress shape individual and population health over the lifecourse (Penkler et al., 2022). While scientists are eager to develop more complex understandings of the environment in their daily practices, they are confronted with established methodological tools, disciplinary infrastructures, budgetary constraints and institutional contexts that favor a reductionist understanding of the environment and individualistic approaches toward health. Reconstructing the pragmatic decisions at stake in the production of knowledge, these authors shed light on the multiple trade-offs scientists face, which lead them to focus on particular factors and easily-accessible data, to produce results that are aligned with the academic publication market, and the need to secure third party funding. It is important to recall, though, that social scientists also reduce complexities and wide, comprehensive sets of data to render them graspable through enmeshments in greater narratives—which also involves selection processes and adopting certain writing styles (Clifford and Marcus, 2010).

Drawing on these insights, in this paper I discuss some of the processes through which the complexity of the social is reduced, and how this reductionism is made to achieve better social integration—in the sense of the recognition, legitimacy and interest of the multiple publics of the environmental public health cohort—in the scientific and policy landscape of Switzerland. More specifically, I explore the becoming of the social in building a population study, a cohort, adopting an exposomic conceptual framework to study the impact of environment on health in Switzerland. Like other postgenomic projects, this health study can be apprehended as a "biopolitical assemblage where samples, data, and techniques from different contexts are temporarily brought together in particular configurations" (Bauer, 2008, p. 418). My objective is to account for the gap I have discerned between the promissory potential of the exposome as illustrated in the quote in the introduction, and the shrinking of holism and complexity I have observed over time. I adopt an empirically informed stance to document how reductionism operates in practices, and what is produced through the different forms it takes. I focus on a specific phase of scientific research—implementing the pilot phase of this cohort. This comprised building the infrastructure for the cohort, that is, setting up a database and a biobank, as well as the data flows necessary for their connection, testing the various procedures, instruments, and work instructions, as well as producing

1 The term refers both to a concept and a subsequent measurement tool, put into use to identify the cumulative physiological impacts of environmental stressors on human health, and tentatively help explain the biological pathways by which social conditions are embodied. The concept is operationalized into a composite score assembling a changing set of biomarkers, which is then correlated with various established measures of social deprivation (Serviant-Fine et al., 2023).

preliminary biomonitoring and epidemiological results. Over the course of its implementation, the cohort's initial design was constantly reworked and negotiated. Thus, the implementation phase provides a relevant site in which to observe how the biological and the social entangle in precision public health "in the making." I will first describe the cohort's origin and the different versions of the environment that brought together the actors involved in this study. I will then analyze three situations of reductionism that I observed. Ultimately, this paper contributes to contextualizing the pragmatic and strategic choices made by scientists, as well as the values (Dussauge et al., 2015) they favor, in a research environment marked by the predominance of biomedicine over public health, to show how reductionism was used to promote the cohort's social integration into the Swiss political and scientific landscape of public health.

2 Methods

This paper is based on a research project funded by the Swiss National Science Foundation in the framework of a Sinergia project: "Development of Personalized Health in Switzerland: Social Sciences Perspectives" (University of Lausanne, Institute of Social Sciences). My socio-anthropological sub-project adopted an empirical stance to explore environment-health relations and the making of "permeable bodies," and to analyze the reconfigurations of public health research when it turns to "precision" or "personalized" approaches. I conducted an ethnography of implementing the pilot phase of a longitudinal population-based cohort which aimed to study the impact of environment on health. I made regular observations over the course of 4 years (2018–2022) by attending operational meetings,[2] studying health examinations, visiting the biobank, and going to related events and conferences. In addition to ethnographic observations and informal discussions throughout the project, I conducted individual semi-structured interviews with members of: (a) the research team (5 from IT and biobanking, 6 with a public health scientific background, 3 with nursing knowledge, and 4 with public health policy expertise, $n = 18$); (b) external public health and biomedical experts and stakeholders ($n = 3$); and (c) cohort participants ($n = 14$). I collated a corpus of: (a) scientific and medical articles on public health genomics, human biomonitoring, exposomics, toxicogenomics, personalized health and public health; and (b) media articles referring to the environmental population cohort under study. Having adopted an engaged anthropology position, I also established a collaboration with the research team to develop a participatory approach. For this, we organized seven online focus groups reuniting 37 cohort participants (Bühler et al., 2023). In this paper, I draw mainly on my observations and interviews with the research team.

