Personalized Genomic Medicine in The Netherlands

An exploratory study of stakeholder friction in the innovation ecosystem and human behavior

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Award date:
2024

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An exploratory study of stakeholder friction in the innovation ecosystem and human behavior

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A thesis submitted for the degree of

Master of Science

Eindhoven, June 2024

Key words: Genomic medicine, ecosystem, stakeholder friction, attitude-behavior gap, ethics.

Preface

In mid-2012, Jennifer Doudna and Emmanuelle Charpentier published their now famous paper in which they described the CRISPR/Cas9 system, a system by which a protein can be programmed to elicit changes in DNA with extremely high precision (Jinek et al., 2012). This method proved so trivial in its use that editing human DNA became more accessible than ever before. Subsequently, at a conference in 2018, the Chinese doctor He Jiankui claimed that he had employed the CRISPR system to make hereditable changes to embryos out of which two, later three, children were born (Greely, 2019). The experiment, which was followed by accusations of irresponsible actions and ethics violations, was aimed at providing these children with increased resistance against the HIV virus. He's actions prompted a large group of scientists, Charpentier included, to call for a global moratorium on heritable genome editing in an article in *Nature* (Lander et al., 2019). Doudna and Charpentier would go on to receive a Nobel Prize in chemistry for their work in 2020, whilst Dr. He is reportedly held in a Chinese prison (The Royal Swedish Academy of Sciences, 2020; Cyranoski, 2020).

These two examples are not the beginning of this story, nor are they the end, nor does singling them out do justice to the decades, even centuries of work (e.g. the works of Wallace and Darwin) that has been done in the field that can now best be described as *genomics*. What they are, however, are examples of events that made the immanency and inevitability of the genetic future more explicit and more widely recognized than ever before. Although the subject of genomics might not be immediately captivating for most, oft used buzzwords such as *designer babies* and revived fears of *eugenics* have made the subject more relatable to the masses (Steinbock, 2008). Speculations about what the genetic future could look like are also nothing new. Aldous Huxley's famous 1932 dystopian social science fiction novel *Brave New World*, although not directly touching upon genomics, covers the implications of a world in which humans are engineered into an intelligence-based social hierarchy (Huxley, 1932). Much later, in 1997, the film *Gattaca* is much more explicit in its references to genomics and explores a society which is defined by its focus on eugenic practices (Niccol, 1997).

Referencing the work of Doudna & Charpentier, He Jiankui, Huxley, and Niccol has become common in publications relating to the genetic future. In addition to the scientific relevance of the former two, these works are highly significant in terms of their cultural relevance in hinting at what our genetic future could look like. In recent years, this future is more and more

becoming the present, and many agree that what the human species is experiencing today is a veritable "*genetic revolution"* (Metzl & Martin, 2019, p. 5).

Although definitions do vary, this genomics revolution is generally perceived as a convergence of several (exponential) trends; an exponential increase in compute power, creation of big-data infrastructure and emergence of artificial intelligence capabilities for the analysis of this data, an exponential decrease in genome sequencing costs, radical breakthroughs in bio-tech tools (e.g. CRISPR-Cas9), massive proliferation of knowledge and capacity (enabled by a scientific community that is more connected than ever before), and lastly cultural changes with respect to the attitudes people hold, and the behaviors they exhibit, regarding medical technologies.

The amount of potential offered by the genomics revolution is not easily summarized and increases with every new discovery made. What is clear is that this new generation of tools *"has opened broad horizons for the development of applications with strong potential for economic growth, social benefits, and cultural enrichment of communities worldwide"* (Jimenez-Sanchez, 2015, p. 4). Current hypothesized applications range from transforming traditional healthcare by making use of newly obtained knowledge about the genetic basis of diseases, utilizing genomic based bio-tech tools in the production of food and new materials, managing, and protecting vulnerable ecosystems, to applications such as radical human enhancement. Whether such developments will be good or bad depends on which values will be incorporated in the to-be designed systems, and the values that one holds. What is clear is that this is a powerful convergence, and thus, the importance of engaging with this subject and deliberating about what humans want this future to look like is imperative.

The above is an ultra-condensed sketch of the broader landscape the current work is situated in. Understanding that the topics to be discussed are part of a much broader and much more radical, unquestionably technology-enabled, societal transition is vital for grasping the significance of the issues raised. As a student of innovation sciences and human-technology interaction, interested in radical technologies and ethics, the developments described above grabbed the author's attention. The potential for innovation, the potential to improve human lives and to progress as a society, is captivating. Simultaneously, the potential risks involved are significant. History is full of examples of projects created by engineers, politicians, and others, who deemed that they could and should improve the lives of citizens in radically new ways, the results of which did not always prove as beneficial as intended. Ever since engaging with the material of technology and society as a young engineering student, these broader

aspects of technological progress have been the focus of the author's perspective on issues of technology and innovation. The paper *'Do Artifacts Have Politics'* by Langdon Winner (1980) has been formative in this regard and has kickstarted an interest in the value-laden aspects of technology and innovation.

What follows will be an attempt at exploring and illuminating some important aspects of this genomics revolution. This thesis will focus on an application that is most imminent, and which the author deems will affect the lives of large groups of people in the short term. Therefore, this study will examine the large-scale incorporation of genomic technologies into regular healthcare for the establishment of a system of predictive and personalized healthcare.

The departure point of this study are the EU's plans for the digital transformation of health and care, which seeks to employ the power of contemporary and future technologies, including those belonging to the genomics revolution, to radically transform healthcare within the European Union. The Netherlands is actively participating in this digital transformation and is home to an ecosystem of genomics innovators eager to capitalize on the opportunity to radically transform healthcare. The author's focus is on alignment or misalignment of the different factors and actors that are involved in this transition. Central to this is the role played by the individuals that are both subject of and subjected to this new system of healthcare.

Circumstances are such that there is enormous potential for medical and bio-technological innovation within both the European Union and the Netherlands. The author deems that capitalizing on this opportunity will be tremendously valuable for people, both from a quality of life and an economic perspective. However, for this to happen it is important to be vigilant about those circumstances that might pose an obstacle to harnessing the potential benefits afforded to us. The following is an attempt to uncover the value frictions at play between the different stakeholders involved with the transition to genomics based personalized healthcare. Furthermore, it is an attempt to uncover the relevant human behaviors at play for those impacted by genetic testing, both patients and their relatives.

It is the author's hope that this thesis will contribute to a tradition of research in this field that seeks to harness the power of the genome, whilst making sure there is harmony between the rights and interests of different actors and stakeholders, whether they are actively involved or passively subjected generations from now. Ideally, this study will serve as a building block, no matter how small, towards a fair and just genetic future for all.

Table of contents

1. Introduction

A radical healthcare transformation is taking place. This transformation entails transitioning from a system of reactive and generalized care to a system of *predictive*, *preventative*, *participatory*, and highly *personalized* medicine (Liao & Tsai, 2013; Horgan at al., 2017). Due to these four characteristics this new paradigm of healthcare is also referred to as *P4 medicine* (Jakka & Rossbach, 2013; Flores et al., 2013). The great promise of this system is to truly put the individual citizen at the center of healthcare using the power of genetics. It is described as *"a new approach to medicine in which inter-individual genetic differences help diagnosis, prevention, and treatment of a health-related condition"* (Salari & Larjani, 2017, p. 209).

Whilst up until recently the notion of such a large-scale healthcare transition was regarded as speculative, at present the core elements of the P4 vision have gained widespread acceptance (Flores et al., 2013). Some even speculate that *"within the next decade, healthcare professionals will be using genomic data to diagnose and manage their patients"* (Josephs et al., 2019, p. 269; Chute & Kohane, 2013). Although targeted forms of genetic testing are already common in healthcare, this new system is so fundamentally different from the current one that this transformation is regarded by some as a *paradigm shift* in the field of medicine (Weston & Hood, 2004; Belliger & Krieger, 2018). It is noted in reviews that, whilst not exactly similar in meaning, the terms genomic medicine and personalized medicine are largely used interchangeably in literature (Salari & Larjani, 2017).

The genomic technologies that drive this change are regarded as disruptive and transformative (Gaff et al., 2017; Manyika et al., 2013). One of the main catalysts of this transformation is an increased understanding of the human genome and an increased ability to translate this into knowledge that is applicable in everyday medical practice (Horgan et al., 2015). Major drivers of these developments have been several recent breakthrough developments in the field of genomics, as well as developments in other fields that converge to enable this radical transformation (Brittain et al., 2017).

For example, next-generation sequencing methods (NGS) allow for the collection and sequencing of human genomic data on an unprecedented scale, whilst new tools (such as models of analysis employing forms of Artificial Intelligence) have radically increased the amount and nature of meaningful information that can be extracted from large datasets (Goodwin et al., 2016; Koboldt et al., 2013). This extracted information can subsequently be

fed back into the system to provide care based on an individual's genetic profile. Multilateral knowledge sharing and cooperation will only amplify the effectiveness of this system (Bogaert & Van Oyen, 2017). Specifically, based on population data, individual genetic profiles can, for example, be employed *"to identify the best possible drug and therapy for a given patient and reducing adverse effects"* (Jakka & Rossback, 2013, p. 1). It is thus genomic data that will be the catalysts for a radical healthcare transition. A transition to a genomics-integrated healthcare system can also be expected to elicit profound changes in ideas, behaviors, organizations, and institutions (Perez, 2004; Gaff et al., 2017). The issue at hand is thus one that affects both individuals and society at large.

Although the potential of genomics to transform clinical care was recognized long before some of the more radical recent breakthroughs, progress towards practical implementations has been relatively slow (Manolio et al., 2013). Some argue that the incorporation of genomics into clinical care is unlikely to occur by diffusion, and instead requires targeted support to be realized (Hamilton et al., 2014; Gaff et al., 2017). To better understand the current pace of progress and to examine where additional support might be needed it is useful to understand the *innovation ecosystem*, a *systems approach* in studies of complex phenomena (Granstrand & Holgersson, 2020). Important elements of the innovation ecosystem are *"the evolving set of actors, activities, and artifacts, and the institutions and relations […] important for the innovative performance"* (Granstrand & Holgersson, 2020, p. 1). This entails that there needs to be alignment between actors and factors in the innovation ecosystem for innovation to be realized. In this case, this requires understanding the values that each of the stakeholder groups hold, and how these translate into their requirements of the overall system. It also requires an understanding of how such requirements relate to the available resources. Although genetics is important, environmental and behavioral factors significantly influence individual health. Understanding the potential of a healthcare transition thus also requires a proper understanding of human behavior.

One of the most important stakeholder groups in this transformation is the public at large, both as a collective and as individuals. Bioethicists have shown great interest in this topic, for example with regards to common good issues of public health and those of individual and collective privacy (see Salari & Larijani, 2017). Although this ethical perspective is of great importance, it fails to capture another valuable perspective. It has been shown that the way an issue is conceptualized, and thus the amount of psychological distance to that issue experienced, influences prediction, preference, and action. This is known as the Construal-

Level Theory of Psychological Distance (see Trope & Liberman, 2010). Approaching the issues at hand from an abstract ethical perspective takes place on a different construal level than the cognitive process of individuals, as patients and consumers, when directly interacting with healthcare system (Trope & Liberman, 2010). The scope, type and amount of information considered, and how this information is weighed is expected to vary between the two. Indeed, across literature, it is found that abstract thinking leads to stronger moral judgments (Mårtensson, 2017). This could give rise to value-friction between what is valued from a more abstract, moral perspective, what is valued by affected individuals, and the actual behaviors exhibited by individuals as patients in this new healthcare paradigm.

Further complicating the matter is the phenomenon of the intention-behavior gap, the observation that individuals often behave in ways inconsistent with their stated intentions (Sheeran & Webb, 2016). A related phenomenon is the attitude-behavior gap, the observation that individuals often behave in ways inconsistent with their stated attitudes (Farjam et al., 2019). For example, research from the field of ecology shows that environmentally conscious attitudes are not necessarily reflected in an individual's consumer behavior (Gupta & Ogden, 2006). With regards to privacy, this observed dichotomy between attitudes and behavior is referred to as the privacy paradox (Kokolakis, 2017). Understanding the complex interactions between intention and behavior is imperative if one aims to utilize genetic information to promote and support health directed behaviors in patients.

The European Union has recognized the potential of a genomics-based healthcare transformation and has made the digital transformation of health and care (also referred to as EU eHealth) a core part of the EU's *Digital Single Market* (DSM) strategy (European Commission, 2018). The shape of the system resulting from this transformation is thus in part dependent on the policies set forth by the EU. However, it remains unclear how to capitalize on this opportunity in a way that is in the best interest of the citizens. Doing so requires striking a careful balance between the values and interests of the different stakeholder groups. One broadly voiced concern is that *"poor decisions could greatly reduce the benefits that could potentially arise from genomic medicine"* (Gaff et al., 2017, p.1). The nature of this research is largely exploratory; it aims to outline and disentangle the issues and conflicts at play regarding this emerging phenomenon in the ethics-policy-behavior triangle. This study will examine and map both possible (value-) friction between different stakeholders and the role of human behavior in a system of personalized healthcare, focusing on the developing innovation ecosystem in The Netherlands.

1.1 Research-questions

There is significant capacity and willingness, both nationally and in an EU context, to capitalize on the afforded opportunities that enable the extraction of the latent value of genetic data for improved healthcare. The incorporation of genomic innovations into clinical care is however unlikely to occur by diffusion and instead requires targeted support to be realized. Therefore, for this innovation to be realized, alignment needs to be established between the different actors and factors that make up the innovation ecosystem. Supporting such alignment encompasses understanding the values held by each of the stakeholder groups and how these values translate into requirements of the overall system. This research aims to identify loci of (value-) friction within or between different stakeholders and resulting obstacles for the coherent implementation of personalized healthcare. Realizing outcomes that relate to a specific value might require one to compromise on another value, held by oneself or other stakeholders. The first research question is as follows:

RQ1: *Which (value-) frictions exist within or between different stakeholders, and what are the obstacles they pose for the implementation of personalized healthcare?*

Additionally, this research takes a special interest in the role of patients and their behavior in relation to a system of personalized healthcare. The research aims to characterize patients' and relatives' engagement and responses in relation to genetic healthcare, to discuss these and their possible implications for a genomics-integrated system of highly personalized healthcare. The second research question is as follows:

RQ2: *What are the reactions and behaviors exhibited by patients and relatives in relation to the process of genetic testing in healthcare, and which factors have influenced them?*

The research will consist of semi-structured interviews with a diverse set of relevant stakeholders, a method of exploratory inquiry that is well established in the social sciences. Although this project is placed within the broader scope of the EU transformation of health and care, the geographic scope is limited to The Netherlands. By constraining the scope to The Netherlands specifically, the stakeholders are not just occupying a space in a theoretical ecosystem. Rather, many of the stakeholders that will participate will be engaged in actual relevant interactions or collaborations with each other. This means that the data obtained with regards to value frictions will be contextualized by the actual frictions experienced between stakeholders.

2. Literature review

The current section will provide a review of relevant literature and is aimed at gaining an understanding of the broader genomics revolution, the dominant ethical issues discussed in literature, and the psychological mechanisms relevant to individual behavior in this domain. In addition, the role of the EU in facilitating and building (inter-)national ecosystems is covered.

Relevant literature was identified through both online searches and expert polling. An initial search was performed based on the broad topics genomic medicine landscape, ethical issues in personalized healthcare, and psychological factors in individual behavior in the context of healthcare. Based on this preliminary search, search terms were formulated and refined. Subsequently, relevant academic articles and studies were identified through web-searches in online repositories and databases, predominantly JSTOR, PubMed, and Google Scholar. A significant amount of literature was identified by examining references included in the literature identified through database searches. Additionally, literature was identified through direct recommendations from supervisors to the project and other academics. Relevant publications from the European Union have been identified through web-searched in the EU Publications Office's online database and on the European Commission's website.

The literature review begins by introducing the ecosystem approach to innovation and illustrating why it is an appropriate approach to analysis the genomic medicine transition. Subsequently, the concept of a genomics revolution is explored, as well as its implications and desirability. This is followed by a short discussion of the current role of data in healthcare.

Next, several of the key ethical issues surrounding genomics-integrated healthcare and the value-tradeoffs within or between stakeholders are explored. Subsequently, the psychological mechanisms underlying inconsistencies between individuals' values or intentions and their overt behavior are examined.

Lastly, the potential for a genomics revolution in Europe and the steps taken by the EU to facilitate this are examined. The section concludes by summarizing which insights are currently missing from the literature and outlining the contribution this project aims to make.

2.1 Ecosystem approach to innovation

The current project takes an ecosystems approach to examining the innovation taking place. Innovation ecosystems describe *"collectives of heterogeneous, yet interdependent, actors who*

jointly (co)create a system-level output" (Ritala & Thomas, 2023, p. 3). The ecosystems approach emphasizes synergistic value-creation, which allows actors to meet complex long-term macro-level challenges unlikely to be met independently. In an attempt advance the conceptual rigor of the concept, Granstrand & Holgersson (2020) defined innovation ecosystems as "*the evolving set of actors, activities, and artifacts, and the institutions and relations, including complementary and substitute relations, that are important for the innovative performance of an actor or a population of actors"* (p.1). Alignment between elements of the ecosystem is required to realize this system-level outcome. Misalignment can induce friction between elements of the ecosystem and can pose barriers to realizing the intended outcome. Eco-system approaches are used both descriptively to analyze, and prescriptively to build, innovation ecosystems.

The transition towards a genomics-integrated healthcare system is indeed a case in which heterogeneous, interdependent, actors are working to co-create a system-level output. Expertise and activities in important elements of the system (such as data collection, analyses, diagnostics, and interventions) are spread across a set of actors and require alignment for value to be created at the aggregate level (Horgan et al., 2017). European and Dutch initiatives regarding the transition to personalized healthcare emphasize eco-system building activities in their approaches, including stimulating collaboration between a diverse set of stakeholders, and the creation of unified infrastructure and governance frameworks (European Commission, 2018; Nationaal Groeifonds, 2021).

Given the above, the innovation ecosystem approach is the most suitable approach to analyzing the transition to personalized medicine in this study. It is aimed at understanding the values that each of the stakeholder groups hold, how these translate into system requirements, and how such requirements relate to the available resources in the ecosystem. Based on this, friction that is present between elements of the ecosystem can be identified.

2.2 Genomics Revolution

The topic of interest is situated within a broader landscape that is currently undergoing a radical transformation that is referred to as the *genomics revolution* (see Yudell & DeSalle, 2002; Jimenez-Sanchez, 2015; Metzl & Martin, 2020). This genomics revolution is perceived as a *super convergence* of several key trends, some of which are exponential in nature: an exponential rise in computing power, rise in big-data infrastructure, rise of *artificial intelligence* capabilities for data analysis, exponential decrease in genome sequencing costs,

radical breakthroughs in genomic bio-tech tools, accelerated proliferation of knowledge and capacity due to globalization of science and technology, and a cultural landscape with increasing acceptance and adoption of medical technologies (Bauer et al., 2014; Hassan et al., 2022; Metzl & Martin, 2020). Especially with regards to the tools for data management and analysis, some state that it *"is impossible to imagine how the genomics revolution can be clinically implemented without a future in which we use technology to acquire data inputs required for risk analysis"* (Snape et al., 2019, p. 276). Applications based on this new generation of genomics *"show a significant potential to contribute addressing global challenges, such as human health, food security, alternative sources of energies, and environmental sustainability"* (Jimenez-Sanchez, 2015, p. 2). Due to this widespread nature of possibilities afforded, this progress is also referred to as *genomics innovation* (Jimenez-Sanchez, 2015). Although this has given rise to plenty of interesting hypotheses about the future, the scope of the current project will be limited to what these developments mean for the imminent transformation of regular healthcare.

This project thus concerns what is referred to as *genomic medicine*, which is most concisely summarized as "*the use of information from an individual's genome in the diagnosis and management of their condition*" (Gaff et al., 2017, p. 1). Although genomic medicine in some form has been practiced for decades (previously referred to as *medical genetics*, see e.g., Roberts & Pembrey, 1963), current developments make it such that genomic medicine in its contemporary form *"will become increasingly relevant to a broad range of health practitioners"* (Gaff et al., 2017, p. 1). Before discussing some of the current applications of (genomic) data in healthcare, it is important to consider why a genomics revolution is desirable, and for whom. That is, what are the benefits afforded by a system of genomics-integrated healthcare, and which of the stakeholders would be affected by these benefits.

To illustrate some of the proposed benefits of genomic medicine it is useful again emphasize the 4 P's that are core characteristics of this new paradigm of healthcare; *predictive*, *preventative*, *participatory*, and highly *personalized* medicine (Liao & Tsai, 2013; Horgan at al., 2017; Jakka & Rossbach, 2013; Flores et al., 2013).

Currently, there are several possibilities to screen for a variety of simple disorders, such as single-gene disorders, in specific cases. Such applications have become widespread, as *"genetic testing results for highly penetrant 'pathogenic' variants (mutations) have been used in clinical practice for several decades"* (Bauer et al., 2014, p. 482). One example is in the

case of *preimplantation genetic diagnosis* (PGD) during IVF treatment, where embryos are screened for a variety of single-gene disorders, especially when they are deemed at risk due to known heritable disorders in one or all of the parents (Simpson et al., 2017). Prenatal genetic diagnosis does the same but with respect to a fetus instead of an un-implanted embryo (Bauer et al., 2014). Other examples include *"pediatric and adult-onset genetic conditions, and predictive testing for highly penetrant adult-onset conditions and treatment of cancer"* (Bauer et al., 2014, p. 482; Shashi et al., 2014). Advanced in genomic profiling of cancers has also resulted in an increase in the availability of targeted therapeutics (Ginsburg, 2013).

Another example of the potential of genetic data to facilitate personalized interventions is found in the field of pharmacogenomics. Pharmacogenomics is concerned with genomic influences of drug metabolism and can provide care givers and patients with insights into the effectiveness and possible complications of certain drugs for an individual, and help medical professionals determine the optimal dose for a patient (Biesecker et al., 2012). A recent study across seven European countries showed a significant reducing of clinically relevant adverse drug reactions when using pre-emptive pharmacogenetic testing to tailor treatment and dosage for patients (Swen et al., 2023).

Some genetic tests have been so well established as being capable of identifying a large variety of disorders that they "*have inspired stakeholders with commercial interest to provide direct-to-consumer (DTC) testing for genetic variants associated with certain health conditions"* (Bauer et al., 2014, p. 479). At the same time barriers to the widespread incorporation of such tests into routine medical practice have proven tough to overcome. Cited by clinicians as the predominant reasons for not incorporating genetic testing into patient care when assessing predisposition to diseases and drug response are both uncertainty about the available tests and a lack of training and guidelines (Najafzadeh et al., 2012).

A genomics-integrated healthcare system would improve this situation in two major ways. In such a system, genetic screening would not be an exception applicable to specific situations, but rather the norm. In addition, due to an increase in tools, genomic data can be *deciphered* to identify and diagnose increasingly rare and complex disorders (Josephs et al., 2019). In this way, a genomics-integrated healthcare system would offer the potential for screening for both simple and complex disorders on a population level. Being able to apply such techniques to large groups is a true breakthrough, as *"being able to reduce morbidity and mortality by identifying individuals at risk for developing a condition is not a new concept but screening at*

a genomic level is" (Snape et al., 2019, p. 276). Not only would this radically improve health or disease management for the individual, but it would also allow for improved risk stratification for relatives (Josephs et al., 2019). The widespread availability of genetic data of patients would also allow for general *preemptive genotyping*, the practice of predicting drug safety and efficacy based on genomic information (Ginsburg, 2013).

Another important characteristic of the widespread of use genomics in healthcare is the potential for an even greater overlap of healthcare and medical research. Already, to provide just one example, *"the application of massively parallel or next-generation sequencing (NGS) to large-scale cancer genomics discovery projects has revealed extraordinary new information about the underlying genomic drivers of cancer development and progression"* (Berger & Mardis, 2018). Such discoveries in turn lead to the development of new treatments. More broadly, the widespread availability of genetic profiles op patients offers new potential to carry out Genome Wide Association Studies (GWAS; see Visscher et al., 2012 for a review of this experimental methodology). In turn, the insights obtained from such studies will be fed back into the healthcare system to improve care for increasingly rare and complex disorders. The potential for such overlap is demonstrated by the enormous research output of DTC genomics companies such as 23andMe, which has demonstrated the capacity to capitalize on their client-enabled proprietary biobanks (Stoeklé et al., 2016).

A genomics-integrated healthcare system would entail major changes in the way clinicians and other healthcare professionals work. One argument that is often raised in favor of the use of technology in the workplace, usually in the context of automation, is that it would relieve part of the workload such that professionals can focus on those aspects of the task in which their human skills are most valuable. NASA researcher Paul Schutte refers to this as *complemation*, *"complementary technology that is designed to enhance human skills and abilities"* (Schutte, 1999, p. 113). In the context of genomic medicine this would entail that the medical practitioners are provided with crucial information based on a patient's genome, which would *"enable the clinician to focus more on the clinical skills requiring human interaction – face-to-face shared decision making, with a holistic approach encompassing educational, cultural and personal issues"* (Snape et al., 2019, p. 276).

2.3 The Datafication of Health

Although the transition to this new system of healthcare will be a radical one, there are already elements with regards to the use of data present in the current system. One example is the use

of Electronic Heath Records (EHR), a central repository of information related to a patient, to facilitate dating sharing between different healthcare providers to improve quality of care (Kierkegaard, 2011). Whilst some EU countries have been successful in implementing this system, others have not, resulting in "*a patchwork pattern of eHealth use*" (Kierkegaard, 2011, p. 504). This is one of the reasons for the emphasis on integration and interoperability in the development of the current generation of EU eHealth tools (European Commission, 2018).

Other examples include the increased popularity of self-tracking devices or apps by individuals, such as wearable health and fitness trackers (Fox, 2012). It has been shown that users of such devices feel empowered to make some decisions pertaining to their health (Pingo & Narayan, 2019). Observing the results of such decisions also resulted in a sense of gratification and control (Pingo & Narayan, 2019). Furthermore, willingness to share information collected by self-tracking devices with health care providers has been observed to be relatively high (Rising et al., 2021). These developments have led some to argue that self-tracking may become a key element of personalized medicine (Norris, 2012). However, as the use of ever more complex data in clinical decision making is increasing, *"the implications of data volume, complexity, and in some circumstances ethical and legal issues add new dimensions to the implementation of genomic information into patient care*" (Chute & Kohane, 2013, p. 1467; McGinnis, 2009).

The increased collection and use of data pertaining to our individual and collective health, by individuals as well as institutions, is referred to as the *datafication of health* (Ruckenstein & Schüll, 2017). The term datafication is used more broadly to describe the developments in which data-intensive practices have come to strongly influence contemporary life. It refers to the large scale *"conversion of qualitative aspects of life into quantified data*" (Ruckenstein & Schüll, 2017, p. 261; Mayer-Schönberger & Cukier, 2013). The movement toward datafication has already come to affect health and healthcare in two separate ways. There is the first, which applies to healthcare institutions, in which datafication of health can be seen in the use of tools such as electronic health records, as previously mentioned. In recent times, datafication of health has also been patient driven, with ever increased use of self-tracking apps and devices through which patients themselves are empowered to quantify health related aspects of their lives. However, one might be warranted in questioning who exactly is empowered in this context (Ruckenstein & Schüll, 2017).

One of the important issues raised by the literature on the datafication of our lives is the power that data both provides and exerts. For example, some scholars have pointed out the

"asymmetric relations between those who collect, store, and mine large quantities of data and those whom data collection targets" (Andrejevic, 2014, p. 1673). This asymmetric relation is often said to lead to a divide between the data-rich and the data-poor (Boyd & Crawford, 2012). Such asymmetric power relations raise questions about the power and role of individual behavior and decision making within the system, and to what extent a preference for policy that empowers the individual might be warranted.

There are examples of consumer genetics companies that have successfully partnered with the pharmaceutical industry to monetize the data that is provided to them by their costumers, as mentioned earlier in relation to 23andMe's research output (Van Dijck & Poell, 2016; Stoeklé et al., 2016). Fears of privacy violations voiced by critics of the company were confirmed when it was revealed that a 2023 security breach had exposed the personal information of 6.9 million of their costumers (Helmore, 2023). In his book *The Politics of Life Itself*, on the politicization of medicine, human life, and biotechnology, Nikolas Rose refers to the value that our health data holds as *bio-capital* (Rose, 2006). In addition to being a scientific, social, and ethical matter, the genomics revolution and accompanying healthcare transition is also an economic issue. The value that this data holds could therefore be one of the possible loci of friction.

Due to the value that it holds some scholars warn about the risk of exploitation of personal health data (Nafus & Neff, 2016; Clarke et al., 2003). According to Nafus & Neff, the commodification and exploitation of personal health data are just two dimensions in the much broader trend of biomedicalization. This broader process is not limited to new modes of *"production, distribution, and consumption of medical information but also new forms of technoscientific objectification of bodies"* (Ruckenstein & Schüll, 2017, p. 264) as they are *"abstracted from real time, actual location, and social space"* (Lock, 1993, p. 371). Others have warned that *"the advent of big data brings with it new and opaque regimes of population management, control, discrimination and exclusion"* (Kennedy et al., 2015, p. 1). Concerns for such asymmetric relations and control do apply to governments but are also often raised with regards to the involvement of private entities. On the other hand, private investment in the development of tools and services that make up the ecosystem of personalized healthcare is driven by search for financial returns, and a lack of financial incentive for private investment in the sector might hamper or delay innovation.

2.4 Ethical Perspective

The issues surrounding a potential genomics-integrated healthcare system are an example par excellence of how the interaction between humans and technology can give rise to ethical issues. Not only is human biology the subject that is codified or *datafied* through these technologies, but it is also humans that will be subjected to a new system of healthcare. In a broader sense, it is by way of these new technological tools that the way humans relate to themselves, and others is mediated, and so helps to constitute both humans and our morality in a different way. Post-phenomenological literature would describe this as technological mediation of moral subjectivity (e.g. Verbeek, 2008). This also relates once again back to the theory of biomedicalization, the idea that *"biomedicine is being transformed from the inside out by densely elaborating technoscientific interventions*" (Clarke, 2014a, p. 137; Clarke et al., 2003). This process, and the interwovenness of human bodies and technology, brings with it increasingly complex ethical dilemmas and tradeoffs. Whilst there is some precedent for dealing with similar issues in the context of traditional medical genetics, the ethical challenges at play here are qualitatively different. Especially the breadth and width of the information obtained through new methodologies such as GWAS *"requires rethinking of how to implement core ethical principles*" (Ormond & Cho, 2014. p. 211).

As with any socio-technical transformation, part of the relevant ethical considerations concerns the technical aspects. In the case of genomic medicine, ethical issues arise, for example, with regards to the technologies used for sequencing and diagnosis (for examples, see Matthijs et al., 2016). Although there are many, two examples of such issues are the reliability and analytical and clinical validity of diagnostics (Bunnik et al., 2011). Whilst traditional genetic testing might have focused on single gene mutations, the diagnostics that are part of the genomic revolution will concern complex interactions between a massive number of genetic mutations. Before such methods are implemented, they must be proven to be reliable, and work as intended. In turn, this requires new methods for evidence and validation. Although it is important to be cognizant of the existence of such issues, issues relating purely to the technical aspects of sequencing and diagnosis are beyond the scope of the current work.

The remainder of this section will focus on the ethical issues relating to integration of genomics in the healthcare system. The next section describes some of the ethical issues that relate to the core premises of a system of genomic medicine and the genomic innovation taking place. Subsequent sections each cover specific ethical issues relating to genomic healthcare.

2.4.1 General ethical issues

Some of the ethical issues do not concern any specific characteristic of the use of genomic medicine, but rather the whole concept of genomic medicine itself. Some have argued that *"a focus on genetic factors as causes of disease will downplay other important influences"* (Clarke, 2014b, p. 2). This phenomenon is referred to as 'geneticization' and mirrors some of the arguments voiced with regards to *genetic determinism* and the reductionist nature of *datafication* in general. Clarke argued that geneticization comes with a political agenda, as focusing on the individual genetic basis of disease diverts attention away from public health measures that might impact collective health in a meaningful way, stating that it is *"therefore attractive to those who wish to diminish the scope of public and collective action"* (Clarke, 2014b, p. 2). This shift in focus could, for example, impact funding priorities of public health institutions (Evangelatos et al., 2017). However, genomics also provides the tools to specifically separate the environmental and lifestyle contributions to disease from the genetic ones, thereby enabling a more nuanced understanding of both.

Possibly one of the one of the most relevant ethical concerns is the clinical utility of genomics-based healthcare, and the timeframe within which such clinical utility will be realized (Bunnik et al., 2011). Clinical utility refers to the likelihood that some intervention will result in improved health outcomes. In order for novel methods for diagnosis and treatment to be implemented in an ethically sound way, it has to be assured that the benefits of such an intervention outweigh the risks negative health effects for patients. Those risks relate to the procedures themselves, for example, risk of inaccuracies in diagnostics for complex conditions, or in the form of risks of unintended side effects of certain types of doses of medication. Beyond direct clinical utility, risks to patients' health also include the added stress and worry from predispositions that might never end up manifesting.

Currently, there are no widely accepted standards for sequence quality and analytic validity (Ormond & Cho, 2014; Feero, 2020). This is problematic, as diagnosis through WGS is currently still subject to several types of errors in accurately identifying pathogenic mutations (Chrystoja & Diamandis, 2013). The number of direct-to-consumer services that employ WGS to make insufficiently corroborated claims with regards to a wide variety of conditions is cause for concern (Hogarth et al., 2008). Some countries (including The Netherlands) therefore only allow licensed clinics to perform any kind of human gene sequencing (Abbing, 2009). In addition, a protocol adopted by the Council of Europe requires that *"genetic testing services meet generally accepted criteria for scientific validity and clinical validity, that clinical utility*

be assessed, and that all genetic testing, whether offered direct-to-consumer or through a medical practitioner, be accompanied by genetic counseling" (Ormond & Cho, 2014, p. 216; Lwoff, 2009). DTC testing services are nevertheless broadly available, as policies are either unapplicable or challenging to enforce for providers based abroad (Rigter et al., 2021).

In the transition to personalized medicine, it is crucial to assess not only the effectiveness of interventions on an individual level but also their broader impact on the healthcare system for the collective benefit. While it is important to assess in which cases and contexts a transition to a genomics-integrated healthcare system can lead to improved healthcare outcomes for individuals, evaluating such outcomes should consider the amount of (public) resources they require in relation to the amount of benefit derived. Scholars have argued for an evidence-based approach in assessing where and when genomics-based healthcare can impact health outcomes for patients (Ormond & Cho, 2014; Evans & Khoury, 2013). Evans & Khoury advocate for carefully considering *"which of the many promising facets of this new field offer real and tangible improvements in care"* (2013, p. 268).

As alluded to before, scholars also warn that premature and casual implementation of an attractive technologies, without the due diligence that is required, may result in premature termination (Salari & Larijani, 2016). In the past, such hasty implementations have irreversibly damaged the image of promising technologies, possibly resulting in prolonged suffering by those that could have benefited from the technology had its rollout been more cautious. An example of this is the 1999 death of Jesse Gelsinger, an 18-year-old man participating in a gene therapy trial for a genetic disorder, who died due to a severe immune reaction triggered by the treatment (Lezaun, 2010). The regulatory scrutiny and extensive reassessment of safety protocols as a response to the exposed unforeseen risks and inadequate safety measures delayed the progress of gene therapy research for years. Especially in the field of medicine this is problematic as *"the zero-sum landscape of health-care funding can least afford it"* (Evans & Khoury, 2013, p. 268). That is, resources can quickly be diverted away from promising research projects as political support dwindles in the wake of events such as the Gelsinger case. The fact that genomic technologies are an attractive target for hype increases the need for evidence-based based approaches in assessing their potential (Hansson, 2010).

Whilst the issues touched upon so far are quite general, there are many specific examples of relevant ethical issues. Although not exhaustive, the remainder of this section will summarize some of the most relevant and pressing issues with regards to personal genomic medicine.

2.4.2 Informed consent

One of the central values in Western healthcare systems is that of patient autonomy (Varelius, 2006). This value entails that patients have a moral right to make autonomous decisions about their own bodies (Rego et al., 2020). Generally, this moral right to autonomy is accompanied by a legal right. This has led to the practice of gathering informed consent, which is *"the process by which clinicians and biomedical researchers gather autonomous authorization for a medical intervention or research participation"* (Rego et al., 2020, p.2). Autonomous authorization in informed consent is based on four core presuppositions; *competence, voluntariness, adequate information, and comprehension* (Bunnik et al., 2013). The informed consent process in genetic testing involves counseling to ensure all information about the medical intervention or research study is both adequately conveyed to and understood by the patient. Although definitions vary, informed consent typically requires that *"a competent patient be provided with sufficient information about a procedure and the associated benefits, risks, and limitations to make an informed decision about whether to proceed with treatment"* (Ormond et al., 2010, p. 1749). Developments in the field of genetics, such as WGS, however *"demand a rethinking of traditional interpretations of the concept of informed consent [as they] challenge the feasibility of providing adequate pre-test information and achieving autonomous decision-making"* (Bunnik et al., 2013, p. 348).

The models of informed consent practiced with regards to traditional genetic testing can be characterized as thorough and conservative, with high specificity with regards to the data that is collected and the information that is reported back to the patient. This approach is possible as traditional genetic testing is highly targeted and generally performed with regards to a specific condition (Bunnik et al., 2013). In this context, genetic testing is typically performed as a result of either clinical indications or a family history. Patients are informed at length about testing options, risks, benefits, and possibly limitations, and can discuss these with healthcare professionals such as, but not limited to, clinical geneticists and genetic counselors (Ormond & Cho, 2014). This the process of counseling extends beyond the informed consent procedure and includes the return of results. Psychological research has demonstrated that patients often have difficulty understanding and applying the concepts of risk and probability (Peters et al., 2006). During the process of genetic counseling, these professionals aim to effectively address and support a patient's emotional response to the outcome of the test, which can be amplified if there is a family history with a disease (Skirton et al., 2013).

In contrast, WGS in the context of genomic medicine is untargeted and allows for huge amounts of information to be extracted. In addition, the information obtained can increase even long after initial testing, as knowledge about the genetic basis of conditions perpetually expands. Even though most of the information obtained from WGS will be of unknown meaning and significance, the average person might need to be informed about around a hundred risk factors found in their genome (Ormond et al., 2010). With a limited amount of counseling resources, this makes it unfeasible to, when obtaining informed consent, discuss this information at the same level of detail as when informing patients about a single risk factor. This has led some to question *"whether it is even possible to satisfy the previously accepted standards for informed consent for tests with such expansive implications"* (Rego et al., 2020, p. 4).

Solutions have been proposed to mitigate the issues regarding informed consent caused by the large number of results obtained through WGS. Some of these solutions have taken inspiration from how incidental or secondary findings (IF) are currently treated. An incidental finding is the unintentional discovery of a certain condition during evaluation or treatment for another condition, or during participating in a research study. Two approaches to informed consent regarding IF are generic and preference-based consent (Elias & Annas, 1994). In a generic consent approach, the focus is on informing patients about possible outcomes and implications in general terms rather than in-depth coverage of the specifics of all possible outcomes. Patients are thus informed in general terms about which IF might arise and whether or not they consent to being informed about them. The goal is to *"provide sufficient information to permit patients to make informed decisions about […] screening yet avoid to information overload that could lead to misinformed consent"* (Elias & Annas, 1994, p. 1611). The untargeted nature of WGS might however require a more stratified approach to generic consent. In a preference-based approach to generic consent, outcomes are categorized in specific ways and patients are enabled to indicate which categories of information they would like to receive (Appelbaum et al., 2014). This would put more control in the hands of the patients by providing them with a manageable number of choices to make.

A remaining issue is what happens with those that do not consent; to what extent will patients be able to participate in a genomics-integrated healthcare system when they wish to refrain from genetic testing. Individuals have the autonomy to decide which kind of medical assistance they seek, which includes deciding to refrain from engaging with genetics. It is thus important to examine how a future system strongly integrated with genetic testing would accommodate the needs of patients that do not wish to participate in genetic sequencing.

2.4.3 Return of results

The return of results from genetic testing is another area that poses unique ethical challenges. Whilst appropriate informed consent procedures can be used to mitigate some of the ethical issues surrounding the return of results, other issues remain. The fact that a patient has consented to receiving certain kinds of information does not necessarily imply that healthcare professionals will provide this information when available. In other cases, healthcare professionals might elect to disclose information for which consent is more challenging to establish, such as when contacting at-risk relatives.

Opinions on this matter roughly map onto a spectrum between two extremes. On the one hand, there is both ethical and legal *duty of care* argument, which says that (provided that the information has clinical utility) there is a duty to disclose relevant genetic information, whether to a patient or their relatives (Dove et al., 2019). On the other hand, there is an argument based on *individual autonomy* which holds that individuals have a right to informational self-determination, and thus have a right not to know their genetic predispositions (Andorno, 2004).

The extreme individual autonomy argument is challenged in several ways. Firstly, in the cases of results that apply to relatives, there is the challenge of knowing whether someone wants to exercise their right not to know without at least disclosing some information in the process of inquiry. Therefore, *"the exercise of an autonomous choice seems necessary for the functioning of the right not to know"* (Andorno, 2004, p. 438). Second, unless the value of individual autonomy is absolute, it might be restricted on the basis of a duty to disclose information to patients by healthcare professionals, or the value of solidarity with and responsibility for relatives in cases where there is a risk of serious harm to others. A duty to disclose is also not absolute, nor is solidarity with or responsibility for relatives. For healthcare professionals, there are several considerations regarding the ways they choose to exercise their duty to disclose.

Some have argued that, provided informed consent is established, patients have a *"right to receive all of their genetic information, even if they are deemed clinically irrelevant by the laboratory and clinician"* (Ormond & Cho, 2014, p. 213). This is the approach of many of the DTC genetic testing services. It is however argued that providing patients a full return of results, *"particularly risk variants for complex diseases and/or results that are not clinically actionable, will be overwhelming and anxiety provoking for many individuals"* (Yu et al., 2013, p. 687). Beyond the issues of providing patients with indiscriminate access to test results, some have questioned whether there is value in providing information to a patient that is not medically actionable, even if the patient has theoretically consented to it (Berg et al., 2011).

There is consensus that at least *"analytically valid and medically actionable [findings] should be offered to patients"* (Lohn et al., 2014, p. 463). Although such strategies might be appropriate in some instances of WGS, the authors emphasize that to *"maximize the use of WGS in the public health context, a very high bar must be set for reporting results"* (Berg et al., 2011, p. 500). The authors thus not only consider the rights of individual patients with regards to disclosure, but also the effect of disclosure policies on the broader system.

Some have proposed creative solutions, such as releasing the results partwise over a longer period of time through a self-guided management system, stating that the question should not be how to constrain the information that is provided to patients, but rather *"how we can improve access and translation, through effective education, meaningful communication, and the preservation of individual preferences"* (Yu et al., 2013, p. 687). An added benefit of this approach is that it can accommodate both changes in patient preferences as well as an expanding base of genetic knowledge. In this way, the results obtained in WGS are treated *"as a dynamic resource of information from which results should be 'managed' over the lifetime of an individual"* (Yu et al., 2013, p. 684).

Research on patient preferences with regards to the return of results indicated a *"diversity of attitudes toward the return of incidental findings and a diversity of justifications for those attitudes"* (Clift et al., 2015, p. 38). Most participants did however prefer a patient-centered approach, indicating that people value active patient involvement in the decision-making process rather than being governed by a universal framework guiding disclosure.

Return of results has so far predominantly been discussed with regards to the disclosure of results to a patient that underwent genetic testing and was themselves able to competently participate in an informed consent procedure. There are however two cases in which third parties are put in a position to make disclosure decisions for others worth discussing separately, being children and relatives.

In the case of children, especially when it concerns adult-onset conditions, the dilemma with regards to the disclosure of results affects both parents and healthcare professionals. Some recommend against predictive testing for adult-onset conditions in children, claiming it could negatively impact a child's autonomy and right to self-determination (Ross et al., 2013). This is also referred to as the child's right to an *open future*. Whilst the right to an open future is important, it is only one of the values one could consider when making disclosure decisions on behalf of a child. Garret et al. therefore posits that in such cases *"predictive genetic testing is*

ethically permissible in principle, as long as the interests promoted outweigh potential harms" (2019, p. 2190). An interest-based framework is proposed by which clinicians evaluate and weigh 13 different interests pertaining to a wide array of aspects to a child's current and future life to come to a decision regarding testing and/or disclosure of results (Garret et al., 2019). Others have argued however that such a *best interest standard*, in which healthcare professionals judge what would be in the best interest of the child, is problematic in several ways (Rhodes & Holzman, 2014). They argue that the best interest standard is subjective, leads to polarizing behavior, and that appeals to it are often indeterminate, as even reasonable people can disagree. Instead, Rhodes & Holzman propose the *not unreasonable standard*, by which *"parents' decisions would be respected unless they were deemed unreasonable"* (p. S126). A framework is proposed by which healthcare professionals can assess if and when it might be warranted to refuse to comply with parents' wishes.

Other ethical issues arise in decisions regarding the disclosure of results to relatives. As alluded to before, the scope of the information obtained during genetic testing extends beyond the tested individual to all those genetically related to that individual. In some specific cases, information obtained might even be of little relevance to the patient, but highly significant to relatives (Ormond & Cho, 2014). Although many of the issues relating to disclosure of results to relative's mirror those in traditional medical genetics, the scope and scale of genomic medicine changes the context of this issue. Whereas traditional testing only reveals information about very limited parts of the genome, whole-genome sequencing reveals practically all there is to know. Furthermore, widespread application of WGS will significantly increase the number of affected relatives.

Making any kind of decision concerning disclosure to relatives requires trade-offs between different values. The conflict here is once again between a duty of care towards relatives on the one side and respecting their individual autonomy on the other. A duty to disclose could also conflict with a duty of patient confidentiality, if a patient does not want this information to be shared with genetic relatives (Dove et al., 2019). This illustrates the difficulty that professionals can experience in navigating between these coexisting duties and their legal professional responsibilities. In practice, patients are generally strongly encouraged to share relevant information regarding genetic risks with their relatives. However, research has shown that conversion is often inadequate, even in the case of first-degree relatives (Hodgson & Gaff, 2013). This in turn warrants the question of which duty is stronger, and whether a clinician can ever break patient confidentially to inform relatives of a pressing risk (Ormond & Cho, 2014).

2.4.4 Genomic privacy

As with any kind of medical or sensitive personal data, the privacy of the patients or participants from which the data was obtained is an important value. First, privacy is often seen as an intrinsic moral value, and a violation of one's privacy can be regarded or experienced as a violation of one's personal autonomy. Second, in the case of personal medical data, privacy is an important value, as a breach of privacy or confidentiality might lead to harmful consequences for affected individuals. Examples of such harmful consequences can be economic, in cases of genetic discrimination by employers or insurance providers, or social, in cases of stigmatization of certain conditions (Juengst et al., 2012).