3 The "environmental" origins of the cohort

In 2008, concerned by the lack of knowledge about the impact of chemical exposures on health, a Green Liberal parliamentarian submitted a postulate asking the Swiss Federal Council to develop an assessment tool (Moser 08.3223), which was followed by similar postulates (FOPH, 2023). The Federal Council agreed to address this proposal and mandated an evaluation of existing biomonitoring data and projects. After identifying the important gaps that persist in the country concerning chemical assessment, the pilot phase of a human biomonitoring cohort was launched. This was in line with the national Health Strategy 2020's declaration that it is important to use biomonitoring to improve the quality of life, and with the government's legal requirements to regulate chemical products and surveil the population's health. Molecular epidemiologists joined the project, aiming to advance exposome science by expanding the scope of biomonitoring to enable the collection of large sets of health data and biological samples. Through developing a prospective, longitudinal population-based health cohort, the initial focus on chemical exposure was extended to the broad domain of health, and renamed from a biomonitoring study to a health study. This setting brought together several groups of actors: (a) molecular epidemiologists, public health physicians and exposure scientists working in public health academic institutions and conducting research; (b) public health officers in charge of regulating chemical products; (c) IT and biobanking experts responsible for developing the infrastructure necessary to manage biological samples and health-related data; and (d) citizens, especially those selected as cohort participants. I refer to cohort participants as *cohortees*, and to the team of experts implementing the cohort, as *cohorters*.

The pilot phase of this health study ran from 2017 to 2022, produced a report that was approved by the Federal Council in June 2023, and showed the feasibility of a general population cohort at the national level. Two public health centers were involved, one in the German-speaking part and the other in the French-speaking part of Switzerland. Both aimed to recruit 500 residents, aged between 20 and 69, from their respective cantons[3]. The cohortees were randomly selected by the Federal Office of Statistics and received an official letter from the Federal Office of Public Health asking them to participate. They could then provide consent, and access several questionnaires to fill in on an online platform. Once those were completed, they were invited to a clinical research center where they underwent several health examinations, answered additional questionnaires on exposure and health status, and had anthropometric measures taken. During the visit, blood and urine samples were also collected. Some biosamples were analyzed directly, whereas others were prepared for biobanking and then sent to the cohort's central biobank. The chemical products analyzed in the study were heavy metals, glyphosate, and Per-and polyfluorinated Substances (PFAS). Cohortees were also asked if they would like to use an app to record their meals for 2 weeks and wear a portable device—an accelerometer—to record data about their physical activity.

2 Operational meetings reunite the cohorters in charge of elaborating and implementing the technical procedures and work instructions necessary to build the cohort infrastructure, that is, all the steps necessary to recruit participants, obtain ethical approval, collect data and samples, establish data flows and biobanks.

3 Switzerland is a federal country composed of 26 cantons, the federated states. Each has its own constitution, parliament, and government.

The impact of environment on health was a common concern that brought these actors to work together to develop the pilot cohort. Environment was a concern for some citizens,[4] who worry about the health impact of living in a polluted, industrialized world, and the extent to which chemicals permeate their bodies and affect them in negative ways. Environment was a concern for public health representatives who are legally responsible for protecting the population's health from chemicals. The pilot evaluation report showed that Switzerland lacks the evidence needed for an efficient state apparatus that regulates chemical products and assesses their risks. Environment was also a concern for molecular epidemiologists wanting to advance exposomic research. The prospect of building a longitudinal population-based cohort to investigate a great variety of forms of exposure in the general population, related to chemicals, but also to the built environment, nutrition, lifestyle and quality of life, provided a much-needed opportunity not only to evaluate the level of exposure (as in human biomonitoring), but also to "open the black box of the body" and understand how the environment affects health over the long term. Different realities of the environment relating to policy, science, and society thus constituted a common matter of concern, bringing together the actors implementing the cohort into a setting that was valued as suitable for responding to their needs and expectations. In addition, in the exposome's conceptual framework, the environment can be understood as the external environment—social and individual—and the internal one—biological—all three being entangled. In the next sections I look at three situations of reductionism encountered in this cohort, which each represent different versions of the "social" environment and the way it relates to its biological counterpart.

4 Results

4.1 The substances of chemical exposures

A dozen people sit in a room, in the facilities of the Federal Office of Public Health (FOPH), looking at the slides projected on a screen. The room is small and I take notes on my lap as there is not enough space for us all to sit around the table. The goal of today's operational meeting is to decide what kinds of chemical substances will be included in the study's design. One of the team's junior scientists, who has done some research to evaluate the costs and feasibility of chemical analyses, presents her results. I am impressed by the long list of substances appearing on the Excel spreadsheet and feel a kind of excitement at the idea that the study would account for the complexity of multiple forms of chemical exposures, if they were all included. However, it quickly becomes clear in the discussion that drastic choices will need to be made. The budget is tight, tubes are expensive, analyses are expensive, lab work is expensive. As the discussion goes on, the initial list shrinks more and more, until it finally includes only a little selection of substances. The discussion ends with the decision to get more information and discuss directly with the lab the price of the tubes and analyses.