At the same time, critical enablers of a system of personalized medicine are large-scale association studies into the genetic basis of complex conditions. In this case, there is friction between the value of confidentiality and personal privacy, and the value of obtaining knowledge for public benefit. Such issues are referred to as issues regarding *genomic privacy*. These values are not necessarily in conflict with each other, rather the challenge here is to create value for public benefit from large collections of genetic data, whilst also protecting the privacy of each of the individual donors. Whilst the UK's half-million participant biobank facilitating over 26.000 research projects demonstrates the potential of such large-scale genomic data repositories for research, others have demonstrated the vulnerabilities that these types of projects can face (Conroy, 2023). For example, researchers have already demonstrated ways in which the anonymity of actual bio-bank participants can be compromised, even from anonymized data (Gymrek et al., 2013).

There are several concrete challenges that form a barrier to balance the desire to obtain valuable insights through the sharing of genetic information on the one hand, and responsibility to safeguard patient or participant privacy on the other. Firstly, the larger the amount of genetic information that is stored and spread over different locations, the greater the risk of unauthorized access or accidental release (Ormond & Cho, 2014). This risk is amplified if data is shared across borders, where there could be significant differences in judicial frameworks with regards to medical genetic data (Kaye et al., 2009). Second, the larger the amount of genetic and related information that is available relating to any individual, the greater the potential for this individual to be uniquely identified (Gymrek et al., 2013).

2.4.5 Intellectual property

There has been a longstanding debate about the merits of patents and other forms of intellectual property protection, and whether they facilitate or hamper innovation (Chesbrough, 2003).

Patents limit what others can do with a specific invention, and in addition serve as a public disclosure of information, enabling others to build upon the provided information in multiple ways (Gambardella, 2023). Gene patents in medicine are different however, as the patents concern specific gene sequences that were not constructed but rather discovered (Paradise et al., 2005). In the US, the Supreme Court has ruled unanimously that human genes are a product of nature and are non-patentable (Kesselheim, 2023). The European Patent office guideline, however, specifies that *"if a gene, discovered in nature, has a technical effect, that effect may be patentable, eg, the use thereof in gene therapy"* (Demir & Stamhuis, 2023). It is required that such sequences are isolated or produced using a technical process, and that this process is disclosed in the patent application. In the EU, these are the crucial elements in discriminating between a non-patentable discovery and a patentable invention. When it comes to the human genome, patents are the privatization of the ability to capitalize on specific information and technical processes, which hold both promises and risks for healthcare innovation.

One of the main arguments in favor of patents is that it would incentivize private parties to undertake risky research projects that they would otherwise not have committed any resources to. However, patents held by one party can also constrain what another party is able to do. Any new project can be severely constrained when it is reliant on a larger number of patents that others hold the rights to (Heller & Eisenberg, 1998). Patents are especially valuable in the case of genomics, as there is often a lack of possible substitutes for patented gene therapies. Gene patents therefore *"limit what can be done in the realm of scientific research and medical care because there are no alternatives to a patented gene in diagnosis, treatment, and research"* (Paradise et al., 2005, 1556). Despite some claiming that *"gene patents have not had quantitatively important effects on follow-on innovation"* (Sampat & Williams, 2019, p. 232), overly broad patenting practices have led to as much as 84% of the genes in the human genome being patented in the US before the 2013 ban (Rosenfeld & Mason, 2013). This would have provided patent holders with an extraordinary amount of leverage. A compounding problem in the field of biomedical research is that intellectual property rights often belong to *"a large, diverse group of owners in the public and private sectors with divergent institutional agendas"* (Heller & Eisenberg, 1998, p. 700). Furthermore, due to cognitive bias (attribution bias), each of the rights holders is likely to overestimate the value of the contribution of their patent and underestimate the value of the other's (Tversky & Kahneman, 1974). Dealing with many rights holders with diverging interests, which also tend to overvalue their own contribution, will require significant resources from any party planning to perform research and development in

this field. Heller & Eisenberg (1998) refer to this as a tragedy of the anti-commons; an underutilization of specific resources when too many parties have a right to exclude others. As a result, *"intellectual property policies and practices appear to have had a significant impact on the translation of knowledge about genes into clinically useful genetic diagnostic tests for personalized medicine"* (Ormond & Cho, 2014, p. 214). For example, in a 2013 study that compared the human-genome project (engaged in open sharing of data) with the firm Celera (which protected its IP) it was found that the practices of the latter resulted in a 20-30% reduction in subsequent research and product development (Williams, 2013). The important question here is thus what form of patenting policies and practice would serve the best interest of the patients, and the development of personalized medicine in general. Failing to capitalize on the available opportunities due to patents would result in a decreased quality of care. Such ethical issues thus lead us to question *"the appropriate role of researchers and academic institutions in technology transfer for medical applications"* (Ormond & Cho, 2014, p. 214).

The extensive patenting of the human genome has presumably facilitated *"the development of clinically available and commercially viable products such as genetic tests or gene-based therapies"* (Ormond & Cho, 2014, p. 214). Some argue that, given that much biomedical research is conducted by commercial entities, without patents and the protections they afford, actors would be insufficiently incentivized to develop genetic tests and treatments. Others argue that through the patenting of genetic information itself, follow-up discovery and development is hindered. This raises ethical issues, as patents possibly *"decrease access to and quality of clinical genetic tests, raise costs, or prevent research and development and improvement of diagnostic services"* (Ormond & Cho, 2014, p. 214).

A survey amongst laboratories involved in clinical genetics found that a great majority, 65%, had received notifications regarding potential patent infringement (Cho et al., 2003). As a result, a quarter of laboratories discontinued clinical genetic tests, and about half decided against performing any new research to develop genetic tests. Two-thirds of those interviewed by Cho et al. felt that patents hindered them in conducting research, whilst 85% indicated that the sharing of information amongst researchers was limited as a result. On the other hand, other research found that a significant number of researchers themselves did delay publication of findings due to patent considerations (Murdoch & Caulfield, 2009; Blumenthal et al., 1997). Even if patents would not influence the type of research that is conducted, delays in the dissemination of knowledge can still negatively impact innovation, and thus eventually the quality of care, especially in a fast-moving field like this one. Furthermore, every patent

application also creates uncertainty for others that might benefit from the discovery, as *"each potential patent creates a specter of rights that may be larger than the actual rights"* (Heller & Eisenberg, 1998, p. 699). This leads to uncertainty and hesitation for others as the exact scope of the patent rights is often unclear until the patent is granted. Such uncertainty and delays might cause well-intentioned actors to divert valuable resources into another direction.

As is characteristic of the genomics revolution, a careful balance between stakeholder interests must be found. Intellectual property policies and practices must be such that research and development will benefit the quality of care to the patients, whilst also ensuring that researchers and producers are sufficiently incentivized to participate.

2.4.6 Ownership and proprietary data

In the case of gene patents, although the findings on which they are based might be accessed, they cannot be utilized outside of the restrictions set forth by the rights holder. There are, however, other ways of restricting access to information that will be of critical importance for the development of genomics-based personalized healthcare.

The availability of data on genotype–phenotype associations (the relation between genes and how these are expressed in a person) is critical for the development of personalized care (Ormond & Cho, 2014). However, aware of the value that this data holds, laboratories (both commercial and academic) increasingly lock away this data in proprietary databases, which is detrimental to the free flow of scientific knowledge (Caulfield et al., 2014). On top of the biobanks held by such laboratories a new industry has spouted, taking advantage of people's desire to undergo direct-to consumer genetic testing, to establish fully commercial biobanks based on their costumer's data (Stoeklé et al., 2016). As mentioned before, this two-sided business model of DTC testing services forces these companies to make trade-offs between which side's interest they choose to represent. This locking away of data curbs the ability of others, both researchers and practitioners alike, to independently interpret this data, once again providing a barrier to the swift dissemination of information. Therefore, it is argued that due to its clinical significance *"it is unethical for patent holders to keep this information in proprietary databases, even if it enhances market value of a genetic test"* (Ormond & Cho, 2014, p. 216). Bolstering this argument even further is the fact that many of the gene–disease association discoveries that such databases are comprised of have been (at least partly) publicly funded. From a justice perspective thus, with regards to big data analytics, there are ever stronger calls to treat socially valuable data as a kind of common good (Deming, 2021; Boyd & Crawford, 2021). In such an ideal *by the people – for the people* case, genetic data provided

by the public would be utilized for medical innovations that would benefit everybody (provided that they would be reasonably accessible to all). A striking example of how the open sharing of genetic data can and will be beneficial came during the 2020's coronavirus pandemic. By releasing the sequencing data of the novel coronavirus publicly as soon as it was sequenced, a single Chinese laboratory enabled countless other labs around to world to start vaccine development within a matter of weeks, even though actual samples were not yet widely available (Frist, 2021).

There are concrete efforts to find solutions for this data-sharing and bio-banking problem. In Europe, 24 EU member states have committed to a project for joint bio-banking and data-sharing (European Commission, 2022). Globally, an alliance of 69 institutions (calling itself the *global alliance*) aims to address the problem by developing standards and policies to facilitate the free flow of information in genomic medicine (Hayden, 2013). In addition to the privacy and confidentiality issues raised by data sharing, these initiatives will need to reach consensus on technical standards, ensure the interoperability of data infrastructure, and resolve possible legal barriers associated with the sharing of such sensitive and personal data. Nonetheless, some data remains locked away in non-participating and commercial biobanks.

2.5 Behavioral Perspective

Although it has become commonplace to refer to the ethical issues, considerations, and values regarding the developments of the genomic revolution, even in publications that are not mainly concerned with those issues, the same cannot be said in relation to human behavior, specifically behaviors relating to the engagement with and responses to genomics. Although prima facie these issues seem at least similar in nature, there are important distinctions between them. One explanation for this can be found by assessing the *construal levels* at which appraisal of these developments takes place. The ethical perspective is an abstract and, in some sense, external perspective that provides a holistic appraisal of the system. Although the issues raised from this perspective are valid, they do not necessarily correspond to the perspective of the individual. Likewise, the perspective of the individual as a distant observer does not necessarily correspond to the perspective of that same individual in situ. As shown across literature, the level of abstraction in cognition influences moral judgements (Mårtensson, 2017). The current section aims to expound on these mechanisms behind this through both Construal-Level Theory of Psychological Distance and the concept of the attitude/intention behavior gap (Trope & Liberman, 2010; Sheeran & Webb, 2016; Farjam et al., 2019).

2.5.1 Construal-Level Theory of Psychological Distance

The amount of psychological distance that is experienced in relation to a situation or event affects the way in which that situation or event is conceptualized, which in turn influences perception and judgement (and in turn, for example, prediction, preference, and action; Trope et al., 2007). The greater the psychological distance that is experienced, the greater the level of abstraction at which a situation is construed. The Construal-Level Theory of Psychological Distance (Trope & Liberman, 2010) describes how psychological distance affects the level of abstraction at which people mentally represent the world around them. Situations which are experienced as psychologically distant are represented by central, abstract, and general features, whilst situations that are experienced as less psychological distant are presented by more incidental, peripheral, concrete, and specific features (Liberman & Trope, 1998; Wakslak et al., 2006). These different kinds of mental representations are referred to as a high-level construal and a low-level construal, respectively. High-level construals are more concerned with meaning, whilst low-level construals are more concerned with actionable or goal-directed details. The relation between construal level and the experienced psychological distance has been shown to be bidirectional (Bar-Anan et al., 2006; Liberman et al., 2007). The influence of psychological distance on cognition complicates the study of human behavior in relation to genomic medicine, as psychological distance varies between contexts and individuals. Furthermore, differences in psychological distances between health-related issues and, for example, socio-economic issues, can influence health-directed behaviors.

Trope & Liberman (2010) have specified four different dimensions of psychological distance; *temporal distance, spatial distance, social distance and hypotheticality.* The four dimensions are closely related to each other (Soderberg et al., 2015; Trope and Liberman 2010; Wang et al. 2019). It is important to note that it is not the actual distance that is of relevance, but only the subjective distance as experienced by an individual. Trope & Liberman (2010) emphasize this in stating that psychological distance is egocentric, *"its reference point is the self, here and now"* (p. 440). Temporal and hypothetical distance are of most relevance to the current project.

Across literature, strong support has been found for the effect of psychological distance on *"both level of abstraction in mental representation and the downstream consequences of abstraction"* (Soderberg et al., 2015, p. 525). To provide just one concrete example, it has been shown that across all four dimensions, the amount of psychological distance experienced in relation to the issue of climate change has a significant effect on both concern about climate

change and willingness to act (Spence et al., 2012; Weber, 2016). Such findings also make sense intuitively; to put it quite bluntly, the less someone thinks something will affect them, the less likely they are to care about it. There are strong indications that this effect of psychological distance is universal, as it has been observed to be stable across cultures (Soderberg et al., 2015). Others, however, have argued that there are also mediating effects of culture on the relation between construal levels and psychological distance (Mårtensson, 2017).

Temporal psychological distance refers to the perceived distance in time to a future situation, and is the first of the four described by Trope & Liberman, initially referred to as *temporal construal theory* (Liberman & Trope, 1998; Trope & Liberman, 2003). The theory states that *"distant future situations are construed on a higher level (i.e., using more abstract and central features) than near future situations"* (Liberman & Trope, 1998, Trope & Liberman, 2003). Situations that are more distant in time are thus mentally represented with other features than those that are closer in time. Specifically, *"in distant future construals, peripheral, incidental, subordinate, and contextual features are either omitted or replaced by more central and abstract features, resulting in more coherent representations*" (Liberman & Trope, 1998, p. 7).

Hypotheticality in psychological distance refers to how likely some future scenario is deemed to be (Trope & Liberman, 2010). Thus, the perceived probability of some situation or event is conceptualized as psychological distance, with events being deemed more psychologically distant as the perceived probability of their occurrence decreases. Across seven different studies, Wakslak et al. (2006) have shown that events with low perceived probabilities are indeed represented on higher construal levels than events with higher perceived probabilities. Particularly interesting is the observation that when comparing low- and high-probability events *"participants increasingly preferred to identify actions in ends-related rather than means-related terms"* (Wakslak et al., 2006, p. 641). This shows that psychologically distant situations are represented more in terms of meaning, whilst situations that are psychologically closer are represented in more actionable terms (Sagristano et al., 2002).

The underlying mechanisms for temporal and hypotheticality effects on psychological distance have been linked to the concepts of temporal and probabilistic discounting, which hold that situations that are either distant in time or deemed unlikely to materialize are valued differently than those closer in time and perceived as highly likely. Studies into the topic of temporal discounting point to parallels between intertemporal and risky decision making (Keren &

Roelofsma, 1995; Prelec & Loewenstein, 1991). It is even proposed that the similarity between these two forms of discounting suggests a single underlying process (Rachlin et al., 1991).

In general, psychologically distant events or situations are those that are not part of an individual's direct experience (Wakslak et al., 2006). This entails that psychologically distant events are those that have taken place in the past or have some probability of taking place in the future, rather than being experienced in the present moment (Wakslak et al., 2006). For situations that are being experienced in the present moment, a rich amount of information is available. This leads to mental representations that are more concrete, and thus take place on a lower construal level. In contrast, a lack of direct experience influences the amount and nature of information available to an individual, which leads to an *abstract processing orientation* (Wakslak et al., 2006). This leads to mental representations that are more abstract schematic, and thus take place on a higher construal level. An event or situation does, however, not necessarily need to be experienced for mental representation to take place on a lower construal level. Rather, *"when an event is proximal (i.e., minimally removed from direct experience), we treat it as if we would an event that we directly experience and approach it with a concrete processing orientation"* (Wakslak et al., 2006, p. 642).

The genomics revolution in healthcare is an ongoing transformation with an uncertain future endpoint. Even for those that are either informed or involved there is considerable uncertainty about what this future state will look like, and at what timescale it will be realized. In other words, a genomics-integrated healthcare system is temporally distant (irrespective of the actual magnitude of this distance) and there is some degree of hypotheticality applicable to the different possible forms this system could take. For members of the public that are not very knowledgeable about or cognizant of the developments that have been described in this paper it is even more challenging to relate to this future state. The same applies to the concept of genomics itself. From an individual perspective, the link between a person's (unseen) genome and its somatic expression is unintuitive and complex and is not part of one's lived reality. This adds to the psychological distances experienced, which in turn would result in higher construal level evaluations of genomics.

Research does indeed suggest that public knowledge about genomics is low and insufficient for informed decision making (Haga et al., 2013; Syurina et al., 2011). This is unsurprising, as building and maintaining health literacy across a population has become *"more complex because of the unprecedented scientific development, at an unprecedented speed"* (Geanta et

al., 2022, p. 204). Simultaneously, there is a *"need to keep target groups adequately informed in order to enable them to access state-of-the-art health care"* (Zimani et al., 2021, p.1).

Over the past decade, the expectations regarding personalized medicine held by both professionals and the public have been influenced by newspaper headlines, speculation, and optimistic promises. Because of this, some have claimed that *"personalized medicine is a paradigm that exists more in conceptual terms than in reality"* (Lesko, 2007, p. 807). On the other hand, coverage in popular media about the subject could also serve to bridge the hypotheticality gap. On top of this, individuals also vary in the extent to which they have encountered traditional forms of genetic testing, either directly through relatives, or the experience they have with novel direct-to-consumer genetics products. Other individuals might have obtained more specific knowledge through education or occupation. Therefore, the psychological distance to a genomics-integrated healthcare system is expected to vary between individuals. Subsequently, conceptualizations or mental representations of such a system and thus the construal levels at which it is appraised by any individual is expected to vary even so.

Central to this thesis is the question of what is valued with respect to a genomics-based healthcare system. However, the mechanism described above makes it complex to research opinions or attitudes with regards to hypothesized future states, as the responses provided by participants have been shown to be contingent upon whether an issue is conceptualized as near or far (in either a temporal sense or with regards to perceived plausibility of future scenarios; So et al., 2021). For example, it has been shown that people utilize more abstract concepts, such as traits and values, with regards to more psychologically distant behavior (Nussbaum et al., 2003). Contrarily, psychologically proximal behaviors are referred to in more means-related terms (Sagristano et al., 2002). This is similar to problems of hypothetical bias in economics studies, where participants have been found to provide different responses to hypothetical situations compared to real world situations (Cumming et al. 2020; So et al., 2021). This leads to the expectation that appraisal of a genomics-based healthcare system as a distant hypothetical takes place on a higher construal level than an appraisal of such a system from the perspective of direct experience as a healthcare receiver, for example. In addition, it remains questionable whether it is possible for others to make a distinction in validity between what is valued by individuals from these different perspectives.

In more general terms, it is expected that the different degrees of psychological distance experienced from the perspectives of ethical thinking, individuals as distant observers, and

individuals as patients will result in different moral judgements with respect to the system of personalized healthcare. There is a respectable body of literature covering the topic of construal level theory and moral judgements (for a review see Mårtensson, 2017). Across studies, it is found that abstract thinking leads to stronger moral judgments. These findings are consistent with the expectation that a larger psychological distance is associated with a larger focus on values. Although there have been some contradictory findings, these are predominantly attributed to *"the domain in which the moral judgment is construed, the procedures used to induce high- and low-level construals, and cultural differences"* (Mårtensson, 2017, p. 34; Žeželj & Jokić, 2014).

Some interesting observations have been made with respect to the somewhat related subject of gene editing. In a study assessing public opinions on the likelihood and permissibility of gene editing it was found that perceptions of the likelihood of gene editing applications varied significantly between participants (So et al., 2021). This study also identified a strong positive correlation between the perceived likelihood of gene-editing applications and participants views on its permissibility across the majority of different applications of gene editing technology included in the study. It was also found that participants *"lacked a strong sense of which applications were considered realistic by scientists"* (So et al., 2021, p. 486). Higher levels of prior knowledge did not significantly improve estimates of the timeframe over which different applications of gene editing could become feasible. Although So et al., do not provide an explanation for this finding, they do note that those with more prior knowledge *"thought that almost every application would be more imminent, including dubious cases like lifespan extension"* (2021, p. 487).

One of the explanations for this is sought in the fact that *"abstracted scenarios tend to retain central features like rationales over subordinate features like questions of feasibility"* (So et al., 2021, p. 475). This could cause participants to be more permissive of certain applications when described in surveys as opposed to when they would be offered in real life (Soderberg et al. 2015; Todorov et al., 2007). It is further noted that participants seem to apply core values (such as morality-based judgements) more easily to situations that are more psychologically distant, e.g. those that are conceptualized on a higher, more abstract construal level (So et al., 2021). This would be consistent with the expectation that appraisal of a personalized healthcare system would be based on different considerations between individuals as distant observers and individuals as patients. In the latter situation, higher level moral considerations could be overruled by those that are more practical in nature (Trope and Liberman, 2010).

2.5.2 Value-action Gap

Although there are some differences between the observations referred to as the attitude-behavior gap, intention-behavior gap, belief-behavior gap, or value-action gap, all demonstrate that that individuals often behave in ways inconsistent with their stated attitudes or values (Boulstridge & Carrigan, 2000; Sheeran & Webb, 2016; Farjam et al., 2019; Flynn et al., 2009). There is a long tradition of research into the value-action gap in relation to conscious consumer behaviors (see Hassan et al., 2016 for a meta-analysis). Research shows, for example, that environmentally conscious attitudes are not necessarily reflected in an individual's consumer behavior (Gupta & Ogden, 2006; Farjam et al., 2019). There are other topics that seem to be widely researched as well. For example, the value-action gap in relation to online privacy has been so well established across literature that this observed dichotomy between attitudes and behavior is referred to as the privacy paradox (see Kokolakis, 2017; Gerber et al., 2018). While there are many more examples of this phenomenon, all amount to humans exhibiting behaviors that are inconsistent with their stated attitudes or values. The existence of this privacy paradox with regards to digital data has led some to questions to what extent this privacy paradox extends to include medical data as well (for an elaborate example, see Büschel et al., 2014). In a study into the privacy paradox in mHealth (mobile health) applications, it was found that perceived benefits have a larger impact on mHealth users' disclosure intentions than privacy concerns (Zhu et al., 2021).

It has been shown that consumer intention to adopt innovations is an inadequate indicator of actual adoption behavior once such innovations become available in the marketplace (Arts et al., 2011). One of the reasons for this is that *"evaluative criteria consumers use in both stages of the adoption process weigh differently"* (Arts et al., 2011, p. 134). It is here that findings from research concerning the construal-level theory and those concerning the value-action gap exhibit significant parallels. Research into construal level theory has shown that appraisal of a situation is contingent upon the psychological distance to it. Similarly, research into the value-action gap shows that value judgements about a situation are often inconsistent with the actual behaviors exhibited in situ. Such value judgements of a situation that is not directly experienced are thus with respect to a situation that is psychologically distant, whilst in situ behavior is exhibited with respect to a situation that is directly experienced and psychologically close. On the other hand, research does suggest that exhibited behaviors can be a reliable indicator of attitudes (Kaiser et al., 2007). This implies that studying patient behavior in relation to genetic testing could be a way to derive their attitudes and judgements.

Taken together, the theoretical and empirical basis of both the Construal-Level Theory and the Value-Action Gap provide significant reason to assume that behaviors and responses in relation to genetic testing and personalized medicine will vary between individuals based on a variety of contextual factors. The stated attitudes of individuals with regards to the system cannot be assumed to be an accurate predictor of the behavior they will exhibit. Studying (the absence of) health-directed behaviors in patients could however be a way to derive the attitudes and contextual factors that influenced the behavior. Such information is crucial for the design of an accessible personalized healthcare system designed to support health-directed behavior. In this exploratory study, relevant patient behavior will be examined through the expert contributions of medical professionals, such as genetic counselors.

2.5.3 Genetic counseling

Genetic counselors are healthcare professionals that support patients throughout the process of genetic testing. Due to their proximity to the subject and practical experience with patients, genetic counselors are deemed to be a valuable source of information regarding the experiences of patients and their own capacity to meet changes in demand resulting from increased genetic testing. Therefore, this group is of special interest to the empirical portion of this study. This section provides a short overview of the role fulfilled by genetic counselors and will elaborate on why they are integral to the successful implementation of personalized care.

Genetic counseling refers to the guidance patients receive prior to and throughout the process of care when genetic testing is involved and is generally described as *"a client-centered communication process, designed to help people understand and adapt to the medical and psychosocial consequences of either having, being at-risk from or passing on a genetic condition"* (Middleton et al., 2017, p. 250). Such guidance is often necessary, as the patient is required to make several significant decisions, whilst the process and results of genetic testing can be challenging to understand. Genetic counselors help to *"prioritize informed and autonomous patient decisions regarding their genetic health"* (Stoll et al., 2018, p. 1). In addition to all matters regarding the individual patient, genetic counselors also *"focus on the psychosocial and family communication issues that may arise from genetic (i.e., shared) information"* (Middleton et al., 2017, p. 250).

As information obtained from genetic testing, and the potential consequences they entail, can negatively impact patients, ensuring psychological wellbeing is one of the primary goals of genetic counseling (Athens et al., 2017). The process of genetic counseling usually includes

the involvement of specially trained medical professionals, such as genetic counselors and psychologists. Due to its patient centered nature, genetical counseling is praised by some as *"ideally suited to help realize the goals of the precision medicine"* (Stoll et al., 2018, p.1). On the other hand, one could also claim that, in the proliferation of personalized healthcare, rather than a valuable addition, genetic counseling is a necessity in ensuring patient well-being.

It is suggested that genetic counseling requires balancing two components: *teaching* and *counseling* (Kessler, 1997). The teaching component is focused on providing factual information from a place of authority, and correcting any misperceptions a patient might have. However, an overemphasis on teaching might promote psychological passivity in the patient. The counseling component is therefore focused on understanding a patient's needs and promoting confidence and autonomy. According to Kessler, counseling is *"about understanding the other person and providing appropriate help in the form of how to think about and work through life problems. This is accomplished in a way that empowers the person, fosters their autonomy, and evokes their competency"* (Kessler, 1997, 293).

Athens et al. (2013) note several challenges in the systematic study of the effectiveness of genetic counseling practices. Between these are lacking consistency in how outcomes are measured and insufficient data collection from end-users. Nevertheless, other systematic reviews show positive effects of genetic counseling interventions. For example, results from a 2017 meta-analysis *"suggest that genetic counseling can lead to increased knowledge, perceived personal control, positive health behaviors, and improved risk perception accuracy"* (Madlensky et al., 2017, p. 361). A 2009 review indeed also suggests that risk perception accuracy is positively impacted for patients that engage in genetic counseling (Smerecnik et al., 2009). Madlensky et al. (2017) furthermore suggest *"decreases in anxiety, cancer-related worry, and decisional conflict"* (p. 361). A more recent controlled study into genetical counseling and patient empowerment found significant improvement following genetic counseling in the two domains they refer to as cognitive control and emotional control (Yuen et al., 2020). The results also revealed *"a need to cultivate hope and facilitate the alleviation of negative emotions in patients during genetic counseling"* (Yuen et al., 2020, p. 246).

Whilst genetic counseling is applied effectively and widespread with regards to traditional genetic testing, when it comes to the proliferation of personalized healthcare *"traditional service delivery models are insufficient and unsustainable"* (Stoll et al., 2018, p. 1). One of the reasons for this is the increase in the scope of genetic testing. Whereas traditional genetic tests

are highly targeted, the amount and scope of information obtained from a full genomic profile is much more extensive, requiring more intensive genetic counseling.

Another reason is that there will be an increased number of patients seeking personalized care. Amplifying the importance of genetic counseling in this is that *"early data suggest that these individuals will have different motivations for pursuing genomic sequencing and will be less knowledgeable about and less confident of the benefits of genetic testing"* (Ramos, 2020, p. 1). There is already evidence that suggests that patients seek out healthcare professionals to help them understand results they obtained through commercial DTC testing services (Brett et al., 2012). The above entails that genetic counselors would need to help an increasing number of patients navigate an increasingly complex set of information. As a result, there are concerns about the workforce's capacity to meet this rapidly growing demand, and the effect this will have on the intensity and quality of counseling available to patients (Stoll et al., 2018).

2.6 Genomics revolution in the European Union

There is a multitude of initiatives around the world that aim to establish systems of healthcare that employ the technologies of the genomics revolution to offer personalized genomic medicine (Manolio, 2015). The World Economic Forum has recognized personalized medicine as *"a priority area for development, emblematic of genomic science's economic importance"* (Ginsburg, 2013, p. 1463; World Economic Forum, 2012). Although this study is focused on The Netherlands, national developments cannot be seen as isolated from the EU's efforts to establish a tightly integrated healthcare system across the union.

As one of the core elements of the EU Digital Single Market strategy, EU eHealth makes the transition towards a more personalized and datafied form of healthcare (and thus the need to deal with its related issues) imminent rather than distant (European Commission, 2018). Under the right circumstances, EU policymaking and standard setting can be a powerful enabler of innovation (especially in uncertain markets; Pelkmans & Renda (2014). This does, however, require a proper understanding of the integrated system of social and economic activity to which it applies (Firth & Mellor, 1999). Given the goals of the DSM strategy, the EU should have a major interest in understanding the value-landscape of this transition.

Organizing personalized healthcare on an EU level offers benefits over organizing on a national level. Within the scope of EU eHealth, the most important aspect is the sharing of citizens' *genetic data* between participating member states. Stakeholders have consistently emphasized

the need for *"a more consistent and comprehensive policy and regulatory framework that would facilitate data exchange among service providers across EU MS [member states] and ensure equity of access to eHealth services for all citizens"* (ESPON, 2019, p. 2). Next to potentially enabling research and subsequent predictive and personalized healthcare for citizens, sharing of data within a tightly integrated European knowledge network could make the European Union a frontrunner in terms of healthcare and bio-tech innovation (European Commission, 2018; Manolio et al., 2013; Golubnitschaja et al., 2014). All this will contribute to improved healthcare for EU citizens and ensure Europe's leading place in health research.

This Digital Single Market strategy for the European Union (EU DSM) is aimed at closely integrating the 28 national digital markets into a single market and enhancing the unions' position as a world leader in the digital economy. It is thought that *"there are massive gains within easy reach for science, research, medicine, healthcare resources, and patient outcomes. But these gains are still to be grasped"* (Horgan et al., 2017, p. 171). A coordinated effort might be the only feasible way to elicit such a radical transformation, as *"most health systems around the world are not fit to shepherd genome sciences into routine health care"* (Ginsburg, 2014, p. 453). As the latter leads to decisions being often made on an ad hoc basis, it is here that the EU is highly relevant as a driver and coordinator (Gaff et al., 2017).

As of December 2022, 24 European member states (including The Netherlands), the UK, and Norway have committed to: bring together fragmented infrastructure and expertise supporting a shared and tangible goal; one million genomes accessible in the EU by 2022 (1+MG), leverage and maximize the investments already made by Member States at national and EU level, particularly in sequencing, bio banking and data infrastructure, and reaching a larger cohort that will provide a sufficient scale for new clinically impactful research (European Commission, 2019; European Commission, 2022). Instrumental to this is the creation of a shared European data infrastructure to *"enable secure access to genomics and the corresponding clinical data across Europe for better research, personalized healthcare and health policy making"* (European Commission, 2022). An example of measures aimed at closer integration would be the setting of European standards regarding data generation, analysis and sharing, and standards regarding interoperability of health informatics systems (Horgan et al., 2017). According to the Commission's roadmap, implementation and deployment of this system should take place between 2022 and 2027 (European Commission, 2022)

The European Union is regarded as being in a great position to capitalize on the genomics revolution and become highly competitive in the genomics sector (Golubnitschaja et al., 2014). Across its member states, the EU has a large and heterogeneous population, diverse ethic population, genetic isolate populations, cohesive and social health systems, similar values and comparable structures, similar legislation, and scientific and technological capabilities in genomics and beyond (Horgan et al., 2017). However, the large degree of fragmentation and lack of coordination between loci of knowledge and expertise is generally regarded as one of the big obstacles to being able to fully capitalize on a healthcare transition. *"Bringing together world-leading practice and expertise that exists in pockets across countries and sectors will make it possible to apply their collective knowledge and skills to address universal health challenges and provide a network for sharing best practice"* (Horgan et al., 2017, p. 173). It is thus of crucial importance that Europe can focus its knowledge capital and transform it into innovation and subsequently into successful commercialization. Although the technical challenges should not be underestimated, *"the greatest challenges are economic, not scientific"* (Jakka & Rossbach, 2013, p. 1).

2.7 Present research

As the transition towards a genomics-integrated healthcare system is a novel and evolving phenomenon, the availability of studies on this topic is limited. Although reports are available on the developments and progress of individual parties and stakeholders, a holistic characterization across interdependent stakeholders is currently lacking. Through an exploratory study using an ecosystems-approach this project aims to provide such a characterization.

Expertise and activities in important elements of the system are often spread across a set of actors and require alignment for value to be created at the aggregate level. Loci where insufficient alignment occurs in a way that poses a barrier to ecosystem success are referred to as loci of friction. Loci of friction that have been identified in a European context relate to the setting of standards regarding data generation, analysis and sharing, and standards regarding interoperability of health informatics systems. Fir for purpose regulatory, policy, and legal frameworks are cited as requirements for successful international collaboration. Knowledge and skill fragmentation and lack of coordination are sources of friction as well. Literature points to additional possible sources of friction or conflict, such as the power and economic value that data holds, the ability of stakeholders to exclude others from accessing their recourses, and the

new modes of cooperation between stakeholders that are required. Furthermore, friction can occur with regard to the requirements a personalized healthcare system poses on the healthcare workforce. Other possible friction in the transition to personalized medicine takes the form of ethical issues, such as those relating to consent, privacy, return of results and information disclosure to relatives. Other prominent ethical issues are the questions a personalized medicine transition raises with regards to accessibility, personal and collective approaches to public health, and the risks of (bio)medicalization and reductionism.

While similar frictions, especially to those identified in a European context, are expected to be present, a comprehensive review of friction of the Dutch personalized medicine innovation ecosystem is currently lacking from the literature. Through expert interviews with ecosystem stakeholders this study aims to provide an overview of frictions present in the ecosystem. The first research question concerns understanding the possible (value-) friction within and between ecosystem stakeholders that could pose obstacles for the successful implementation of a system of personalized healthcare.

RQ1: *Which (value-) frictions exist within or between different stakeholders, and what are the obstacles they pose for the implementation of personalized healthcare?*

One of the objectives of the interviews is thus to obtain information regarding friction experienced by the stakeholders, either within their own stakeholder group or between their own and other stakeholder groups. It is aimed at understanding the values that each of the stakeholder groups hold, how these translate into system requirements, and how such requirements relate to the available resources. The focus is thus not solely on *what* different stakeholders desire from the system, but also on *why* these specific things are desired.

When studying the behavior of individuals in relation to a system of personalized healthcare, the concept of psychological distance is relevant, as participants have been found to provide different responses to hypothetical versus real world situations. It is expected that for most individuals, genomic healthcare concerns psychologically distant concepts that are not part of an individual's direct experience, and therefore psychologically distant. The link between a person's genome and its somatic expression is unintuitive and complex and is not part of one's lived reality. This influences mental representations, which in turn influences the health-directed behavior exhibited. Furthermore, research on the value-action gap shows that individuals often act in ways at odds with their attitudes or intentions, caused by a variety of contextual factors. Exhibited behaviors can however be a reliable indicator of attitudes.

As a step towards behavioral research that explores relevant behaviors in detail, this study aims to characterize the relevant health-directed behaviors and responses exhibited by patients in relation to the process of genetic testing in healthcare. As this is an exploratory study, this study will not directly study patient behavior, but will characterize relevant aspects of behavior through the expert contributions of healthcare professionals, such as genetic counselors. These professionals, due to their practical experience in the field, are vital in charting the relevant aspects of human behavior for the establishment of a system of personalized healthcare.

Understanding these behaviors requires an understand of the factors that might have influenced the cognitive representation of concepts and the decision-making process. Beyond the behaviors and responses, themselves, this study is thus interested in the mechanisms behind different kinds of behaviors. Furthermore, this study is interested in the contextual factors, such a socio-economic factors and health-literacy, that influence individuals' health-directed behaviors. Examples of important issues in relation to health-directed behaviors is an individuals' ability to understand the concepts of genetic healthcare, individuals' ability to engage in competent decision making, individuals' particular reasons for (not) acting on certain information, and fears individuals might have about the broader implications of genetic testing.

The second research question thus focuses on the role played by individuals in a system of personalized healthcare and is concerned with engagement and responses in relation to this system. This information is relevant to both ensure that the system meets the needs of patients and that resources are employed such that they will empower patients to engage in health directed behaviors.

RQ2: *What are the reactions and behaviors exhibited by patients and relatives in relation to the process of genetic testing in healthcare, and which factors have influenced them?*

The second objective is thus to characterize patient behavior and the factors that influenced the behavior in the context of genetic testing in healthcare. A distinction is made between the different phases of the process, specifically about engagement and responses before, during, and after engaging with genetic testing. The before state also explicitly includes those that are potential patients, such as informed relatives of those with hereditary conditions.

3. Method

This research will perform data collection through semi-structured interviews and data analysis through subsequent thematic analysis. The semi-structured interviews allow rich data to be obtained from a set of heterogenous stakeholders, whilst thematic analysis allows for the extraction and characterization of dominant themes between these stakeholders.

A semi-structured interview approach is chosen to ensure that the same basic information is obtained from each interviewee, whilst also affording the possibility to probe deeper into subject matter specific to a stakeholder (Adams, 2015; Magaldi & Berler, 2020). As the research concerns stakeholders which exhibit both overlap and divergence in the roles and functions they occupy within the innovation ecosystem, the flexibility of semi-structured interviews is uniquely suited to this research. Methodological guidance for the interviews was predominantly obtained from Brinkman & Kvale (2018) and Roberts (2020), and from the IRP framework by Castillo-Montoya (2016) for the interview guide.

Data collected during the interview phase will subsequently be analyzed using thematic analysis in order to extract themes with regards to the research topic which re-occur between the different stakeholders. Using thematical analysis in this way is consistent with the exploratory approach that this research takes. The thematic analysis will follow the six steps from the process developed by Braun and Clarke (2006). The thematic analysis will result in a list of themes, each consisting of several sub themes. These sub-themes will be characterized and excerpts from the data will be used to illustrate the presence of these themes in the data.

Although the characteristics of the selected methods make them uniquely suited to the current research, the limitations of these methods should also not be ignored. Therefore, before presenting the remainder of this section, the next paragraph outlines the steps taken to ensure rigor throughout the interview process and thematic analysis.

3.1. Researcher reflexivity

Reflexivity refers to a researcher's effort and ability to explore, acknowledge, and guard against the influence of biases and assumptions in the research process (Magaldi & Berler, 2020). Personal biases will be managed throughout to mitigate the influence of researcher subjectivity, and to ensure the empirical process remains discovery oriented in rather than confirmatory (Elliott et al., 1999). The current research is performed by a single researcher, formulating the

research questions, and conducting both the interviews and data analysis. Ensuring an adequate level of researcher reflexivity is thus of major importance. One major element of managing biases has been frequent discussion with at least two supervisors on the research project, intended to detect any individual assumptions or biases.

From the research questions, objectives for the interviews were formulated. These are formulated such that they emphasize the types of information that is to be obtained from participants, without assumptions regarding any specifics. Research questions were generated from these objectives in an iterative manner, with each step including discussion with and feedback from the supervisors to the project. Questions were critically evaluated for the way in which they might introduce subjectivity, and if required, adjusted accordingly. An initial interview was conducted to assess the way questions were understood by the participant, and questions that left room for interpretation were again adjusted accordingly.

Extensive familiarization with the transcripts took place prior to coding to ensure proper understanding of participants responses and spot any biases or assumptions in interpretation. Initial coding was kept close to the data and devoid of subjective interpretation. Two full rounds of coding were performed to aid reliability in assigning codes and evaluate existing codes for subjectivity. Themes were formulated close to the data, and associated excerpts preferably highlighted a multitude of perspectives on this common theme. A third round was performed to ensure proper alignment of excepts with theme definitions. Code and theme definitions and accompanying notes were employed to ensure consistency in inclusion and exclusion of data during coding. The software packed employed ensured that all data could be organized and managed efficiently and effectively. During and subsequent to coding the data, identified themes and underlying data were discussed with, and critically evaluated by, the supervisors to the project.

3.2 Interview guide

The nature of the semi-structured is such that it allows for both convergence and divergence with regards to the information that is obtained from each interviewee. An interview guide was developed to provide basic structure and focus to the interviews (Brinkman & Kvale, 2015). Interview questions were developed such that they ensure appropriate coverage of the dominant and overlapping subjects indicated by the objectives between all interviews.

The interview guide consists of a list of open questions to be asked, and instructions to the interviewer to encourage the participant to share freely from experience (Seidman, 2013; Brinkman & Kvale, 2015; Roberts, 2020). Furthermore, the interviewer is instructed to probe deeper into relevant information provided in a response by the participant. No strict order of the questions is prescribed, although an order is suggested, nor does it prescribe predetermined follow-up questions. It therefore affords the interviewer significant flexibility in conducting the interview. As all the interviews will be conducted by the same interviewer, this freedom and flexibility is not expected to lead to inconsistencies impacting the reliability of the results. Questions deemed to fall outside of the scope of expertise of a specific participant will be omitted from the interview, to ensure the focus remains on those subjects for which the participant is able to provide valuable information.

The interview guide was developed following the Interview Protocol Refinement (IPR) framework set forth by Castillo-Montoya (2016). This framework was introduced to *"strengthen the reliability of interview protocols used for qualitative research and thereby contribute to improving the quality of data obtained from research interviews"* (Castillo-Montoya, 2016, p. 811). The framework is centered around a four-phase process: *(1) ensuring interview questions align with research questions, (2) constructing an inquiry-based conversation, (3) receiving feedback on interview protocols, and (4) piloting the interview protocol*. As the development of the interview guide is an iterative process, some of these phases have been completed multiple times.

In order to ensure alignment between the interview questions and the research questions, the interview questions are developed on the basis of the objectives set forth in formulating the research question. Developing the interview questions started with an initial brainstorm, resulting in a list of questions broadly covering the issues at hand. Care has been taken to ensure the formulation of questions did not influence participants to provide responses that are in line with any predetermined expectations. Questions concern predominantly the values and interests of respective stakeholder groups, changes in values over time, the way in which values influenced actions, instances in which these values caused friction within the group or with other stakeholder groups, and the barriers this poses. Additional questions have been formulated regarding experience and behavior of individuals. Questions were subsequently evaluated considering the objectives, the research question, and the other potential questions.

Questions deemed too similar in nature were either combined with each other, or discarded if one of the questions made the other superfluous. Some questions were adjusted to represent their scope more clearly, whilst others were adjusted to prevent the use of confusing language. The process resulted in a list of 11 broad questions that were deemed to align with both objectives set forth and were intended to serve as a guide for the generation of a larger number of more detailed questions.

These initial questions were discussed in a meeting with the supervisors of this project to determine whether coverage of the subject matter was sufficient, and adjustments were made to these broad questions to ensure generation of an appropriate set of improved questions. Additional questions were generated to accompany existing questions, which included a question inquiring about how knowledge about stakeholder values was obtained, and a question to explore a specific trade-off between values. Questions pertaining to the individual were split up to discriminate between people in general and patients specifically. Based on the adjusted main questions and the additional feedback provided, a list of 22 questions was generated, from which an initial full interview guide was constructed. This interview guide was evaluated using the *Activity Checklist for Close Reading of Interview Protocol* from the IPR Framework (Castillo-Montoya, 2016). Where relevant, changes were made to the interview guide based on any shortcomings revealed through close reading with the IPR checklist. Important for the reliability of any responses obtained is whether the interview questions are sufficiently well understood by the participants, and whether such an understanding is consistent with the expectations of the researcher (Castillo-Montoya, 2016). Since internal feedback is only of limited use in this regard the initial interview guide was tested in situ during an initial interview. In addition to any notes pertaining to the content of the responses provided by the participant, the interviewer was tasked with logging any other observations of relevance.

The initial interview guide together with the notes from the pilot interview were discussed in another meeting with the supervisors of this project. The pilot interview revealed that core concepts (such as values, for example) might not be as self-evident as initially assumed, and participants understanding of the questions might be aided by providing a definition of the core concepts and checking whether the participant has understood them as such. It was also found that some questions might need to be repeated if multiple relevant stakeholder groups are discussed to avoid ambiguity in interpreting the participants responses. Other changes included subtle changes to questions to entice participants to include more concrete examples in their

answers, and have participants illustrate how their experiences relate to factual situations. The final 22 questions can be found in Table 1 and Table 2. The final interview guide verbatim can be found in Appendix A. As all interviews were performed in Dutch, the final list of questions was translated to Dutch prior to the interviews.

Number	Question
1	How would you describe [organization]'s role in contributing to a system of personalized healthcare?
2	How do [organization]'s activities contribute to accelerating personalized health?
3	How would you describe the relevance of [organization] in the ecosystem?
4	To what extent is the approach that [organization] takes value driven, versus values just playing a role in the process?
5	Which values are important in [organization]'s role? Can you provide concrete examples?
6	Which stakeholders do you consider, and what values are important to one and not the other?
7	How were these values uncovered? Where the stakeholders asked directly?
8	If you trade off value [X] against value [Y], who is impacted and in which way?
9	Are there any value conflicts or value friction that you encounter?
10	Are there major changes over time in values that parties bring to the table?
11	How would the values that you hold dear be embodies in advice you give, or how would they be implemented in real world cases?
12	How do you weigh the interests of researchers, citizens, care providers and industry (against each other)?
13	What is the public response towards your activities?
14	What are some major barriers that you see, and what is their nature?
15	How are the collaborations between stakeholders going?

Table 1 *List of the 15 general interview questions*

Number	Question
16	What are the dominant subjects about which people seek information in relation to genetic testing?
17	What are the dominant subjects that people express concerns about in relation to genetic testing?
18	How would you characterize the types of reactions patients have when they are initially involved in the process of genetic testing?
29	How would you characterize the types of reactions patients have to the return of results of genetic testing?
20	In the process of genetic testing and return of results, are there any changes over time in the information patients seek or the concerns they express?
21	To what extent does the process of genetic testing and return of results impact health directed behaviors in individuals?
22	In practice, how do healthcare professionals deal with findings that apply to relatives of the patient?

Table 2 *List of the 7 behavior specific interview questions*

3.3 Selection of participants

Interviews were conducted with a total of 8 participants, all of which were representatives of one of the stakeholder groups. It should be noted that that, despite best efforts, stakeholder representation is not exhaustive. Nevertheless, given that the major stakeholder groups are all represented in some way, the group of 8 participants is deemed to be of appropriate size and distinction. Broadly, six categories of stakeholder groups were identified to be included in the interviews: *(1) government, (2) industry, (3) academia, (4) healthcare sector, (5) patients, and (6) the public*. Specifically, governmental bodies concerned with regulating the use of personalized medicines in healthcare, industry parties involved with the development and provision of personalized medicines, academics focused on the ethical and legal aspects of personalized medicine in healthcare, academics performing research in the field of personalized medicines, healthcare professionals such as medical geneticists and genetic counselors, and independent bodies representing patient and public interest. Demarcation of stakeholder groups is not strict or exclusive, as for example, patients also belong to the public, and entities in the healthcare sector might show affiliation with industry and/or academia.