This discussion illustrates how the complexity of the exposome and its ambition to capture a broad range of different exposures over time was reduced in respect to the number of chemicals studied. How did this reduction operate and how was this preliminary selection of chemicals made? Should substances be selected for their scientific interest and potential scientific value? To fill the knowledge gaps encountered by policy-makers in the context of risk regulation? Or to respond to the concerns of the citizens who alerted the government to their responsibilities in the first place? Scientific, policy, or social values were entangled in this situation of selecting which substances to analyze, but reducing their number meant that actors had to prioritize some over others. What emerged first in this situation was the evident financial gap between the cohort's limited means and the price of the analyses needed to advance exposomic science. To reach the ideal of the exposome goal, a large amount of data and biological samples is needed. Quantity, including a very large sample size, is required to detect significant small differences and determine causal relations of ill-health, especially as exposures are chronic and low. The same is valid if one aims to understand how multiple forms of exposure interact and possibly potentialize each other, in what is called the cocktail effect. For this, a long-term approach is necessary, as a senior molecular epidemiologist explained:

> *The distribution of chemicals is one thing, but many chemical effects are not understood, so you need to follow up on these people, especially mixture effects like low dose interactions between chemicals, for that you need to cohort with biobanks (molecular epidemiologist).*

However, high quality data and samples are also needed to capture the complexity of chronic low-dose exposure to multiple forms of chemicals, as one of the cohorters expressed:

> *Given that we are exposed to multiple substances, and that the effects are sometimes very weak, and sometimes unknown also, we need a great number of top quality samples to be sure that the variations we observe are not due to another factor (public health officer).*

Omics analyses, such as metabolomics and proteomics, are highly sensitive to their immediate environment, so great care must be taken to maintain the quality of each sample. Quality refers here to controlling the parameters which may impact the samples, and tracking the samples from the health examination room where blood is drawn to the centralized biobank in another city where they are stored, including their passage via a preanalytical lab where plasma is separated through centrifugation and the blood samples are aliquoted. When debating which substances to include, the materiality of the blood or urine tubes was also discussed. Depending on the tube's materiality, the biological substance within—e.g., blood—can be contaminated, rendering it difficult to determine whether exposure has come from the tube or from the external environment, thus possibly biasing the analyses' results and rendering the cohorters' work worthless.

Financial constraints and limited resources mean that some pragmatic and strategic choices need to be made. Trade-off situations

4 Environmental concerns were only one of the motivations to participate in this cohort (see Bühler et al., 2023).

such as the one described above are commonplace in scientific research practices. It is part of scientific work to have to adjust a project's ambitions of what should or could ideally be done from a scientific perspective to match realities on the ground, such as financial limits and the materialities at stake. But, beyond this ordinary aspect, the responses given, the choices made, and the form of these trade-offs can teach us a lot about how reductionism operates, and the different enacted values attached to the versions of the "social." In this case, when confronted with the choice of prioritizing some substances over others, the cohorters decided to select those which are of concern to the population: glyphosate for example, a chemical present in pesticides whose effects on health in Switzerland, as in other countries, are highly controversial (Adams, 2023); but also mercury, which is a chemical of concern for both the population and the regulators, since an industrial leak occurred in the canton of Valais, and there is a lack of threshold exposure values in the Swiss population (Parvex, 2014; Lambiel, 2017). Public health value was thus prioritized over the scientific one, in the sense of doing analyses which are relevant in the Swiss context, rather than favoring analyses which have great potential to be published in high-ranked academic journals. The value of public health was also visible in that the cohorters were responding to the population's demand. By deciding to select substances that are debated socially and for which there is a high demand for scientific evidence, the cohorters' objective was not only to meet the legal obligations for chemical regulation, but also to increase the interest of the population, who were envisioned as potential participants and beneficiaries of environmental health policies.

Several practical strategies were adopted to balance the need for high quantity and quality within financial limits. First, most omics analyses were postponed for later. This postponement strategy enabled the cohorters to reach maximal quality from a scientific point of view, within their financial limits in the present, as a guarantee of good analyses in the future, when other sources of funding might be available, or other teams and other projects could take over. Rather than cumulating the quantity of substances to analyze, they prioritized the quality necessary for exposomic analyses. The exposome's holistic ambitions and chemical complexity were thus reduced for the sake of future scientific value. Another strategy consisted of making alliances with other teams which were interested in a specific substance, and could fund the analyses. "*We know more about water and soils than about human health in this country.*" This remark, heard several times during my fieldwork, expressed cohorters' frustration concerning the lack of a large and comprehensive database about many kinds of exposure, and reflected the siloed distribution of monitoring responsibilities among the federal offices—one in charge of agriculture and food control, another in charge of surveilling water and soil, and a third in charge of chemical products used by humans. This institutional fragmentation of evaluating the presence of chemicals in humans, consumer products, and the environment is at odds with the comprehensive goal of the exposome and points to one of the institutional constraints the team met. To mediate this fragmentation, but also to increase the number of substances included in the analyses despite the cost, they established collaboration with several other federal offices and sub-projects focusing on more specific questions, for example, relating to nutrition and the substance of cadmium. Therefore, substances were added depending on the contextual interest and ability to fund analyses by parallel teams, with which specific agreements were made.

Looking at how reductionism operates indicates two important elements. First, it reveals the lack of public investment and the difficulties of obtaining sufficient funding for public health, especially cohort studies, in a country where there is no centralized database of exposures: data which could potentially be included to advance exposome science. In total, 68 million Swiss Francs (CHF) of public money were invested in the Swiss Personalized Health Network (SPHN)—launched in 2016 to develop the infrastructure necessary to enable the nationwide use and secure exchange of health data for research. For the cohort discussed in this paper, funding came from various sources, added over time, eventually reaching a total of about 3 million CHF (plus in-kind contributions from the scientific institutions) which, in comparison, shows lower public investment. While cohorters embraced the development of the pilot cohort as a way of advancing population-based research and environmental public health, in contrast with hospital-based molecular-focused projects such as those funded by the SPHN, the difficulties and reductionist choices they had to make reveals the challenge of reconciling the technoscience of the exposome with national goals to protect the population's health in a country characterized by a historical weakness in this domain[5] (Monod, 2022; Thieme et al., 2022). The financial difficulties encountered over the course of the project, balanced with efforts to increase its social integration, uncover in the background the high financial and human costs of implementing such a longitudinal population-based study, which are at odds with the lack of government investment in public health research.

4.2 The biology of social exposures

> *The biggest user of Roundup[6] in Switzerland is the national railroad company, because they weed their tracks with it. So if, all of a sudden, we could show that in Switzerland this makes a difference … also we are going to ask questions about mobility. If we realize that there's a link between people who take the train and the quantity of Roundup, I can imagine that a fairly easy public health measure would be to say, well, stop using Roundup to weed train tracks, you've got to change, you've got to switch, no matter what the Monsanto lobby says, change now![7]*

5 The Swiss health system is highly biomedicalized, individualized, and privatized. It has been described as "highly complex, combining aspects of managed competition and corporatism (the integration of interest groups in the policy process) in a decentralized regulatory framework shaped by the influences of direct democracy" (De Pietro et al., 2015). Health insurance schemes reimburse mostly medical treatments and not prevention and health promotion programs. Those are also mostly geared toward individual responsibility, rather than promoting population or structural measures. Thieme et al. (2022) also show how processes of economic rationalization, bureaucratization, and digitalization frame the Swiss healthcare system.

6 Roundup is the name of a herbicide containing glyphosate, initially commercialized by the firm Monsanto, then purchased by Bayer, a German pharmaceutical and agrochemical firm.

7 This interview was done at the beginning of the study. The study results show that cohortees' urine levels of glyphosate are far from any threshold of concern.

> *Interviewer: You mean measures that wouldn't target individuals as such, but that would make it possible to act to improve the population's health by intervening on the national railroads?*
>
> *Yes, a structural measure! I'm very fond of structural measures because they're the simplest. For individuals it's the simplest, well here we've put fluoride in your water and it protects you from cavities and you're not even aware of it and you don't even have to say, "ah those public health doctors who prevent me from doing this or that"… So I like structural measures, you're starting to know me. To improve walkability in the city or certain neighborhoods, we could imagine something very simple. If we realize that in more or less disadvantaged neighborhoods we find that people do less physical activity because they don't have the time, because in terms of health knowledge, it's not enough, well we could imagine putting in place urban planning or measures like that to improve physical activity without them even realizing it! (molecular epidemiologist).*

The enthusiasm of this molecular epidemiologist was contagious, and I remember being hooked by the promise of a science that would eventually reinforce so-called structural public health measures, intervening in the environmental sources of ill-health, rather than targeting individuals and making them responsible for their own wellbeing. In this cohorter's narrative, these measures were associated with simplicity, freedom, and a lack of the moral judgment that often accompanies interventions aimed at individual behaviors. Instead of blaming or stigmatizing people for their lack of physical activity, the epidemiologist preferred measures targeting their living environment. Nevertheless, the ideal of structural measures defended here appeared to me at odds with the great expectations for biomarkers this scientist expressed later in the interview. The cohort's potential to identify biomarkers, and the ability to improve scientific understanding of how the classical social determinants of health might cause ill-health, by "un-black boxing" the body to evaluate and improve public health interventions was palpable in many of the discussions I had with cohorters. Their hope that the 'social determinants' credibility and legitimacy would be strengthened, if they could prove the biological impact of social exposures by identifying biomarkers, was especially striking, as the following quote illustrates:

> *If we can show that being poor for forty years leads to different biomarker profiles, like cytokines levels—because we have this tendency to only believe biological facts—it will help people to understand that poverty is not some esoteric concept, that it has a biological correlate (molecular epidemiologist).*

This quote illuminates how public health scientists invest in exposomic science because of the biologization or molecularization of the social it brings. The idea of finding biomarkers, or biological signatures of the social which inform about the molecular pathways leading to chronic conditions, is invested with much promissory potential concerning the possible public health measures deriving from such a study. Molecular reductionism in this sense is searched for, as a condition of the possibility to be taken seriously by health authorities and to make a difference in public health interventions. The exposomic ideal is not only about understanding the causal molecular pathways of disease, but also about finding actionable knowledge to address or prevent it. Finding causes is deeply entangled with the possibility of interventions. However, the molecular signature of the social and the possibility of intervening structurally become almost interchangeable in cohorters' discourses around biological reductionism, a strategic passage point, as the following quote illustrates:

> *I think the biggest opportunity of these biomarkers and, by data, I mean all mixed markers and imagery markers, is that we can investigate mechanisms between lifestyle and environment to disease development so we can look into the biology on the pathway from these risks to a health effect, and we know that one of the important factors of causal understanding is understanding biology. To me, it is the biggest tool of preventive research and that's what exposome research is about (molecular epidemiologist).*

These quotes illustrate well the predominance of a biological regime of proof. A molecular understanding of ill-health is envisioned as being both the most solid scientifically, able to produce more robust evidence of the impact of social determinants of health, but also as being more actionable, as biomarkers might be used to develop evidence-based public health interventions.

What is the social correlate of these biological traces? How are poverty, living environment, walkability or use of public transport translated into the scientific idiom of the cohort study? Discussions about which variables and questionnaires to include provide another situation of reductionism. The exposome's holistic ambitions were reduced, not only through the predominance of biology's capacity to translate the social determinants of health into biomarkers, but also in the social elements which were covered. In the cohort, two questionnaires aimed to document different situations of exposure, and included the channels through which chemicals might permeate bodies. In addition, there were questionnaires on participants' quality of life, nutrition, medical history, and general state of health. Using an app to record their physical activity and photograph meals was also proposed to cohortees. Due to the biomonitoring origin of the cohort in regard to the FOPH's legal mission to monitor exposure, and its focus on the chemical environment, exposure questionnaires were more detailed than those on socio-economic health determinants. However, the idea was to be able to characterize cohortees' socio-economic backgrounds by recording their history of occupational activities and the nutrition questionnaire, and possibly to understand how far these were related to their health.

Reductionism operated in different ways here. Exposure was understood as contact with a substance and the identification of the parts of the body, or activity that could lead to it. To determine targetable causes, there was a need to offer distinct variables that cohortees could select in questionnaires. Situations of exposure were predefined and some specific practices used as a proxy for how much a person was exposed to a substance: for example, how many times in the last few days someone may have held a grocery store receipt, which might contain the endocrine disruptor bisphenol, or how often they encountered difficulties making ends meet, as a proxy of precariousness. In addition, for data to be recognized scientifically and be comparable with other similar studies or combined with other datasets to possibly increase the quantity of data in the longer term, the questionnaires needed to be validated. This meant that they had

already been developed and validated in other studies. Thus, the need for scientific standardization limited the possibility of asking more detailed questions about multiple and dynamic forms of exposure, how those might change over time and how they are situated in a broader socio-cultural context and in interactions. Thus, standardization and interoperability informed the prospective design chosen. It implied that the goal was to collect as much data and samples as possible, with the idea that, in the longer term, the cohort could be scaled up to the whole Swiss population, and datasets and biobanks used in comparison or in combination with others. This reductionism operating in the name of future science and interventions clearly illustrates the methodological challenge of shifting from epidemiology to an exposomic data-driven approach, and the ways that harmonization and standardization principles at the core of personalized health initiatives shape the becoming of the social in such a cohort. While the social context of exposure, as well as social health determinants such as poverty are in a way reduced through their datafication, the greater value granted to biomarkers due to their ability to be used in interventions can be read as a means to make public health better recognized and more robust scientifically. Moreover, favoring standardization is also a condition of increasing the possibility for data and samples to circulate and gain increased scientific value in other studies. By not focusing on a specific disease or hypothesis, and taking a prospective approach to health which aims to collect as much data as possible, the goal is to keep the possibility of discovering key health determinants or biomarkers open. It is thus regarded as a way of reinforcing scientific prevention and health promotion in the future.