Two approaches to scouting prospective participants were taken. The first was to identify relevant institutions, associations or interest groups that represent the interests of relevant stakeholders. Information from collaborative initiatives in the field of personalized medicine was consulted to identify parties engaged with a transition towards the application of personalized medicine. This also led to the identification of relevant governmental bodies. Information about the Dutch academic hospitals was examined to identify which hospitals and departments had relevant expertise and preferably involvement in relevant personalized medicine initiatives. Relevant academic research groups were identified through recent contributions to literature and personal communications with researchers at different universities. Identified stakeholders include administrative bodies, industry associations, professional associations, and academic medical research groups.

The second approach was to directly identify individuals with relevant expertise. Academics were again identified both through recent contributions to literature and through consulting other academics in relevant disciplines. Medical geneticists and genetic counselors were identified both directly via the academic hospital's department website, or via recommendations via the secretarial offices of such departments. Most individuals approached, including all the individual geneticists and genetic counselors, proved unwilling to participate

in the interviews. Emphasizing and elucidating the relevance of their expertise did not change this. In such cases, it was decided to have this group represented by their respective association.

An invitation letter was sent out to a selection of prospective participants. In initial attempts to contact prospective participants it was observed that some did not deem their expertise to be relevant enough to the subject to participate in the interviews. For example, two genetic counselors informed the researchers that they did not want to participate in the interviews as they were not involved with personalized medicine. This even though the researchers deemed genetic counselors to be a prime source of information regarding patient experience. Therefore, a new invitation letter was crafted, aimed at both illustrating the relevance of the subject, and the relevance of the prospect's expertise in relation to the subject.

An initial email expressing interest in interviewing a representative and a general description of the research was sent to a diverse group of purposively sampled stakeholders. If positive follow up was received, the invitation letter for the interview was sent to the representative. In the cases in which a prospective participant with relevant expertise was directly identified, the interview invitation letter was sent or addressed directly to the individual. The specific parties approached for the interviews were deemed to be appropriate representatives of the different stakeholder groups. In total, 24 organizations or individuals have been approached to participate in the interviews, of which 8 have resulted in a positive response and subsequent participation in an interview.

With regards to stakeholder value friction, the number of representatives per group is lower than desired. However, as most of the interviewed parties are associations or bodies specifically tasked with representing the interests of the group, all the stakeholder groups are deemed to be sufficiently represented. With regards to human behavior and responses, the last interview with a representative of this stakeholder group did not result in significant new information, and saturation was deemed to have been reached. An anonymized overview of the participants and a general description of their relevant expertise can be found in Table 1.

3.4 Interview procedure

Consent forms were provided through email and collected in advance of the interview. Consent for the recording of the interview was established again prior to the recording being started. All interviews took place in the form of a virtual meeting using Microsoft Teams, and the interviews were conducted by a single interviewer. The same interviewer conducted all

sessions. Rapport was built throughout the interview but did not receive any special attention due to the predominantly factual content of the interviews.

The interviews started with the interviewer thanking the participant for their time, and a short summary of the research and the goals of the interviews. Participants were offered the opportunity to ask any questions they might have had, and any insecurities were resolved. Participants were made aware of the fact that data would only be presented in anonymized form and were encouraged to speak and associate freely.

The interviewer would continue the interview by asking the questions from the interview guide. Participants were provided with as much time as they needed to provide an answer. After an answer was provided, the interviewer would generally ask a follow up question or provide clarification to elicit as much relevant information as possible. When the participant had provided enough relevant information, either directly or after following up, the interviewer would move on to the next question. Whenever a question was encountered that was not relevant to the current participant it would be skipped. After completion of the interview guide participants were thanked for their time and were made aware that any questions or remarks they might have after the interview could be sent to the researchers over email.

Participant	**Description**
Participant 1	Representative for a non-profit initiative working to establish an integrated health data infrastructure for research and innovation, to improve personalized medicine
Participant 2	Representative for an independent administrative body concerned with the accessibility of healthcare
Participant 3	Representative of a trade association for pharmaceutical companies involved in the development of new medicines
Participant 4	Representative of a trade association for pharmaceutical companies involved in the development of new medicines
Participant 5	Pediatric pulmonologist, involved in pharmacogenetic research using organoids for personalized medicine
Participant 6	Representative of a national information center focused on heredity and genetics
Participant 7	Assistant Professor Ethics & Philosophy of Medicine, focused on Precision Public Health
Participant 8	Representative for a scientific association for medical specialists in the field of clinical genetics

Table 3 *List of participants and description of relevant expertise. Participant numbers correspond to the order in which the interviews were conducted.*

3.5 Transcription

Edited literal transcriptions were produced from the recordings. After the interviews, recordings of the interviews were downloaded from Microsoft Teams and stored in a protected environment. The open-source FFmpeg Python library was used to extract audio from these video files for each of the interviews. Subsequently, in a local Python environment, the automatic speech recognition system Whisper by OpenAI was used to perform speech-to-text conversion on each of the extracted audio files. The medium-sized multilingual model (OpenAI, 2023) was used, with the original language parameter set to Dutch. This resulted in a text file with an initial literal transcription for each of the audio files.

The initial transcriptions were examined, and samples were compared to the original recording to validate that the output produced by the automatic speech recognition system was of sufficient quality. The output was deemed to be of good quality, with only minor transcription errors present. All initial transcriptions were subsequently manually formatted, and any transcription errors were resolved. In addition, any grammatical errors from the original interviews were resolved, and repeated words and non-lexical vocables were removed from the transcript. When necessary, the researcher would refer to the original audio file.

Subsequently, these transcriptions were examined again and formatted to prepare them for analysis. Paragraphs were created to delineate between the different relevant units of analysis. Any sections of the transcript that did not contain information that was of direct relevance to the analysis (such as the formalities at beginning and ending of the interviews) were removed at this point. This resulted in the final edited transcripts.

3.6 Analysis

A thematic analysis was performed on the transcripts following the process described by Braun and Clarke (2006). This process consists of six distinct phases: *(1) familiarizing yourself with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes (5), and (6) producing the report* (Braun & Clarke, 2006, p. 87). These six phases are steps in an iterative process that will be performed multiple times. The software package Atlas.TI (Atlas.TI, 2023) was employed to facilitate efficient coding of the transcript, theme generation, and management of excepts.

Familiarization with the data started during the interviews, all of which were conducted by the same researcher that is performing the thematic analysis. Familiarization with the data continued during the formatting and preparation of the transcripts and was followed by a

minimum of three full read throughs of each transcript over the course of two weeks. This phase revealed several potential themes throughout the data set.

After familiarization a first full round of coding was performed on each of the transcripts. Coding in this initial round was deliberately kept close to the data, with codes representing specific concepts. As many of the transcripts as possible were coded, with the number of uncoded excerpts kept to a minimum. After the initial round of coding, the codes were evaluated and those that represented a similar subject were grouped under a theme. For example, all codes representing different loci of friction between stakeholders were grouped under the overarching theme of *friction*. Some codes were renamed to better capture what they represented across the transcripts. Each code was provided with a short definition, and if necessary, additional notes to aid inclusion and exclusion decisions during coding.

After revising and grouping the codes generated during the initial round of coding, a second full round of coding was performed on each of the transcripts. Excerpts with codes that poorly represented them were judged for their relevance and either assigned a new code or discarded. Uncoded parts of the data that showed a good fit with existing codes were assigned this code. After the second round of coding, some codes were assigned to a different theme if it were judged to be a better fit. The second round of coding resulted in 179 unique codes grouped under 10 unique overarching themes. These themes were reviewed, provided with a definition, and renamed if appropriate. An overview of themes and codes was shared and discussed with three members of the research team and one external researcher. This resulted in a selection of 10 themes which most closely and exhaustively characterize relevant aspects of the data.

A third round of coding was performed with two main objectives. First, to reduce the number of unique codes per overarching theme by merging them into distinct sub-themes. Second, to select excerpts from the data which illustrate and contextualize the presence of the theme in the data. To do this, the 10 themes selected in the previous phase were evaluated again, renamed if appropriate, and provided with a definition for that overarching theme. Then, all coded excerpts were evaluated for their fit with the defined theme. Excerpts judged to be suitable representatives of a theme for inclusion in the results were labeled as such.

Of the 10 themes, 4 were judged to be overarching themes, whilst 6 were judged to be a sub-theme of one of the overarching themes. Combining these 6 with 17 sub-themes from merged codes gave 23 sub-themes in total. Additionally, 6 of these sub-themes further break down into 23 sub-themes, resulting in 38 unique sub-themes. Figure 1 presents the full thematic map.

4. Results

The current section will present the results from the thematic analysis. This section will first cover the results with regards to stakeholder friction in the innovation ecosystem and subsequently covers the results regarding instrumental barriers, ethical issues, and human engagement and responses. Themes are presented and contextualized with excerpts from the interviews, with participants indicated by their number as presented in Table 1.

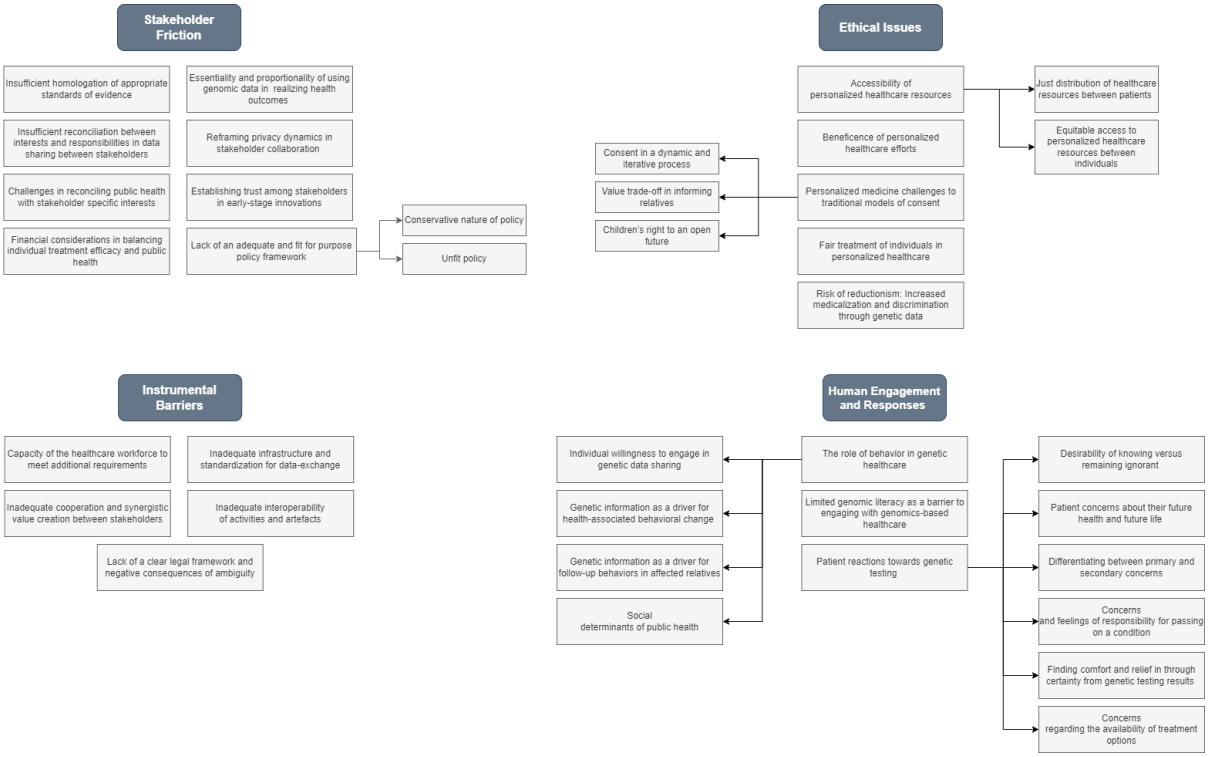

Figure 1 *Full thematic map*

4.1 Stakeholder friction in the innovation ecosystem

Figure 2 presents a sub-section of the thematic map pertaining specifically to stakeholder friction within the ecosystem. Stakeholder friction refers to the issues and challenges stakeholders experience in the cooperation, collaboration, and/or interdependencies with other stakeholders. Some of these frictions are the result of a clear value-conflict, whilst others take the form of process, operational, or regulatory friction in the absence of a clear value-conflict.

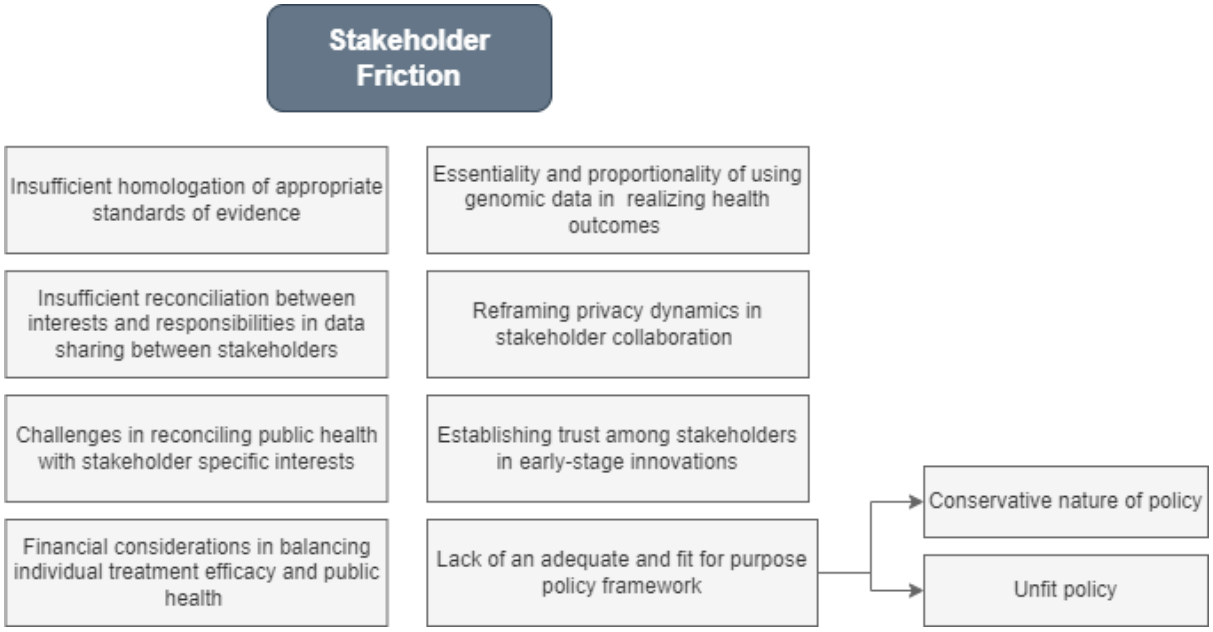

Figure 2 *Thematic map of themes and sub-themes relating to stakeholder friction in the innovation ecosystem*

4.1.1 Insufficient homologation of appropriate standards of evidence

This locus of friction concerns the standards of evidence for the introduction of new diagnostics and interventions in personalized medicine. It concerns a discrepancy between the evidence demanded by policies or laws for the adoption of new interventions and the evidence that can be provided by those developing personalized medicines. Current evidence-based medicine frameworks are based on notions of collectivity, focusing on group-centered studies, and are not well suited to assess a new generation of highly personalized medicines. The type of friction here is structural and regulatory misalignment through bureaucratic inertia. Regulatory bodies and legislative processes are comparatively slow-moving, which creates a lag between the development of personalized medicines and their official approval and adoption.

Friction predominantly occurs between the pharmaceutical industry as producers of personalized medicine and the regulatory bodies that determine which diagnostic tools and intervention are adopted and covered by health insurance. For the approval of new medicines, governmental bodies are bound by frameworks with specific requirements for the evidence of the medicine's safety and effectiveness, which executive institutions cannot independently alter. These frameworks are based on collectivity, where evidence-based assessment of medicines is generally based on group studies, large sample sizes, and meta-analysis, and are thus not well suited to assess the new generation of highly personalized medicines.

"Legally, we adhere to the principle of evidence-based medicine. Evidence-based medicine is a scientific methodology that is essentially and fundamentally based on collectivity, so you don't really focus on a single patient. But when you are dealing with a small group of patients, we believe that this methodology is inadequate. How do you then apply a methodology that is based on a collective understanding and all statistical assessments and significance between various datasets, for example, to an orphan drug, for which a limited number of patients are eligible, or to an individual when it comes to personalized medicine?" (Participant 2)

This lack of a proper framework to assess personalized medicines creates friction with those that are attempting to develop such medicines and to make them available to patients. As personalized medicines poorly lend themselves for assessment through traditional methods, even if convincing evidence existed, it would be inadmissible.

"If I collect data point ABC and conduct a comprehensive analysis on it, and that analysis is really well-structured, with a clear causal relationship, but the person ultimately responsible for the assessment or payment wants to see data point XYZ, then my analysis can be as perfect as it can be, but in practice, I can do very little with it. And then the barriers, in this case, are purely in the realm of governance, so to speak, and not because we lack information." (Participant 4)

For those medicines that do find approval, there is friction with regards to the available forms of diagnosis. Doctors will not be able to make personalized medicines available to those that could benefit from them if these patients cannot be successfully identified. In addition, the pharmaceutical industry might also decide against making a medicine available in a specific market if only a fraction of patients can be successfully identified.

"If you look at the situation in the Netherlands, for example, where a number of medications are coming onto the market, and the diagnostic structure we have in the Netherlands doesn't align with how we have designed our studies. As a result, I'll give you an example, only 5% of the expected number of patients are being found. This is, of course, challenging for our companies […] because you can't achieve your expected revenue, and you can't help the patients even though you know they exist. On the other hand, it's also challenging for doctors because they might have such a patient in front of them, but they can't identify them due to the lack of proper diagnostics. Ultimately, this creates a conflicting interest within the system." (Participant 4)

4.1.2 Insufficient reconciliation between interests and responsibilities in data sharing between stakeholders

This locus of friction concerns the sharing of data, the rights that come with owning data, and the responsibilities that come with data stewardship. Friction occurs because data sharing between different stakeholders is necessary for the common interest of improving outcomes in the field of personalized medicine, yet each of the parties that wants to share or obtain data might also aim to further or protect their own interests with that data. This type of friction is value-conflict, manifested through conflicting interests, goals, responsibilities, and rights between stakeholders.

One of the risks is that data that is collected based for a specific purpose or within a specific justification would be used (whether by other parties or not) for a purpose that does not align with the initial purpose/justification. For example, if a private entity would be able to generate disproportionate benefits for themselves from data that was provided by individuals under a common good justification, this would clearly be at odds with each other. On the other hand, private parties have an interest in being able to capitalize on their own data and expertise. This could make it difficult for parties to engage with each other if they cannot find sufficient alignment in their goals.

"Other work on how the common good is discussed is also very interesting because it explores how it is justified here: is it worth investigating? Because it also reveals, if you justify it in this way, it says something about the goals you have and what they should achieve. And then you can at least hold someone accountable when you say, 'Well, we ask people to share to contribute to this research.' Well, then you also want to ensure that the commercial parties using it don't obstruct that goal or do something entirely different, which is actually at odds with that goal." (Participant 7)

Difficulty is increased by the fact that once data is shared, it is very difficult to exert control over that data. Especially in a field that is seeing rapid development, and which both novel and incumbent private entities are trying to enter, a lot of parties will eventually be acquired or merged. On the other hand, successful initiatives from the academic side could be spun-off into a private entity. All this makes it difficult to exert control over any shared data and to ensure that the data serves the purpose for which it was collected.

"I can see it here in the hospital to some extent. They have a great initiative, they want to develop a nice app, or something that requires technological innovation. Then they start working with a small, sympathetic company. A few young guys who have a great plan. And they really see something

like, 'I want to make a difference for society, which is better than what big companies do.' But then there comes a point, it works, it performs well, and now what? Because healthcare always involves scaling up. Because, of course, it's enormous. If it's for a specific patient population, you want to make it widely available. Moreover, you have no reason not to. And then there's that challenging step, where indeed such a company, as we're seeing in the example now, is bought by [multinational healthcare company]. And now the rights are with them. So, you have shareholders who call the shots. And now it's stagnating a bit because it's not necessarily commercially very attractive. But especially when it needs to reach a certain patient group, you know. And it stays there." (Participant 7)

"A company always goes for the money and might be taken over. And who knows what they'll do with it? You simply give [the data] away, and it's gone." (Participant 8)

Another important aspect that impacts data sharing is reciprocity in the exchange, and the proportionality of that reciprocity in relation to the interests' parties have in keeping their data shielded. As seen in the previous excerpts, parties from the healthcare system can be reluctant to engage in data sharing due to the fear of loss of control over their patient data, for which they carry a responsibility. On the other hand, parties from the pharmaceutical industry, while wanting to obtain data from other parties, can be reluctant to share proprietary information that was obtained through significant investments. While both parties seem to recognize the value of cooperation, the mentioned factors might prove dominant in preventing data exchange.

"For example, when you talk to commercial parties, they will probably say, 'Yes, all fantastic,' because they are only thinking, 'Bring on the data.' Then you have to tell them, you know, that might also mean that what you generate has to go to other parties. The pharmaceutical industry, for instance, all that information about clinical trials is not readily available. Meanwhile, there is an increasing demand for data from healthcare and academic research. So, you have that conversation about it, and when it becomes clear, yes, but this is what we mean, of course, you also get the response, 'Do you know how much it cost to conduct those clinical trials and generate that data? There are implications if that information becomes public.'" (Participant 1)

What becomes clear from the data is that looking at data sharing from the perspective of ownership of data (whether in a legal or practical sense) is insufficient. Rather, it seems that in the process of data sharing comes with a certain expectation of stewardship. That is, parties want to impose a responsibility on each other to prevent the data from being used in ways that are deemed undesirable by the sharing party. However, as mentioned above, keeping track of data and its use would require a compatible infrastructure.

"What I just outlined about the somewhat more commercial interests and who exactly has control over the data. Very often, it still revolves around ownership, while I always prefer to talk about responsibility. You may want to have it, but you are also responsible for it. And responsible for ensuring that something is done with it, not just sitting in your database. And how? And how do you coordinate that? So, I think these are also things that come up a lot." (Participant 1)

"In this case, I think it's very interesting to study what they claim to do, what promises they make, what does the infrastructure look like, how is it justified, and can you discern from that architecture that it serves that purpose." (Participant 7)

4.1.3 Challenges in reconciling public health with stakeholder specific interests.

Although diverging interests between stakeholders underly many of the other loci of friction, a reoccurring locus of friction that between public health interests and stakeholder specific interests. The latter mainly relates to the particular interests of individuals and the commercial interest of industry parties. This type of friction is value-friction, manifested through diverging interests, and diverging value-priorities with regards to justice and the fair distribution of resources between parties.

One kind of friction, although this might not be experienced explicitly, occurs between the individual and the collective. Although there are countless different ways in which this could occur, all follow a pattern in which individual actions that might seem inconsequential (or even beneficial) to the individual in the short term might lead to long term collective harm. While an individual might not experience any direct harm by sharing their data with any party, such sharing decisions could affect the healthcare system in ways that will harm the collective. This friction also concerns the institutions faced with the trade-offs of allocating resources between the development and provision of personalized versus collective medicines.