4.3 Recruitment and the stratification of exposures

The need to have Swiss data about environmental exposures was one of the main reasons given to justify setting up the cohort. Exposure was thought of as being mediated locally, and the goal was to identify groups of the population who might be more at risk, to develop public health strategies that are more stratified, in the sense of differentiated and sensitive to the geographical and socio-cultural context of individuals' lives, as the following quotes illustrate:

> *If you live in Valais where la Lonza dumped mercury into the "Grossgrundkanal" for 40 years, if you grow your carrots there it's not the same as if you grow them in Schaffhausen. The exposure of people in Geneva is not the same as that of people in Grisons (public health officer).*

> *We might end up with usual lifestyle recommendations, however, what's new is the innovative potential to characterize the situation in Switzerland, and identify groups of the population—geographical areas, age categories, things like that—which are much more at risk than previously thought, or which are under the radar because, in the end, we don't have much data on the whole population, on what happens at the neighborhood level (molecular epidemiologist).*

To this end, a prospective design was chosen. People residing in Switzerland, aged between 20 and 69, were randomly selected by the Federal Office of Statistics and then invited by letter to log in online, where they could give their consent and start filling in questionnaires. There was no specific stratification of the population in advance; the idea was that the random selection ensured that the cohort was representative of the population in the pilot cantons. The randomly selected cohort works as a reduction tool that enables researchers to translate the diversity of the general population's characteristics and specificities. In addition, this recruitment method is considered to be the "gold standard" of epidemiology, as the best design to maximize external validity and thus the findings' generalizability:

> *Prospective design is ideal [from a scientific perspective] because it allows us to avoid the risk that our results may be biased. When you do a retrospective study, you have a lot of selection bias: maybe some of the people you could have taken on as controls are dead, so you are not really comparing everyone if they are not there. But if it is prospective, you choose people randomly from the start, and you follow them over time, then it is potentially representative (molecular epidemiologist).*

To be able to differentiate significative differences between the overall population and "at risk" groups, a great quantity of data must be collected. The more precision that is wanted, in the sense of local and specific, the larger the cohort population needs to be. But it is challenging to recruit and retain people to cohort studies over a long time (Marques et al., 2020). Recruitment and participation rates therefore constituted a major concern for cohorters. During the operational meetings I attended, the choice of the best recruitment strategy was discussed several times. Alternative ways of recruitment, such as mobilizing general practitioners or distributing flyers in pharmacies were debated for example, in the hope that this might increase participation. This would have involved collaborating with healthcare professionals in frontline contact with the population. In an informal discussion with cohorters, the idea that anyone residing in Switzerland could participate if willing, thereby transforming the whole Swiss population into a data reservoir, was also imagined. In all scenarios, logics of exclusion and inclusion were present. Some in the team were more in favor of opening up possibilities of recruitment to increase participation rates—enough quantity to enable a significant stratification of results—while others maintained the importance of random selection as the most robust scientific approach. Randomly selecting the cohortees was preferred for scientific reasons, but a convenience sample based on distributing flyers in strategic places and informing people by word-of-mouth was also tested in a subgroup of the cohort: the vegan and vegetarian individuals. The random selection of a population sample was considered a better option in the sense that it allowed more control for the scientists involved, by enabling them to monitor the recruitment parameters: who was contacted, who gave informed consent, who dropped out. In contrast, relying on word-of-mouth and recruiting people based on their affinities and concerns would reduce cohorters' control, thereby becoming weaker according to scientific criteria. In the latter case, the loss of control might be remediated by the quantity of data, which is more aligned with data-driven approaches. However, opting for scientific robustness by controlling the cohort parameters also related to the prospect of producing better publications based on the results, and thus a better scientific valorization of the work performed in the pilot phase of the study.

To address the challenge of participation, specific efforts were made from early on to understand cohortees' motivations, expectations, and obstacles to participation, in the belief that understanding them could facilitate and increase their participation in the long term. Cohorters tried to balance their scientific need for a large quantity of data with the amount of clinical labor (Mitchell and Waldby, 2010) that could be expected from cohortees:

> *The difficulty is measurement error. None of the tools we have available is perfect. There are measurement errors in all the tools. The challenge is how to do this measurement without it being too much of a burden? We can't send out a 300-question questionnaire to people every week. I mean, after a while, they just get bored. Then there's the photo app [for food], it is interesting to test other models, but taking photos of everything you eat, it lasts a few days but not much more, because you eat every day! You eat several times a day! So how do you find the right balance between capturing the right exposure, measuring it properly, and not, how can I put it… exhaust people? (molecular epidemiologist).*

> *Of course, we can't collect everything either, and it's not our goal to have people wearing sensors 24 hours a day or whatever, but the idea is to have a panel of data that will allow you to start something (public health officer).*

To address this challenge, they developed a questionnaire on attitudes toward research and willingness to participate, and implemented a public involvement initiative with several focus groups. While this was done to increase participation, and thus data collection, it also revealed how cohorters felt about the social integration of the cohort in the population. At the end of the pilot study, the overall participation rates reached 14% (Bourqui et al., 2023), which is similar to those of other cohort studies (Kuss et al., 2022). It also became clear that those participants who were possibly more exposed, due to their poorer socio-economic living environment, were less included and harder to reach through the means of recruitment used in the cohort. Instead of "precision" in the stratification of exposure, the results were valorized as representing the "normality" of the general population, constituting a good basis for comparisons with more at-risk groups, which could be targeted later.

The discussions and choices made around recruitment strategies can be interpreted as another situated form of reductionism of the social, as only a small part of the population was initially selected, and tendentially more socio-economically privileged, more feminine and older people (Bourqui et al., 2023) actually participated, so constitute the representative sample of the population. While attempting to shift epidemiology toward big data and exposomics, this example illustrates how the standard of random selection constraints informed and oriented the trade-offs made by the cohorters. If the results far from provide a biological signature of how poverty shapes environmental exposures, as the cohorters had first envisioned when talking about the exposome, the choices made also reveal what they care for most: the cohort itself and building the infrastructure. In this sense, this reductionism is productive, as it reveals how the social valorization and the scientific value of the cohort combined to pragmatically pave the way to advance such public health cohort studies in Switzerland.

5 Discussion and concluding remarks

In the social sciences of medicine and health, reductionism has been used to criticize the biologization, molecularization, or genetization of complex social phenomenon, such as the embodied experience of ill-health and the multiple enactments of health, illness and healing processes. The complexity of how power, economics, the living environment, interactions, institutions, biomedical knowledge, technologies, or metrics shape health and permeate bodies over the lifecourse gets lost in translating the social into a causalist mechanistic model of health (Yates-Doerr, 2020). Postgenomic approaches renew the understanding of biosocial entanglements, allowing revisiting the tension between holism and reductionism. Do they represent new forms of holistic medicalization, of technoscientific holism (Vogt et al., 2016), or do they open up possibilities for renewing interdisciplinary dialogue and co-laboration (Landecker and Panofsky, 2013; Niewöhner, 2015)? In this paper, I have addressed this question through an ethnographic exploration of an exposomic Swiss cohort in the making. I have approached reductionism as enacted in practice, to understand how it operates in the domain of the exposome, which aims to capture the complexity of multiple exposures throughout the lifecourse, and to bring together technoscientific advancements with public health objectives and agendas.

Examining the tension between holism and reductionism, this analysis has pointed to the important gap between the exposome's promissory horizon adopted by the cohorters in my fieldwork and the realities of research practice. While the exposome is a notion conveying a holistic and comprehensive understanding of the health determinants and forms of exposure affecting individuals over their lifetime, in the realities of research in the field, different forms of reductionism of the social environment can be observed at the: (1) chemical, (2) biological, and (3) population level. In each situation pragmatic compromises and strategic choices needed to be made, and some values emerged as more important than others. In the first situation described above, the limited number of chemicals chosen illustrates the lack of funding for precision public health research, as well as the prioritization of samples' scientific quality and the public health value of the substances analyzed. The second situation illustrates the predominance of the biological signature of the social environment used to develop evidence-based public health interventions, as well as the power of standardization and harmonization imperatives in reducing the social milieu, at stake when epidemiology shifts toward exposomic science. The strategic choices made in the present aim to reinforce the scientific value of the cohort, to be scaled up in the future. Finally, the third situation analyzed shows well the difficulties of reconciling epidemiological methods of constituting a "population" with the data-driven, more open-ended approach of the exposome. Debates about recruitment strategies reveal a tension between prioritizing the *quantity* of data and sample collections, and their *quality*, enabled by optimum control over certain parameters of the cohort's population. While it illustrates random selection's limitations in representing population diversity, and reflects the social stratification of exposures, it also sheds light on cohorters' concern for social recognition of the cohort in the Swiss population and the burden of clinical labor in such a cohort. The three situations account for difficulty in shifting epidemiology toward the technoscientific approach of the exposome in a country characterized by the predominance of biomedicine over public health approaches. While a form of technoscientific holism underlies the whole project

and shapes many of the choices made in the present, in practice the analysis also makes clear that this scientific ideal is far from achieved and that public health utility, as well as population concerns, are also taken into account. In fact, these situations expose attempts to improve the social integration of the study into the Swiss scientific, political and social landscape.