"But yeah, these kinds of very rigid ways to ensure that it's truly fair and just... well, that's not at all the case with commercial parties. And that's because [some uses of] data, of course, cause a kind of harm that is very indirect and implicit and more at the public level than at the individual level. So, it's not necessarily that I feel harmed by sharing my data, but I do feel harmed if, at some point, I no longer receive the same level of care I had ten years ago." (Participant 7)

"If this new form of care is covered healthcare, that means it has to be paid for from premium funds, from our public wallet. Well, it's fine for those who need that care, but the money has to come from somewhere, and you can only spend a euro once. This means that, in a way, making new technology accessible may require that you limit healthcare access in another area." (Participant 2)

A pervasive locus of friction is that between public health interests and commercial interests. One the one hand, there is the risk that some parties will obtain excessive personal benefit from those personalized medicines that will serve a large patient population, although serving this large population is beneficial from both a public health and a commercial perspective.

"For example, 23andMe has a very large database with millions of people, and there are research institutes that apply for access to that data to conduct research with it, so it works the other way around as well. These companies can easily obtain that data, but they are focused on making a profit and earning money from it. If research indeed takes place within a scientific framework with certain restrictions, and no money is made from it, well, personally, that seems better to me, but of course, it depends on who you ask." (Participant 6)

On the other hand, the influence of commercial interests introduces the risk of a lack of development of personalized medicines that will serve only a small patient population, as a smaller market negatively affects the ease with which investments can be recouped and profits can be realized. In the latter case, there is less overlap between public health interests and commercial interests.

"So, there's also a kind of tension there; it's not just that we need big tech to progress. It also hinders things that are necessary but not commercially interesting. The technological innovations that we would all benefit from but aren't very exciting because they simply won't generate a lot of profit. So, that tension is always present." (Participant 7)

4.1.4 Financial considerations in balancing individual treatment efficacy and public health

This locus of friction revolves around the financial aspects of personalized healthcare, and concerns distribution of costs and benefits, and allocation of resources. This type of friction is value-conflict in resource allocation, resulting in a resource allocation dilemma between stakeholders. It concerns trading off individual treatment efficacy versus public health impact.

Those governing the allocation of public funds for healthcare, whether it is for research and development or the actual provision of healthcare, want to ensure that maximum public benefit is created with the provided resources. They are therefore diligent in how such funds are spent and have been quite conservative in including forms of personalized medicine into covered care, especially when more cost-effective alternatives are deemed to be available. It can also be challenging to justify paying for interventions when there are unresolved issues pertaining to the appraisal of evidence concerning the effectiveness of these medicines (as discussed in

the *standards of evidence* theme), and/or when there are other avenues available through which the same resources could create more public benefit.

"There's always a price tag attached, if you invest in point A from the public wallet, you can't invest in point B. Be conscious of that choice; that's what it's all about." (Participant 2)

However, the pharmaceutical industry argues that this approach can also lead to inefficient use of resources. They think that doctors should prioritize the most effective treatments even if they are more expensive, which could lead to cost savings in the longer term. There is thus clear disagreement between those that supply personalized medicines and those that need to pay for them about the most effective application of each other's resources.

"It's like, 'Let's try the inexpensive options first, and if they don't work, then we'll go for the costly ones.' Whereas we say, 'Choose what works best, and if it's cheaper, that's great, excellent, go for it. But if the expensive option is the one that works, it's a bit unethical to give a patient four or five treatments that are unlikely to work, before using something you know for sure will work.'" (Participant 3)

"It's also an entirely new dynamic. You must imagine that in the Netherlands, we primarily view medication through a cost perspective. However, if we consider a scenario where we introduce a new medication to the market, which is essentially introduced as a fifth-line treatment, we handle it differently. For instance, if you use it in the second line. You might pay a bit more, but you gain in sustainability because you use fewer resources, which is a win, and also in productivity." (Participant 4)

However, the arguments made by the pharmaceutical companies do not seem to be convincing to those that influence which medicines are provided to the patients, such as doctors and insurance companies. These parties regard these medicines as unnecessarily expensive.

"These are conflicting interests, yes, they are quite clear when you look at the pharmaceutical industry versus doctors and insurers. Pharmaceutical companies also want to make money, but doctors (and sometimes patients as well) believe that some medical treatments are being priced too high in the market. They question whether it's really necessary. It revolves around conflicting interests, and I especially notice this in the insurance field, which is where we see the effects." (Participant 6)

This friction between the providers of personalized medicine and those that pay for them could lead to pharmaceutical companies delaying introduction or abstaining from introducing certain medicines to the market, even though they could be beneficial to patients.

"If I may provide an example, we're talking about [new medicine], as I mentioned earlier, where a certain number of patients is expected but not found. We hear in the field that companies currently negotiating reimbursement procedures will actually advise their headquarters not to launch these drugs in the Netherlands." (Participant 4)

It is argued that in this way, an emphasis on the cost-effective nature of healthcare could come at the cost of patients not being able to benefit from the available, but more expensive, genomics innovations.

"There is a lot of emphasis on it being cheap. Yes, I understand that, and I completely agree with it. But please, do leave room for innovation." (Participant 3)

4.1.5 Essentiality and proportionality of using genomic data in realizing health outcomes.

A recurring locus of friction is the question of essentiality, that is; to what extent does additional data contribute to a better quality of care. This friction mainly applies to the preventative promises of personalized medicine, for example in relation to lifestyle changes. It is argued that some of these investments in and applications of personalized medicine are superfluous, as the same outcomes can be achieved using simpler and more available means. This type of friction is value-conflict in evaluating effectiveness, necessity, equity and accessibility.

The promise of personalized medicine to contribute to prevention of conditions partly depends on individuals employing insights from their genetic profile to engage in lifestyle changes that would prevent or mitigate conditions for which they are at risk. However, some parties argue that a lack of knowledge about effective lifestyle changes is not a significant part of the problem. Rather, the difficulty is eliciting changes in human behavior.

"It's like with the climate, there isn't a technology fix that will solve this. We will have to adapt our behavior." (Participant 5)

"I think we have our hands full teaching healthy behavior to society as a whole, so I believe it's extremely important to allocate our resources and attention to that. That's the priority, and I think we should only add genetic screening to it, emphasize adding, if it provides benefit. I really believe that healthy behavior and a healthy lifestyle are areas where we still have a long way to go. Think about smoking, think about cannabis, think about drugs, think about alcohol, think about nutrition, think about physical activity. Well, first, try to get 17 million people on the right path. Let's please invest all our resources in that because, in my opinion, that's the biggest gain." (Participant 5)

"You see, there are large warnings on cigarette packages, 'smoking is deadly,' and yet they are still sold. So, it's addictive, it's easy, it's... Knowing a risk profile, well, if someone is overweight,

they can see for themselves that they are overweight, and they probably know they have a high risk for this, this, and this. But it's not an immediate reason to change their behavior." (Participant 5)

Another question that is raised here is, next to what the actual benefit would be, is whom these benefits would affect. Although genomic data is an important part of this data intensive form of medicine, many additional sources of data are employed. One of these sources is self-tracking, in which data gathered by the patients themselves can be used to monitor the effect of lifestyle changes or other interventions. This places an additional requirement on the patient, a requirement which not all patients are equally equipped to fulfill. Rather, it is argued that the patients most able to benefit from this are those that need it the least.

"And the whole point, of course, that came out of our research on data-driven prevention here, is that it's not that interesting. In many cases, the patients who can really benefit from wearables, new data, new information, so to speak, are the tech-savvy, highly educated, affluent people. These people can marginally improve themselves because they already have a lot in the baseline." (Participant 7)

Although most clearly present in cases where personalized healthcare would augment or replace traditional forms of healthcare (as opposed to cases in which it provides abilities unavailable before), friction about the necessity of personalized healthcare is present throughout. As illustrated with regards to the *financial* theme, those allocating public resources have the responsibility to allocate them in a way that maximizes public health. In each instance, these parties thus must be convinced that employing personalized healthcare realizes public health outcomes that could not have been achieved using cheaper means.

"So, everything ultimately comes down to a principle, let's say, we are not against innovation or a new development, even from the influence of the industry. However, show me the data that it does add value. All kinds of personalized self-tests, for example, even consumer genomics, show me the data. Measure in an objective way that it adds value, for the money, for the patient, for society, for productivity, for labor savings." (Participant 2)

4.1.6 Establishing trust among stakeholders in early-stage innovations.

This locus of friction concerns the trust, or lack thereof, stakeholders have when engaged with each other. This is especially relevant in these early phases of the innovation-lifecycle. This is the period during which a standardized infrastructure is being established and processes and procedures for collaboration are still ill defined. Trust is an important factor in the success and

durability of cooperation between parties. This type of friction is process and relational friction, caused by a lack of trust and inadequate preconditions for stakeholders' accountability.

Collaborating parties will have to trust each other not to undermine each other's interests. For example, with regards to data sharing, parties must trust that the data they shared is only used for the intended purposes. However, as illustrated before, this trust is sometimes violated; "*Such a company […] is bought by [multinational healthcare company]. And now the rights are with them. So, you have shareholders who now call the shots.*" (Participant 7).

Other instances where trust (or lack thereof) causes friction are with regards to the reciprocity of a collaboration and the commitment to that collaboration. Parties must be able to trust each other to act in a mutually beneficial way, and trust that neither will be a free-rider on the collaboration. Furthermore, parties must be able to trust that the other party is committed and will not suddenly abandon the collaboration, such as pharmaceutical companies suddenly changing strategies. When collaborating with academic researchers, parties must also be able to trust each other to deliver an appropriate and suitable quality of work.

"People do see that things can be improved, but maybe there's still a bit of a 'seeing is believing' mentality. This whole idea of improving things is really driven from the academic side, so that's why there is still some apprehension about the collaboration between the more academic side and the commercial side. Some people have had good experiences, but there are also many bad experiences. The lack of trust is that commercial parties simply withdraw when their strategy changes. Exiting a collaboration after three years or only taking and not giving. On the other hand, there is the preconception that academic researchers simply don't deliver quality. They're just tinkering in their own labs, and there might be something in a lab journal, but a pharmaceutical company can't use that; they have to do everything from scratch. There's still a lot that needs to come together." (Participant 1)

Even between Dutch academic hospitals, trust seems to influence effective collaboration.

"What's also quite a thing in the Netherlands, is the 'not-invented-here' syndrome; if we haven't been directly involved, we don't trust it. We only have eight UMCs but they have been around for thirty years, and they haven't come up with solutions for these issues." (Participant 1)

4.1.7 Reframing privacy dynamics in stakeholder collaboration

This theme concerns privacy at the ecosystem level. Whereas stakeholders seem to agree that patient privacy is an important aspect in personalized medicine, there does not seem to be a consensus between stakeholders as to what privacy means and what it implies for the design of

the system. The type of friction here is predominantly conceptual and operational friction, although some aspects are clear examples of value conflict with regards to privacy.

Discussion about this sensitive topic seems difficult, as aspects of personalized medicine are framed as detrimental to personal privacy. In addition, some deem warranting privacy to be the responsibility of other stakeholders (such as regulators), and do not seem to have formulated clear requirements about this themselves. It is therefore difficult to define privacy as a locus of friction between stakeholders. However, what is interesting about this locus is that the conflict between privacy and personalized medicine might not be as extreme as experienced by some.

"If you look more towards the government or politics, this is sometimes exaggerated, where it's as if the importance of research is pitted against the privacy of citizens and patients. This is an unwarranted opposition because they are intertwined. Ultimately, both are in the interest of each other. A researcher can conduct research while protecting privacy, and conversely, a researcher may not be able to conduct research, but the privacy of the citizen and patient may still not be protected. So, I think this is currently being exaggerated more in the societal debate than is justified." (Participant 7)

It is recognized by others that if preconceived notions about conflict between the two can be overcome, a productive conversation between stakeholders with diverging interests in this regard might be possible.

"As I mentioned earlier, the rights of patients and citizens in terms of privacy and control versus the right of others to use data, that is indeed crucial. When you look at the underlying aspect, which is the desire to improve healthcare in both cases, it ultimately converges. So, you can also observe that when the conversation shifts in that direction, the more we talk about a learning healthcare system, the easier it becomes to come closer together." (Participant 1)

Friction regarding privacy for individuals in personalized medicine predominantly relates to who has access to which data. Although there is a spectrum of concerns, dominant concerns do not seem to relate to sharing data for legitimate medical purposes, but rather concern fears of data being used in ways that harm, not help, the individual.

"People often don't want it to fall into the wrong hands or be exposed to the public because it can ultimately be traced back to you, as it pertains to your DNA. People don't want that. They want things to remain private because they certainly don't want a situation where, for example, an insurer knows you have a genetic predisposition to a severe illness, and you might be denied coverage." (Participant 6)

Nevertheless, there are also cases in which individuals clearly value privacy much stronger than, for example, sharing data for research and development in medicine.

"I notice that some patients can be very outspoken about what happens to their data. I know someone who says, 'I'm more concerned about privacy and such matters than the future of medicine.' And that's okay; it can go that way too." (Participant 1)

Another interesting observation made by one of the interviewees is that a focus on solidarity and common interests might be a way to reconcile some of the friction between privacy and data sharing practices.

"The rights of patients and citizens when it comes to privacy and control, as opposed to the rights of others to use data, that's certainly very important. And, actually, if you look at the underlying aspect, you'd like the healthcare to improve in both cases, so it all comes together. So, you also notice that when the conversation is steered in that direction, the more we talk about a learning healthcare system, the easier it becomes for us to come closer to each other." (Participant 1)

An additional important aspect of privacy is control. As data in personalized healthcare, once obtained, is not used for a singular purpose (such as diagnostics and treatment) but is used continuously and throughout, it seems that patients find it important to retain some form of control over this data throughout.

"But even if I genuinely think, no, I'm not comfortable with this anymore, I should be able to indicate that I'm not okay with it anymore. I think that's where the main importance lies, along with ensuring that things are safe." (Participant 1)

4.1.8 Lack of an adequate and fit for purpose policy framework.

A reoccurring theme is the national and international policy that governs the personalized healthcare system. Two sub-themes, each a unique locus of friction, have been identified. The first of these concerns disagreement about the right kind of policy to pursue, specifically with regards to policies that are deemed too conservative by industry stakeholders. The second sub-theme concerns policy that is unfit to deal with the unique characteristics of a personalized healthcare system.

4.1.8.1 Conservative nature of policy

There is clear friction between regulators and industry stakeholders concerning policy matters. Especially with regards to development and provision of personalized medicines, the pharmaceutical industry regards the regulators policies as overly conservative. This type of

friction is value conflict between conservative and progressive attitudes with to medical innovations. As illustrated in other themes, governmental bodies have a variety of considerations for making decisions pertaining to public health. On the other hand, others argue that this conservative attitude might harm public health by preventing innovation and denying patients access to new diagnostics or personalized medicines.

"You can argue that Europe is very conservative and resistant to change. And perhaps not just at the European level, but especially at the national level. When you look at how long it took for the NIP test to be used here, we are years behind others." (Participant 3)

"I think we are way too slow, if we're not already behind. When you look at the latest developments, personalized medicines, that's gene cell therapy, Asia and the United States are miles ahead of us. I think nearly 300 new trials started in the last year, compared to just three in Europe. So, that says enough. What's unfortunate is that the knowledge here is quite good. But you shouldn't just have the knowledge and further develop it; you should also be able to apply it. That means you must both be able to develop and use it." (Participant 3)

"You can also ask the question, should the Netherlands remain so strict? Or should we just say we need to start allowing it, as long as those who do it in the Netherlands follow the NEN healthcare standard." (Participant 8)

4.1.8.2 Unfit policy

Another locus of friction is policy that is not fit for the unique characteristics of a personalized healthcare system. The circular nature of personalized healthcare, which implies the blending of healthcare with research and development, requires new modes of cooperation between stakeholders. The type of friction here is structural and regulatory misalignment through bureaucratic inertia.

Especially between academia and pharmaceutical companies there is friction with regards to the division of roles and responsibilities. The roles ascribed to the pharmaceutical companies by the policies in place are deemed unfit in relation to the activities required for a system of personalized healthcare.

‘‘This has to do with the general perception of industry in the Netherlands. The previous director used to say, "When you come to the Netherlands, there's a sign that says, 'Industry, Go Home.' But joking aside, when you see how easily people sometimes think they can take on the role of the industry from academia, make a drug themselves. How easily people think those drugs just come about

on their own. That's, of course, not the case. Especially now with these new therapies. We have regulations that are being debated in Europe, and hopefully, we'll hear more about them next month." (Participant 3)

Another type of policy that is deemed unfit are those that govern international collaboration with regards to research. Whilst new types of genomics-based research are possible, such research requires sample sizes which are unlikely to be found on the national level. Meaningful research in this direction thus requires policy aimed at international collaboration and standardization. It is also argued that such standardization should extend to the admission of medicines, where there is currently friction between policy on an EU and national level.

"We also need to consider the limitation of the Netherlands. Especially when you look at rare diseases, we want to measure things in the Netherlands with maybe 20 patients, with a group that is too small to make any meaningful conclusions. Then we add Belgium, another 15 patients, two from Luxembourg, and so on. If you measure things differently in all these countries, you won't find anything in any of them. But if you dare to collaborate with these countries to determine what you need, what you want to investigate, what you want to measure, then you might have a large enough population to make meaningful conclusions about the outcomes. Well, there's a European initiative aimed at exploring this, but they don't get much further than negotiating the price." (Participant 3)

"And this is related to the fact that many of these medicines are so promising that they often receive fast market approval from the EMA. So, we're very happy because they become available quickly. However, then the Dutch healthcare institute and other payers start to panic because there isn't much known about these drugs yet." (Participant 3)

4.2 Instrumental barriers to ecosystem success

What becomes apparent from the identified frictions is that many of the preconditions that stakeholders require for the establishment of a system of personalized healthcare are lacking or inadequately met. Friction here is not value-based, but rather instrumental friction. Preconditions in this case refer to conditions or elements that need to be in place for the system of personalized healthcare pers medicine to be realized. Within the theme of preconditions, five different preconditions have been identified in the data. Figure 3 presents a sub-section of the thematic map pertaining specifically to instrumental barriers within the ecosystem.

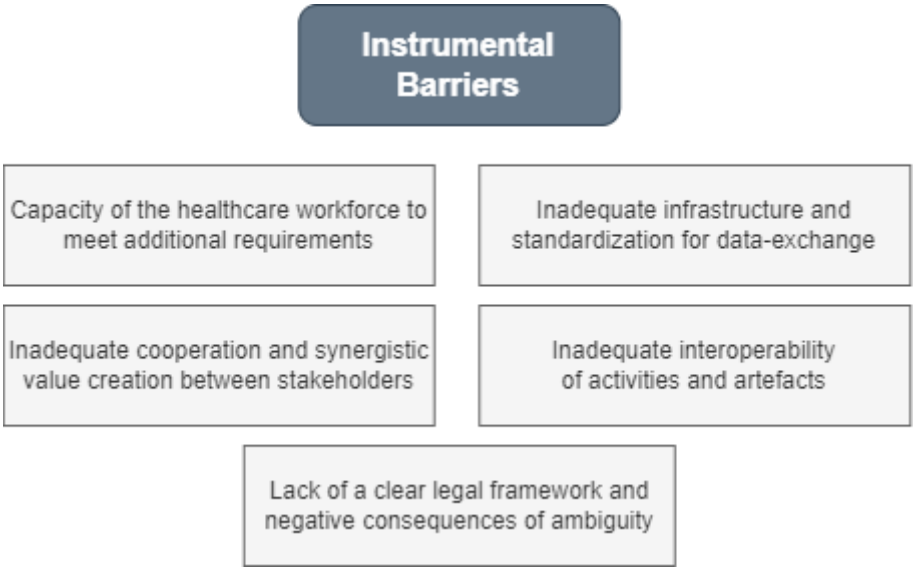

Figure 3 *Thematic map of themes relating to the instrumental barriers to ecosystem success*

4.2.1 Capacity of the healthcare workforce to meet additional requirements.

This locus of friction concerns what is required from the healthcare system in a transition towards a personalized healthcare system and the capacity of the healthcare system to meet these requirements. Capacity both concerns the overall capacity of the healthcare system for certain workloads, as well as the capacity individuals in the healthcare system to accommodate additional or altered tasks. The former relates to the additional demand placed on genetic counseling resources if genetic testing would be broadly employed. The latter relates to additional tasks, such as collection and registration of patient data throughout the healthcare system, that healthcare professionals on many levels are requested to accommodate. This instrumental fiction arises due to resource and capacity constraints, organizational challenges, and implementation barriers.

A full transition towards genomics based personalized medicine would require each individual patient to be sequenced. Even during the current transition, large amounts of genetic data are required for research and development in this field. As the clinical genetic departments struggle to meet the current demand, there is expected to be insufficient capacity to meet this enormous future demand without scaling up these departments or introducing alternatives.

"It's also the case that there are quite significant waiting lists in the clinical genetics departments, so it's difficult if a large number of people suddenly start going there, they can't handle that either. So, it's also a kind of capacity problem, which makes everything more complicated." (Participant 6)

"For instance, in our conversations with several field parties about molecular diagnostics, we sense that there's actually fear in this context. These parties are saying, 'But if we start sequencing the genomes of X number of patients using these diagnostics, there's a significant financial bubble hanging over our healthcare market because we will suddenly identify more patients whom we otherwise wouldn't have treated.'" (Participant 3)

The data that is required for personalized medicine extends beyond the genetic profile, and much of this data will have to be reported by healthcare professionals. This will not only create additional tasks but will also require changes to the ways in which data are reported and registered to ensure compatibility with the broader system. This will thus require organizational changes and education of healthcare professionals on these new systems.

"There are also many healthcare professionals who don't necessarily engage in research, and for them it's a bit of a double-edged sword. On one hand, they naturally want to improve their work. On the other hand, we sometimes ask a lot from this group because we also ask them to change some aspects of their work. For example, we ask if they want to change the way they document their care tasks, how they register them, or if they suddenly want to do things differently. While they were used to simply typing in a text box, explaining how things are going with a particular patient. Now, they suddenly must check boxes and use specific terminology. Because only in this way can we use the data effectively; filling in text boxes just doesn't get us very far. So, it can be quite demanding on individual healthcare professionals at times, but it also affects the entire organization surrounding them." (Participant 1)

Assuming that these organizations are motivated to enact such changes, they still will take significant additional resources to be realized. Even with additional resources it seems it would be challenging for some of these organizations to accommodate such changes.

"An academic hospital also has a significant interest in the research aspect, so they are more willing to invest in it. A non-academic hospital, on the other hand, thinks, 'I'm already fully occupied with patient care, do I also have to make everything absolutely perfect so that it can all be reused?' This really requires a few extra steps in terms of organization and budget. There is simply not enough of that. Who is going to do all of that? So, it's mainly a practical and workload issue on that side. I think that's an additional concern on their part." (Participant 1)

4.2.2 Inadequate cooperation and synergistic value creation between stakeholders

Cooperation between stakeholders is one of the oft stated preconditions for genomics innovation to take place, and at the same time a source of friction. The friction experienced here is operational friction arising from difficulties in collaboration and knowledge- and technology-transfer between stakeholders. For example, even with the best intentions, it can be difficult to involve laymen citizens in the decision-making process surrounding personalized medicines in a manner that affords them actual and fair representation.

"That's also just the constant tension. Even if you wanted to do co-construction here, well, who are you going to invite? A few happy citizens and a PowerPoint, that makes it very easy. You shouldn't expect much resistance then. The point is, you should actually address those scenarios, the pain points." (Participant 7)

There is also friction in the cooperation between parties in the healthcare sector. As illustrated before in relation to trust, the eight academic hospitals in the Netherlands are deemed too fragmented. However, they have been unable to arrange satisfactory cooperation.

"So far, it has mainly been UMCs (University Medical Centers) among themselves trying to push certain things forward, and it kept getting stuck every time." (Participant 1)

Similarly, it is argued that technology transfer between academia and industry is inadequate, which stifles the development of products and medicines. Furthermore, Dutch entrepreneurs also exhibit a lack of cooperation on the national level.