Reduction and reductionism have various meanings, whether in painting, surgery, philosophy, or geometry. Common to all these definitions is the point that reductionism is an operation consisting of translating a whole, an entity, an object, a phenomenon, into something that retains some of its initial characteristics, but also implies a loss of quality, a shrinking, as its negative connotation makes clear. In the context of the exposome, it refers to the reduction of social conditions determining health to differences observed at the molecular level, and to the individualist and causalist explanatory framework of disease origins (Giroux, 2023). Reductionism is inherent to scientific practice. In social sciences and qualitative research, we also reduce the complexity of the realities we observe. We select certain elements over others, as I have for this paper. From this analysis it follows that reducing also involves a condensation, a keeping of what are considered the essential characteristics of the original. I suggest looking at situations of reductionism as moments of friction, trade-offs, and negotiation between different rationales and values, but also as moments of condensation which expose what is important in a specific context. I argue that these situations of reductionism can be understood as exposures of the "research environment" (Pinel, 2022) and exposures of what these scientists "care for" (Penkler, 2022). In the Swiss context of public health research, these situations of reductionism expose what makes the science of the exposome, its material, economic, and methodological constraints, as well as its imaginaries and values.

Rather than opposing holism and reductionism, I would insist on their indissociability in this conclusion, as they constitute two sides of the same coin. The situations I have described here are moments where I felt both enthusiasm and sympathy for what cohorters were aiming to build, and disappointment at the depoliticizing shrinking of the social environment I observed. These situations of reductionism are productive in the sense that they expose what cohorters work toward and care for in the present, and in the long term. They are productive in the present, not in actualizing an exposomic understanding of health, which is postponed to the future, but in bringing together various actors who are interested in public health and environmental health and are willing to place the question of environmental health on the government's agenda. Working to build a national cohort and infrastructure that is scientifically solid can be interpreted as a way of reinforcing public health in a country characterized by the predominance of biomedical actors and institutions. Thus, this cohort can be viewed as a biomedicalization of public health research, as well as an attempt to socialize it through the broad category of the exposome, which leaves enough room to cover multiple understandings of the environment. Different scientific and political agendas can cohabit, but this also obscures their conflicting dimensions and political implications in terms of public health interventions over the long term. Those are postponed to an indefinite future, with the risk of neglecting the problematic issues of the present (Hoeyer, 2019). In the present, situations of reductionism expose rather the intricacies of the research environment in public health and cohorters' work for the cohort's scientific and social integration. Finally, insisting on the indissociability of holism and reductionism in exposomic research brings attention to what was left out but was nevertheless there (Jerak-Zuiderent, 2015). Some holistic forms of the "social" cannot become, in the causalist, determinist, biological regime of proof prevailing in public health research, in the imperative for data standardization and harmonization, in the pressure to publish from the "entrepreneurial university" (Pinel, 2022), in the challenges of recruiting the population. Reductionism is thus not only enacted in multiple ways, but is also a way of exposing the conditions of possibility for some versions of the social environment to become.

Data availability statement

The datasets presented in this article are not readily available because ethnographic data collected in this study are not sharable. Requests to access the datasets should be directed to nolwenn.buhler@unil.ch.

Ethics statement

The studies involving human participants were reviewed and approved by CER-VD Req-2019-01305. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Informed oral consent was obtained at the beginning of each interview.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Conflict of interest

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

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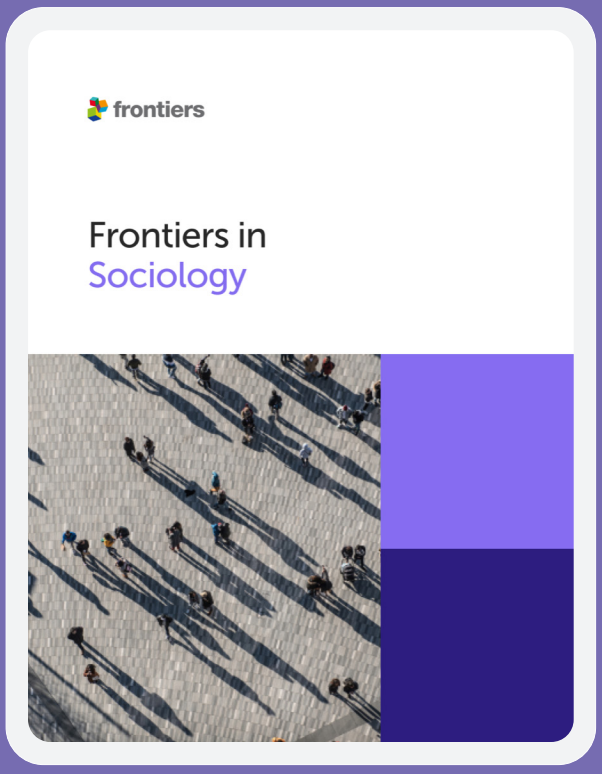

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