"When you look at academia, yes, there is a lot of good research. But look at how much of that knowledge ultimately ends up in a product. That is very limited. And it has to do with the poor technology transfer. Dutch entrepreneurs often aren't smart enough, let's be honest. In the Netherlands, we choose to start a lot of small companies. In other countries, they choose to bring entrepreneurs together, to bring ideas together. They start fewer companies, but those are often more robust. That's another way to do it." (Participant 3)

4.2.3. Inadequate infrastructure and standardization for data-exchange

Adequate infrastructure is another oft stated precondition for genomics innovation, and a lack thereof is currently a source of operational friction in the innovation process. Infrastructure in this case refers to the networks through which resources and information are exchanged between stakeholders. A dominant cause of operational friction in the innovation process is the lack of standardized infrastructure for information exchange between stakeholders.

For example, observing the circular idea of personalized medicine, the pharmaceutical industry would like to be provided with more real-world data from the healthcare sector. However, standardized infrastructure for this is lacking, and it is unclear who will take responsibility to establish such infrastructure.

"There are organizations that simply want more real-world data, and for that, you have to turn to healthcare. They believe that it all needs to be better organized so that they don't have to set up a whole registry again to see if their medicine is effective, but rather can extract that data from healthcare as soon as the medicine is used. That's also much more efficient. In the past, they paid for those registries, so who will do that now? Who will take care of that task? Bringing that data back is still quite a challenging job in this regard." (Participant 1)

At the same time, those that influence which personalized medicines will be available to patients also want to have more data from the healthcare sector. Even for those personalized medicines currently available, a lack of availability of data makes it difficult to which asses which medicines deserve broader availability.

"As you offer even more personalized care, it becomes more important to have an overview of what the various disease profiles, or the trajectories, or care pathways, deliver and what they cost. So, how do we ensure that sufficient insight is created into the practice of personalized care delivery so that we can clearly and conditionally say, here is value for money, or there is less value for money, but also for the quality of care. The challenge lies primarily insufficient availability of data that can demonstrate the real added value of a kind of personalized treatment or personalized diagnosis." (Participant 2)

4.2.4. Inadequate interoperability of activities and artefacts

Related to the sub-theme of inadequate infrastructure is the sub-theme of interoperability, or lack thereof, of the activities and processes of collaborating stakeholders. This does not only entail that the right products and data are provided, but also the right information is exchanged

to enable other parties to work with each other's assets. Operational friction arises from the complexities associated with achieving interoperability and coordination among stakeholders.

Just as infrastructure is a requirement for the development of personalized healthcare, specific infrastructure can also place a requirement on those that work with this infrastructure to make sure exchanged assets are interoperable. For example, standardized infrastructure for data exchange also requires a standardized workflow to be implemented for the formatting of that data. This in turn places additional requirements on those generating or working with the data, which organizations might find difficult to meet.

"A non-academic hospital might think, 'I'm already swamped with patient care, do I also have to prepare everything absolutely perfect for reuse?' This really demands a few more levels of organization and budget, which aren't there at all. So, who will do all of that?" (Participant 1)

One of the core principles of personalized medicine is its circular nature, in which data is used throughout to improve the quality of care. This requires a high degree of interoperability of the processes of each of the relevant stakeholders. However, stakeholders indicate that this has proven difficult to realize in practice.

"It is important for us that the rest of the healthcare system can work with these products. This means that, more than in the past, you can better measure what someone has, the diagnosis. But even when you give a patient treatment, you can measure very well what happens with it and determine if that treatment is meaningful. That's the textbook concept of personalized medicines. But what we notice in practice is that this requires a lot, also from other players in healthcare." (Participant 4)

A clear source of friction can be found between the healthcare sector and pharmaceutical industry with regards to diagnostics for personalized medicine. As the role of diagnostics in personalized medicine is different compared to traditional medicine, this requires a new mode of collaboration between these stakeholders, in which diagnostics becomes an integral part of the system.

"I think it is important for us, is that we really see the drug as a big, essential part of the treatment, not as a separate entity, and that's the diagnostics. It is often funded separately or not funded at all. Without good diagnostics, it is difficult to assess which patient should receive the drug. So, you must take that into account, and that means thinking differently. Diagnostics becomes much more important than in the past for determining the ultimate treatment. So, it shifts from something used to identify a disease to something used to improve a patient's condition." (Participant 3)

This inoperability between the diagnostics which pharmaceutical companies need for their medicines to be researched or applied effectively and the diagnostics that are employed in healthcare influences the availability of personalized medicines for Dutch patients.

" We have studies on a global level or somewhere abroad that prescribe such diagnostics. Then in the Netherlands, we don't have those diagnostics, so those studies don't open in the Netherlands. As a result, patients may have access to those experimental drugs later, and if those drugs successfully pass the study phase, they are also introduced later in the Netherlands because the diagnostics are still not available. So, in that regard, it's essential to look beyond precision medicine and really consider what prerequisites are needed." (Participant 4)

4.2.5 Lack of a clear legal framework and negative consequences of ambiguity

Another instrumental barrier is the regulatory friction stemming from a lack of a clear legal framework and ambiguity in policy with regards to personalized healthcare. This influences stakeholders in two different ways. By creating uncertainty about what can and cannot be done the is an increased risk for parties engaging in research, development, or service provision in personalized healthcare. For example, whilst having been active for over 10 years (and providing similar services that international parties are legally providing to Dutch consumers), the largest Dutch direct-to-consumer genetic testing service could technically be operating illegally if they are indeed testing inside The Netherlands.

"The fact is that we don't have any guidelines for population screening and genetics, they simply don't exist. There is [Dutch DTC testing service], but the healthcare inspection is keeping a close eye on them. I'm not sure where the sequencing is done; they probably do it somewhere in the Netherlands, but they are operating illegally." (Participant 8)

On the other hand, a lack of clear policy can also enable parties to act in ways that are deemed undesirable by regulators or the public. Friction here occurs between those that aim to maintain a tightly regulated healthcare sector and parties that enter this market whilst subverting such regulations. For example, with personalized healthcare being so data and technology intensive, some pioneering industry parties have taken a Big Tech approach to healthcare. Due to the unique and novel nature of the services they provide they are often not subjected to the same regulations' other stakeholders (such as academia) are subjected to. This has enabled some to engage in activities for which they were only later subjected to the same regulation as other stakeholders. Many other stakeholders deem such a move-fast-and-break-things attitude towards innovation to be inappropriate in the context of healthcare.

"Yes, that's actually the constant question and tension. What you're getting now is that Big Tech is also shaping what public healthcare looks like because they are pioneers in this field. The strange thing is that we have very strict protocols for the pharmaceutical industry and all sorts of biomedical research, but for technology development, well, that's a more free-market domain." (Participant 7)

"That is, of course, the sticking point in this. It's also, like [multinational technology conglomerate], which always commits transgressions and then gets recalled, and only then legislation is put in place. I mean, that is really just happening all the time in the medical domain. Just crossing boundaries and then being recalled." (Participant 7)

4.3 Ethical issues

Some of the themes identified relate to the ethical issues surrounding genomics based personalized healthcare. Figure 4 presents a sub-section of the thematic map pertaining specifically to ethical issues.

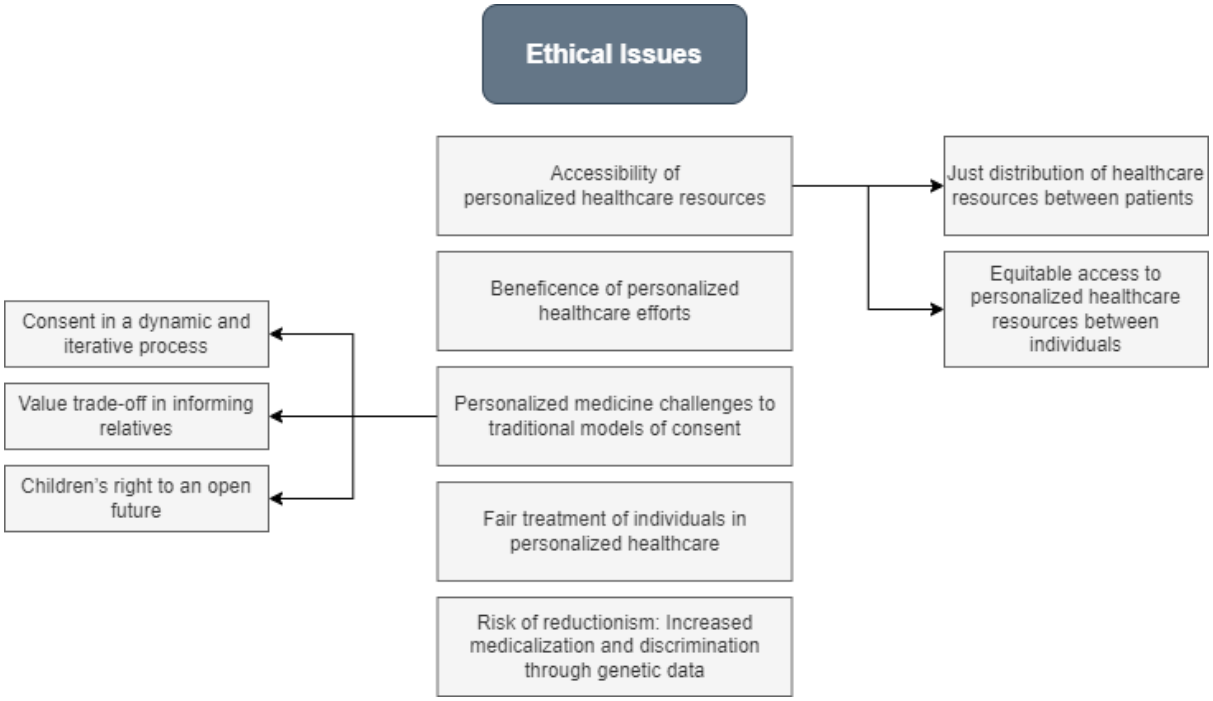

Figure 4 *Thematic map of themes and sub-themes relating to ethical issues*

4.3.1 Accessibility of personalized healthcare resources

One of the themes that is present throughout the interviews is that of the accessibility of healthcare. Within the theme of accessibility, two distinct ethical issues have been identified. The first relates to a just distribution of healthcare resources, and concerns whether some health

resources are theoretically available to specific patients. The second ethical issue relates to equitable access and concerns how health literacy influences the practical accessibility and utility of healthcare resources between individuals.

4.3.1.1 Just distribution of healthcare resources between patients

The availability of personalized medicines is framed as an ethical issue. One side of the argument here is that if there are patients who could benefit from specific personalized medicines, it would be unethical not to make these medicines available to them. As illustrated before, the pharmaceutical industry is critical of policies which currently prevent or delay the introduction of personalized diagnostics and medicines. Furthermore, they are critical of policy which favors the use of cheaper interventions initially and only makes expensive options available at a later stage in the treatment process.

"This is, of course, challenging for our companies as you can't achieve your expected revenue, and you can't help the patients even though you know they exist." (Participant 4)

"But if the expensive option is the one that works, it's a bit unethical to give a patient four or five treatments that are unlikely to work, before using something you know for sure will work." (Participant 3)

The other side of the argument is that, given a limited set of resources, increasing accessibility of personalized medicine and diagnostics would require the accessibility of care in other places to be limited. A compounding issue is that, given the expensive nature of these novel interventions, making such resources available to the individuals that need them might require limiting public health resources that benefit a much larger group.

"It means that in making a new technology accessible, it might entail limiting access to care elsewhere. So, the foundation of the choices you make and the consequences of the choices you either don't make or explicitly make to limit other care is a significant tension between different values." (Participant 2)

4.3.1.2 Equitable access to personalized healthcare resources between individuals

Another important ethical issue is the practical accessibility of personalized healthcare resources, which interviewees often discussed in the context of health literacy. The issue here is that even though resources might be equally available to all, the extent to which individuals

are able to access these resources effectively and employ them to their benefit is limited by what interviewees referred to as (personalized) health literacy.

As discussed in the context of necessity, those that are most likely to obtain benefit from certain resources are those for which such resources are only able to produce marginal benefit, whilst the group for which the most public health benefits could be realized fail to effectively access these resources. There is a limited group of people that are most able to cope with and benefit from resources that require significant knowledge, discipline, and effort on their side.

"In many cases, the patients who can really make good use of smartwatches, new data, new information, so to speak, are tech-savvy, highly educated, affluent individuals. These people can marginally improve themselves because they already have a lot in their baseline. And in that regard, I think we as a society could say that we have a responsibility to care for the right vulnerable individuals in our society." (Participant 7)

The issues caused by limited public health literacy are not limited to self-tracking. The challenges surrounding the provision of genomic information to patients are often referred to in this context. Due to the nature of this information, for example as it relates to measures of risk and uncertainty, it can be difficult to effectively communicate the true meaning.

"People have the right to understandable information. If these resources become readily available, there should be no barriers for people who may not be able to use them even though they could be very useful and relevant for them. You also need to consider a person's background, their own IQ, their health literacy, or their literacy skills. This is often challenging because people often prioritize various other aspects over their health." (Participant 6)

"That's not a small group; there are a few million people like that. So, while we may all want to do something together, we must be careful that we're not just helping the healthy, high-IQ individuals who already know their way around. Literacy is important, no doubt, but you must start from a very basic level. And that's a real problem." (Participant 8)

4.3.2 Beneficence of personalized healthcare efforts

Beneficence refers to the quality of doing good, which can be context dependent. In medicine, beneficence refers to the obligation of healthcare professionals to act for the benefit of a patient, whilst at the same time preventing harm to others. The ethical issues surrounding beneficence thus relate to whether investing in and employing personalized medicines can be expected to

benefit patients overall, whilst also preventing harm to patients overall. Beneficence will be discussed as relating to efficacy, effectiveness, and efficiency of personalized interventions.

Efficacy refers to the capacity of some intervention to, when performed by experts and under ideal conditions, produce some specific effect. In other words, assuming all other factors are controlled for, is an intervention able to produce the intended outcome or effect? This value is important as a vital factor in a transition to personalized medicine is establishing that these novel interventions function as intended.

"Now it's all about cancer, but there are likely markers or genetic hooks to be found for other serious conditions as well, that are strongly associated with them. If research shows that they really say something about a particular disease, then it's useful. But only then." (Participant 5)

"Use it for the people who do need it within clinical genetic care, but only do it for those for whom it is proven, evidence-based, that early testing is actually useful." (Participant 8)

Even if the efficacy of interventions has been established this does not naturally entail that such interventions can also be employed effectively in practice, as the eventual effectiveness of an intervention is affected by multiple factors throughout the treatment. For example, it is not self-evident that efficacious genetic screening will naturally lead to improved health outcomes.

"And then consider, well, what does it actually yield? What becomes of all that screening genetic information? And how does it affect those individuals? Well, that seems to me to be the first necessity." (Participant 5)

A concrete example of this is found in the interplay between personalized medicines and molecular diagnostics, where effective application of such medicines is contingent upon adequate diagnostics throughout the system.

"It is important for our companies that the drugs they produce are used as effectively as possible. In this regard, predictability plays a crucial role, with molecular diagnostics coming into play, which is currently a hot topic. This allows us to expect better predictions of which drugs will have what effect on which patient." (Participant 4)

Efficiency refers to the relation between the outcomes of interventions and the resources employed to achieve these outcomes. Efficient use of resources is a theme throughout, as can be seen in the *financial considerations* theme and the *ethical issues* surrounding *accessibility*. Efficiency is valued at two distinct levels, first in the context of maximizing health outcomes

at a societal level, and second in the context of achieving specific health outcomes at the individual level.

At the societal level, efficiency refers to allocating the limited resources available such that the achieved public health outcomes are maximized. This generally means, to an extent, allocating resources such that they achieve the greatest amount of benefit for the greatest amount of people. This entails careful consideration for how money is spent, for example.

"On the other hand, there's always a price tag, which means that if you invest money from the public purse in point A, it means you can't invest in point B. Be aware of that choice; that's what it comes down to. […] And if, as I noticed, the data clearly indicates that preventive diagnostics for certain specific conditions result in significant cost savings, then something like that becomes particularly interesting to invest in or encourage, or even to include it in the basic insurance package, so that it becomes a standard part of healthcare." (Participant 2)

At the individual level, efficiency refers to choosing the diagnostics and interventions such that health outcomes are achieved with the least number of resources possible. As discussed in the friction theme of *essentiality and proportionality*, some of the experts fear that personalized medicine tools would be employed in cases in which the same health outcomes could be achieved more efficiently through simpler and already available means.

"So that [through genetic testing] you will find things where that could just as well be tackled through simple measures, such taking different fats or a bit more vitamins, or just having more frequent blood pressure checks." (Participant 5)

"Measure in an objective way that it adds value, for the money, for the patient, for society, for productivity, for labor savings." (Participant 2)

4.3.2 Personalized medicine challenges to traditional models of consent

One of the ethical issues discussed in the literature review was also touched upon by interviewees' concerns regarding consent. Consent in this case predominantly refers to whether patients have explicitly agreed to specific uses of their data. The ethical issue here lies in the risk of genetic data being used in ways the patient has not agreed to in advance or does not agree with in general. Consent was discussed in two distinct ways, one relating to the consent for being provided with specific kinds of information, and the other concerns the consent for that data to be shared with others for purposes external to those directly related to the patient's care. Two sub themes regarding absence of consent are discussed separately.

4.3.2.1 Consent in a dynamic and iterative process

Consent in relation to information provision concerns whether patients have provided proper informed consent for being provided with medical findings obtained from their genetic profile. Since the information obtained from the genome is broad it can be difficult to determine whether it is responsible for the information to be shared, even if consent is provided in advance. On the other hand, there are also cases in which both specific information and specific consent are present, yet this information is still withheld from the patient.

"When you see how easily people send in a test or do whatever. We have a colleague who is in the secondary findings committee, where if genetic information mutations emerge in the hospital that are truly concerning, they really wonder, should we share this or not? Everyone has to do a kind of opt-in to want to know, because otherwise, we have a moral problem. Should I break it or not, because you don't want to know. The starting point is that if you do this, you are open to it, but there are still things that are not told to you, if we know that there are few treatment options, and it only gives you a kind of doomsday scenario." (Participant 8)

In other cases, with diagnostics developing rapidly, the relevance of certain information is uncertain, which can be a reason to withhold this information from the patient. For example, in the case of a VUS *(variant of uncertain significance)* this information could be withheld.

"If you can already see what you can find with NGS or WGS, you might find the diagnosis, but you'll also find all sorts of other incidental findings. What do you do with those? How can you interpret them?" (Participant 6)

Due to the nature of genomics based personalized healthcare, research and diagnostics is not a snapshot but a dynamic on-going process. On the one hand, genetic data obtained from patients can be employed for research, and the result from such research can be used to perform new diagnostics on existing genetic profiles. Therefore, obtaining consent at a singular moment in time is deemed to be insufficient. Rather, it is argued, as diagnostics is dynamic, consent should be too. Dynamic consent can be especially hard to implement in cases where genetic data is stored in a biobank and continuously re-used for new research.

"And I would like to add, a dynamic consent. So that you gave consent at the age of eighteen, but that you are asked again at twenty, twenty-two, and maybe want to limit or expand it, or because you've just had children, you want to temporarily pause it." (Participant 8)

4.3.2.2 Value trade-off in informing relatives

A dominant sub-theme within consent concerns the family letter. This letter for relatives (*familiebrief* in Dutch) is a letter that is provided to patients if, during the process of genetic testing, there are findings which are of relevance to relatives. These letters come in varying degrees of information disclosure, but all inform individuals that they might be at risk and urge them to undertake action. The ethical issue here is whether either disclosing or withholding this information would cause more harm, and there is a value-trade-off between beneficence and confidentiality.

"The fact is that not informing people if you don't inform them can be more harmful. So, it's ultimately always a trade-off between not causing harm and good medical practice." (Participant 8)

"Is there a good relationship with the family? Do you know if these people are willing to hear this? Sometimes, people have been in the medical system for a long time without knowing what's wrong. Well, you can help them, which is, of course, the good side. And yes, sometimes there are people who don't want to know, but then you can say, well, we have a very general letter stating that there is something in the family that is relevant. If they want to know more, they can contact us. You can address it that way. But you can't decide for people that they don't want to know if you've never asked them." (Participant 8)

Whilst healthcare workers a cognizant of the ethically sensitive nature of such disclosures, in practice good medical practice is dominant in the trade-off between it and the risk of disclosing information to an individual who had rather not received it.

"I also know that there are family letters where maybe the condition is not mentioned yet. And people can find that information further down in the letter or it's presented in a certain way. Then people can make a choice whether to read further. But it's not that the doctor informs the patient but not the family members. Healthcare providers strongly recommend informing family members. And people can also get help with that." (Participant 6)

4.3.2.3 Children's right to an open future

Another ethical issue relating to consent is the disclosure of information to children and minors. In both cases, whether consent is or isn't provided by either the child or the parents, the disclosure of this information is an ethical issue. Whilst medically actionable information is generally disclosed, there are ethical issues with the disclosure of information regarding late-onset conditions or conditions which are not medically actionable (for example, due to a lack

of treatment options). The right of children and minors not to carry the burden of knowing such information is referred to in the interviews as the right to an open future. The ethical issue here is the trade-off between the right to know and the right to an open future.

"I don't think it serves a child well if you tell them at the age of nine that there's something they can't do anything about later on. You can debate whether it's appropriate to confront a child at a young age with a condition that starts late in life and can be managed. That's another ethical issue. On average, I don't think a child benefits from that, and we shouldn't hide behind legal matters. A child simply has a right to an open future, and as doctors, we must not harm that." (Participant 8)

"When there is a condition that can be somehow influenced during childhood, and the child would benefit from knowing such information, we certainly do not interfere. In such cases, we are practicing good medical care. However, in all other cases, we are essentially reassuring parents or answering their questions. But it's not about the parents; it's about the child." (Participant 8)

4.3.3 Fair treatment of individuals in personalized healthcare

Defining fair and equal treatment in the context of a form of medicine that is strongly tailored to each individual is a nuanced endeavor. In this context, fair treatment does not entail treating everybody the same, which would be incompatible with the personalized nature of personalized healthcare. Rather, fairness in this context seems to be conceptualized as treating every individual as equally worthy and valuable, and with equal respect. From this perspective, personalized medicine can promote equality and fairness, for example in the context of providing different individuals access to an equal quality of care through increased personalization of that care.

"I believe the foremost principle should be that every person counts, that's a very important starting point. Regardless of the condition or deviation one has, every individual is equally valuable and important. It should be the case that when conducting large-scale testing, which is sometimes done in certain population studies, you do it primarily to help and reassure individuals with just as much value as anyone else, who may not have a deviation but could be affected." (Participant 5)

The relevance of equality is also illustrated by the fears issued through the interviews that personalized medicine would promote unequal treatment. There are, for example, fears that equality of opportunity in daily life would be negatively impacted through reductionism or genetic discrimination (discussed in detail in the literature review).

"There is a risk if your entire genetic screening is like a business card in your wallet." (Participant 5)

One interviewee provided an illustration of how access to new types of information inevitably affects the choices that humans make (in literature referred to as technological mediation of the moral subject). In this case, access to this information promotes differential treatment of embryos. Whilst in this specific case this might be defensible from an equal quality of life perspective, the point this interviewee seems to make is that access to this information will inevitably change society.

"With early ultrasounds, you can now see congenital abnormalities as early as 12 weeks into a pregnancy. For instance, open spina bifida. Nowadays, hardly any children are born with open spina bifida. […] Somewhere, I do think we run the risk of this happening as people. That when we know there are abnormalities (and nobody likes abnormalities, we want to be somewhere in the middle or be healthy), life will take this course, knowing about it. I don't think we want to discriminate, but I believe it happens anyway because it becomes part of our behavior and way of doing things." (Participant 5)

Until now fairness has been discussed in terms of equality of access and equality of opportunity. One interviewee has provided two examples of other relevant conceptualizations of fairness. The first relates to fairness in terms of how data from individuals is used. Is this data used in accordance with the consent that has been provided, and is this data used to the benefit of those that have provided the data? In the example below, data obtained from a (marginalized) group of individuals is used outside of the provided consent and to the direct detriment of that same group. In other cases, fairness relates to the distribution of benefits and exploitation. The important question there is whether individuals are fairly compensated for their contribution.

"There are just examples of how it went wrong. For instance, Native Americans, where in diabetes research, their genetic data was examined without consent to trace their origins, ancestors, and interconnections, undermining their heritage and story. In that sense, when you tell such a story, everyone says, 'Oh, you really shouldn't.' Just like Henrietta Lacks, her cell line, the HeLa cell line, she was a Black woman who had cancer, she passed away, but her cancer cells are used in biomedical research worldwide. And her family never received any compensation for that for a long time, yet PubMed is full of articles about the HeLa cell line. These are examples where you can see, 'Is this fair? What do you think about this? How should it be handled?' And if the conversation is conducted in this way, you have a much clearer understanding of when it's acceptable and when it's not." (Participant 7)

4.3.3 Risk of reductionism: Increased medicalization and discrimination through genetic data

Reductionism concerns the ways in which a focus on genetics in relation to health might affect the ways in which humans view themselves and others and are viewed and treated by actors in the healthcare sector. The fear is that an overemphasis on genetics in healthcare will reduce the view of individuals or patients to just genetics, reducing the attention afforded to the many other relevant factors. This overemphasis on genetics could lead to the medicalization of conditions which are of minor relevance or could be attended to in other ways, such as through lifestyle interventions. Reductionism could also lead to forms of genetic discrimination when individuals are treated differently based on their genetic profile. These three, reductionism, medicalization, and discrimination, are examples of mechanisms by which increased use of genetics in healthcare could come to affect society.

For example, in cases of largescale data collection, there are fears that instead of being viewed as patients, the view of individuals will be reduced to data repositories. At an even higher level, there is the risk of a perception of genetic sequencing and data analysis as being self-evident instead of a construct.

"So, the point is that it's also difficult because of that technological nature, is that these big tech companies, it's always a commodity or how do you say it? So that also conflicts with whether I am a patient or a consumer. And in the Dutch situation, we are even stricter in making that distinction. In some situations, that distinction is not so strict at all. Then you are a consumer altogether. But if you do that internationally, then you also must deal with healthcare systems, where you really ask some of those questions, like, are we talking about technology R&D departments here, meant for consumers or healthcare systems?" (Participant 7)

"It's proven that there is a genetic code that makes sense to work with. We can differentiate with medicines and so on. But at the same time, if it becomes performative in the sense that we start seeing people in a way that they are literally like a data reservoir, as if they are a source. Then it does something to how you view and approach people, you forget for a moment that you were the one who created the data and not the person who was the source." (Participant 7)

There are also fears that increased use of genomics will lead to increased medicalization of issues or conditions that can be remedied in simpler ways.

"So that you will discover things where, with some simple measures, like taking different fats or consuming more vitamins, or just having more regular blood pressure checks, you can also prevent things for that person and improve their life at this point of health." (Participant 5)

There are also fears that this reductionism would not be limited to individuals in relation to the healthcare system but could also affect how individuals would view each other, and even lead to forms of genetic discrimination in society. One striking hypothetical, described by the interviewees themselves as an extreme case, is the effect an emphasis on predictive genetics in healthcare could have on the ways in which humans approach partner selection and procreation, or affect people when trying to obtain a specific job or insurance (which is already the case regarding some forms of insurance).

"If we know from the outset that you have this gene or that gene, are we moving towards a world where you indicate on dating sites whether or not you have a particular gene? Because otherwise, I don't want a relationship with you, as it's unfavorable for procreation, to put it bluntly. That's the extreme case, but there is a risk if your entire genetic screening is like a business card in your wallet." (Participant 5)

"The child will turn 18 someday and might want to start their own business (insurance is generally manageable), but in any case, they should be able to face the world with an open perspective. So, if you want to record something genetically, you could, for example, say that we'll put a lock on all those late-onset diseases." (Participant 8)

The fear here is that once genetics becomes a regular part of healthcare, a form of scope creep would cause its applications to extend to progressively more parts of society. The ethical issue here is to what extent is deemed moral to discriminate towards others based on their genetic profile, and to what extent this can be prevented from taking place.

"When we know there are deviations, and nobody likes deviations, we want to be somewhere in the middle, be normal and be healthy. Knowing [about deviations in others through genetic data] will shape our lives. I don't think we want to discriminate, but I believe it just happens because it becomes ingrained in our behavior, in the way we act." (Participant 8)

4.4 Human Engagement and Responses in Genomic Healthcare

Figure 5 presents a sub-section of the thematic map pertaining specifically to themes relating to human engagement and responses in relation to a system of genomic healthcare.

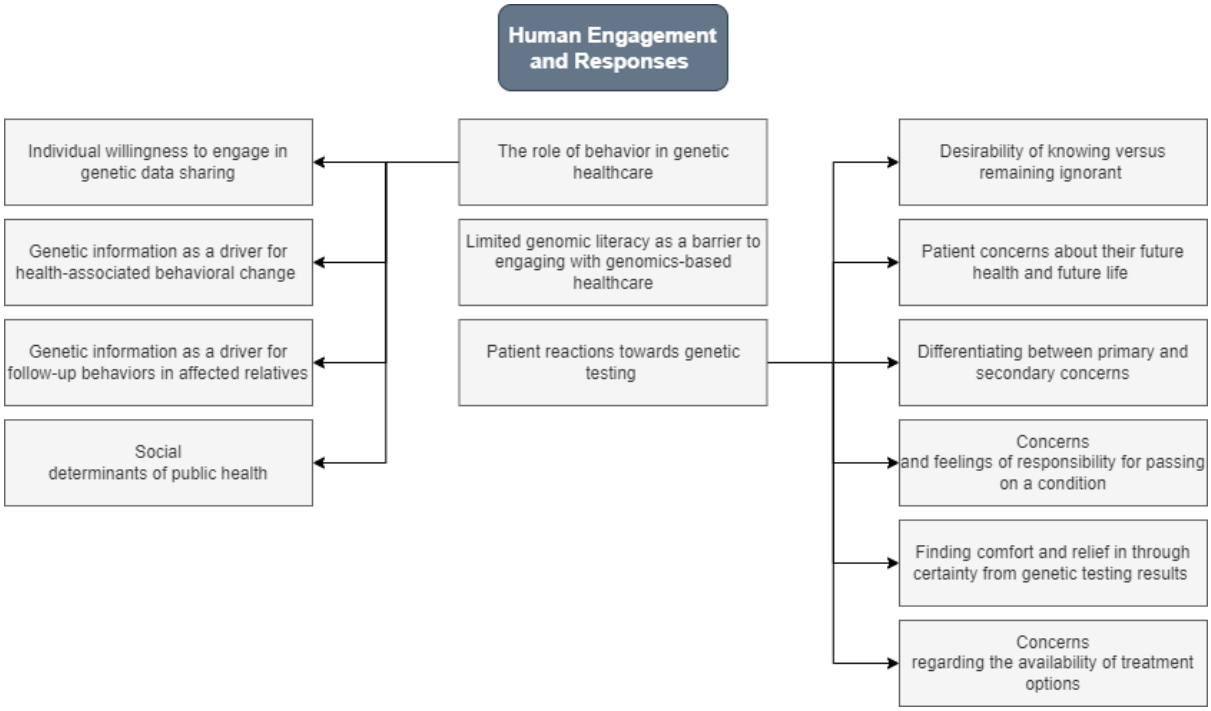

Figure 5 *Thematic map of themes and sub-themes relating to human engagement and responses*

4.4.1 The role of behavior in genetic healthcare

One of the subjects of interest to the research concerns the behaviors exhibited by patients and relatives in relation to the process of genetic testing in healthcare. Based on the contributions of healthcare professionals and other experts, several relevant aspects of the interplay between personalized medicine and human behavior have been identified. From the interviews, four sub-themes relating to different aspects of behavior have been identified.

4.4.1.1 Individual willingness to engage in genetic data sharing.

An important sub-theme is the data sharing behaviors of individuals with regards to genetic data. Interviewees generally observed a positive attitude towards data sharing out of solidarity motives, as long as preconditions such as privacy are guaranteed. Inclination to share is influenced by the fact that individuals can have significant intrinsic motivation to share when this could result in significant positives outcomes for the individual. This is especially the case when sharing genetic information for diagnosis or treatment of health conditions (weather with healthcare professional or commercial parties), where the potential personal benefit is evident.

Additionally, individuals might engage in sharing behaviors if this is experienced as the only way of reaching another personal goal.

"Yes, it's, of course, about bodies and health, life and death, and so on. That's why everyone is so inclined to share in those areas." (Participant 7)

"Those people were indeed aware that these companies in America could use their data for research, and the data could also be used by others. But it was the only way for them to find out who their father was and if they had other family members, so they accepted that risk or disadvantage." (Participant 8)

Another type of sharing behavior is consenting to uses of personal information beyond the scope of diagnosis and treatment, such as for research and development. Individuals can be motivated to consent to data sharing out of solidarity motives.

"One of the things that you could consider as an example is the idea of data solidarity, which you might call a value." "I think what a large part of the people want is for their own data and their bodily materials to be used to improve healthcare for their children and grandchildren. That's often what you hear. And an even larger part is fine with it happening in that way." (Participant 1)

"There are so many people, really so many people here, who come into our consultation rooms and say, 'You know, I have nothing left to gain from this, but hopefully, at least, science or someone else can benefit from it.' I'm sure that sentiment is very widely shared, yes." (Participant 8)

"They could choose whether or not to give permission for their research material, the remaining blood, to be used for further research. So, people are willing to do this anonymously because it's not traceable to the individual." (Participant 6)

4.4.1.2 Genetic information as a driver for health-associated behavioral change

One of the behavioral themes addressed consistently is that of health directed behaviors. One of the promises of personalized medicine is that individuals could employ the insights of their genetic profile to engage in tailored lifestyle changes that would positively impact their long-term health. Interviewees warn that the link between both availability of information and options for lifestyle change and actual behavioral change is complex.

It should be noted that, as discussed in detail in the *friction* sub-heme of *essentiality and proportionality*, it is broadly argued amongst interviewees that there are plenty of general lifestyle changes available that could positively impact individual health without requiring any

form of genetic diagnostics. This leads interviewees to argue that the availability of options and information is not necessarily a strong driver of behavioral change.

"You see, there are large warnings on cigarette packages, 'smoking is deadly,' and yet they are still sold. So, it's addictive, it's easy, it's... Knowing a risk profile, well, if someone is overweight, they can see for themselves that they are overweight, and they probably know they have a high risk for this, this, and this. But it's not an immediate reason to change their behavior." (Participant 5)

Others recognize that some people do intent to change their behavior after receiving information from genetic testing, but also highlight the flipside of people assuming unhealthy behaviors will not have negative health effects when their genetic profile puts them at low risk.

"I think that a diagnosis, in some cases, can make people more aware. You do see that sometimes when people receive a particular diagnosis, in this case, through DNA diagnostics, that they might be at risk for an inherited disease, they do start thinking, 'Okay, by adjusting my lifestyle, living healthily, and being more active, I can prevent certain things.' You do notice that. However, it's also true that when people are told they won't get the inherited disease, they might start living very unhealthily because they believe they won't get it anyway. Even though this might increase their chances of developing other conditions, so that's in play as well." (Participant 6)

4.4.1.3 Genetic information as a driver for follow-up behaviors in affected relatives

The nature of genetic profiling is such that findings may not only pertain to the tested individual but might also reveal risk factors that apply to relatives. One aspect of health-related behavior with regards to genetic testing is the follow-up behavior exhibited by individuals when informed that they might be at risk via relatives.

As discussed in more detail with regards to *ethics*, patients with findings that are deemed to be relevant for family members are provided with a family letter which they are encouraged to provide to their relatives. Interviewees indicate however that follow up of those family letters is low. One of the proposed reasons for this is that people are afraid of the implications of genetic testing. The implications mentioned are not foremost health related but relate to financial concerns and information provision.

"We do hear that as well because few family members of someone with a hereditary disease, come back to clinical genetics. So, that's one thing. But yes, people might also think that they might not be able to get insurance anymore. […] This does have consequences at times." (Participant 6)

"No, [reasons for low follow up] being researched right now, but I think it's often because the information might be quite complicated. Those are more barriers where the information might be too complex. I have to go back to the doctor, and if I get a referral, it immediately costs 500 euros, an appointment with clinical genetics deducts 500 euros from my own contribution; these are all barriers. I think it's more at that level than how people live, that would prevent them from going. So, I think it's more at that level." (Participant 6)

"But of course, there are always some people who don't come, and if they don't come because they don't want to know, that's fine, as long as they make an informed choice. Or do they not come because they don't understand, are our letters not clear enough? I think there is something to be gained there." (Participant 8)

4.4.1.4 Social determinants of public health

One of the factors which affect health directed behaviors is the way in which individuals prioritize different values. Individuals attitude towards and willingness to engage with personalized healthcare is affected by what is valued and which of those values dominate in different circumstances. This might affect whether individuals choose to engage with personalized healthcare, and if they do, subsequently affect the ways in which individuals engage with personalized healthcare.

"I think there's also a difference between a healthy citizen and someone who is critically ill. If you get off the train at Nijmegen station and are asked about medical tech and such, or whether we should do this, you might think, 'That's interesting, I wonder what will come out of it, innovation. Give me that watch!' I'm also curious about what will come out of my sequencing, and you might chuckle about whether I'm a Neanderthal or not. […] But at the same time, when you are really ill and vulnerable, those things quickly become less important. It comes down to very basic, essential things. Is there someone to open the door for me? Am I not alone? Will I make it through tomorrow, and so on." (Participant 7)

"I know someone who says, 'I'm more concerned about privacy and such matters than the future of medicine.' And that's okay; it can go that way too." (Participant 1)

It is suggested that also an individual's broader personal situation at a specific point in time affects the extent to which they are willing and ability to engage in health directed behaviors. Although one aspect of this is value priority in the strict sense, in other cases individuals can feel required to prioritize based on practical necessity.

"And that's where the friction lies, I think. We're all consumers, citizens, and patients, but thankfully, we're not patients for a significant part of our lives. [...] It's not so much that we have conflicting values, but that we prioritize them differently. So, our top 1, 2, 3 values vary. We have both sets of values within ourselves in all their variations, but the most important ones, the ones that rise to the top, depend on your life situation. Are you working? Do you have a job or not? Are you sick? Are you healthy? Are you rich? Are you poor?" (Participant 7)

Especially when to comes to preventative genetic testing, there is likely to be a significant portion of the population who are preoccupied with other tasks to the extent that they will refrain from engaging with personalized healthcare.

"That can be quite tricky because people often have other issues that are far more important to them than their health. They may be more concerned about figuring out how to have enough to eat until the end of the month, or if they can afford their rent. People are often preoccupied with survival rather than contemplating whether they should undergo a genetic test or not." (Participant 6)

4.4.2 Limited genomic literacy as a barrier to engaging with genomics-based healthcare.

Genomic literacy (as an extension of health literacy) refers to the ability of an individual to obtain, understand, and subsequently employ genomic information to make informed health-related decisions. Genomic literacy is one of the factors influencing to what extent individuals can benefit from genomics-based healthcare and influences both psychological state and behavior. Genomic literacy influences informed decision making at the individual level, but also influences the capacity to for an informed debate on a societal level.

Interviewees point to low genomic literacy as a problem for a transition to personalized healthcare. As discussed in relation to the *friction* theme of *inadequate cooperation*, involving citizens in the decision-making process surrounding personalized medicines in a manner that affords them actual and fair representation can be challenging when genomic literacy in society is low. In addition, during genetic care, low genetic literacy can make it challenging for care givers to communicate relevant information in ways that benefit the patient.

"People […] often they don't fully comprehend the consequences, or they haven't thought about it yet. You need to teach people more genetic skills so they can handle it. Offering it is one thing, but if no one understands it, what's the point? You must be able to explain clearly what individuals or society can gain from it. This also expects and requires that people have certain skills in genetics, and that can be quite complex." (Participant 6)

"So, you have a genetic risk profile, and whether you get sick or not, that, of course, involves many more variants. So, if you want to do this, we're dealing with a large group of people with limited health literacy who don't understand any of this. Even a highly educated person finds it challenging to follow. What do they need this knowledge for?" (Participant 8)

The low genetic literacy in society is contrasted with the increasing availability of options for genetic testing without professional supervision and counseling. In cases of DTC testing individuals can be provided with a large amount of information they might struggle to interpret.

"Occasionally, people come to the outpatient clinic saying, 'I've done [DTC testing], I got this, can you interpret it for me?' It doesn't happen often, but it does occur." (Participant 8)

4.4.3 Patient reactions towards genetic testing

One of the subjects of interest to the research concerns the cognitive process of patients as it relates to their engagement with genetic testing or personalized care. As individual patients are not part of the sample, psychological state and cognitive process cannot be inferred. Rather, this section will focus on the reactions of, and concerns expressed by, patients and their relatives during the full process of genetic testing, as indicated by the participating experts. Especially the contribution of the experts in the area of genetic counseling, and in the area of patient information provision relating to genetic testing in healthcare, are highly relevant to this theme. The following section will provide an overview of the different themes that can be characterized in the patient reactions indicated by the experts.

4.4.3.1 Desirability of knowing versus remaining ignorant

Before the process of genetic testing, patients will have to make an individual decision as to whether or not to undergo testing. This requires patients to decide whether or not they want to know their genetic predispositions or not. One of the factors considered in this is to what extent patients perceive that there is something to be gained.

"So, it's always finding that balance between do you really want to know this, will it truly yield you something with respect to prevention." (Participant 5)

Although obtaining certainty can be a strong motive for patients to undergo genetic testing, other times personal convictions make patients not want to know such results. The emotions and concerns experienced with regards to one's health vary between individuals, and some might prioritize other considerations over the potential benefit of genetic testing.

"There will be people who may choose to undergo testing because they simply want certainty, but, of course, there are also people who may not want to do that because they take life as it comes, or they deal with it in a certain way based on religious or philosophical beliefs. " (Participant 6)

4.4.3.2 Patient concerns about their future health and life

Even before any tests have been administered, engaging with genetic testing can induce concerns in patients of what the results will indicate about their future, and subsequent ramifications of the results for their life. Such concerns extend beyond health-related effects to concerns about implications for other aspects of life. Concerns about broader ramifications play a role even before the process of genetic testing or genetic counseling. Patients might develop concerns about the implications of genetic testing on the basis of information received from other care givers, possibly influencing their decision to even engage with genetic care.

"People can naturally have fears and uncertainties about whether or not to test, what their future will look like." (Participant 6)

"There are still patients who don't come here because their general practitioner has said that they won't be able to get insurance anymore." (Participant 8)

It is indicated that after return of results, concerns about implications are often secondary to the experienced concerns about risk and heredity. Furthermore, it is indicated that patients that know they are at increased risk for a certain condition can experience an enduring fear for when this condition will manifest.

"From my experience, people initially want to know if it's hereditary, do they have a chance, and then later, if they may already have a diagnosis or are waiting for the results, they have more questions about what it means for them." (Participant 6)

"It also induces a lot of fear at the same time because you then know from a young age that you have that gene. And you carry it with you all the time; otherwise, you might have had a carefree life until a breast cancer diagnosis, to put it that way." (Participant 5)

Concerns about non-health related ramifications on life often concern fears of a reduction in opportunities, for example with regards to obtaining specific forms of insurance. Privacy concerns were mentioned not as a stand-alone concern, but rather in relation to fears of implications when privacy might be insufficiently guaranteed.

"People also have questions about insurance. We often receive inquiries about whether they can take out life insurance or disability insurance, which is often still possible." (Participant 6)

4.4.3.3 Differentiating between primary and secondary concerns

Genetic testing can induce a range of concerns in a patient. It is indicated that a patient's information seeking is often initially focused on understanding the health risks for them and their relatives implied by the results, or the specific condition they face. It is later in the process that information seeking shifts focus to expectations for the future.

"My experience is that people primarily want to know their risk of developing the disease. It's challenging for them to understand that they have a certain risk of the disease, and they often feel uncertain about whether they have it or not. […] As people receive the diagnosis or progress further in the process, they have more questions about how it will affect their life, their children, and what to expect in the future." (Participant 6)

4.4.3.4 Concerns and feelings of responsibility for passing on a condition

Similar to how patients are focused on understanding their own condition and risk, their reaction includes trying to understand which risks they might have passed on to their children. Although there is a mix of emotions involved, there seems to be both a component of worry for the other person as well as a feeling of responsibility or guilt.

"In general, when you've just received a diagnosis, there's a mix of emotions - panic, grief, anger. It's a part of me, but now I might have passed it on to my children as well. So, there are various emotions at play, and you need to find a way to channel them. We also involve psychologists, of course; there are well-established care pathways for that." (Participant 8)

"So people wonder whether they will get the disease or not, and whether they might also pass the disease on to their children or to their future children, to their descendants." (Participant 6)

4.4.3.5 Finding comfort and relief in through certainty from genetic testing results

When choosing to engage with genetic testing, patients might find comfort and relief in the results. Relief can be experienced when it is found an individual is not at risk for a certain condition. However, in addition, information that does indicate (increased risk of) a condition can also provide comfort, by relieving the uncertainty associated with ignorance.

"When people undergo DNA testing and they have a genetic predisposition, it can provide a sense of relief or a feeling of at least knowing what to expect for some individuals. However, for other people, it can also cause a lot of concerns. But, well, if you at least know what it is, it provides a kind of certainty. Sometimes, especially when a diagnosis couldn't be made for a long time, DNA testing can suddenly provide a diagnosis, for instance in the case of a child with developmental delays. It can give

the parents a sense of certainty. It doesn't mean an instant cure, but at least it gives a name to the condition." (Participant 6)

Results from genetic testing can however also inspire a false sense of security. Whilst health directed behaviors are not a significant theme in patients' reactions, patients can obtain comfort from testing results to the extent that they inspire unhealthy behaviors.

"Oh, I don't have any of this, no risk at all, so I'll just keep snacking, I'll stay sedentary, I'll keep smoking because I don't have that risk profile. Well, that's not a good approach, is it?" (Participant 5)

"But it's also true that when people find out they won't get the genetic disease, they might start living very unhealthy lives because they think they won't get the disease." (Participant 6)

4.4.3.6 Concerns regarding the availability of treatment options

One of the strong and specific initial reactions when receiving the results of genetic testing is information seeking with regards to treatment options or other ways of mitigating the onset of the condition. This reaction seems to relate to medical interventions, as opposed to behavioral changes.

"Other questions revolve around whether, if I do get the disease, if I have the genetic predisposition to the disease and I develop symptoms, is there anything that can be done? Or if I know in an early stage that I have the genetic predisposition, are there any screenings available, or can I undergo surgery to prevent symptoms from occurring, or can I ensure that it is detected in the earliest possible stage?" (Participant 6)

5. Discussion

This project concerns an exploratory study into the transition to a genomics-integrated healthcare system in The Netherlands and the relevant aspects of human behavior with regards to genomics-integrated healthcare. With regards to the transition, the study aims to characterize frictions present between stakeholders in the innovation ecosystem that might pose barriers to the transition to a genomics-integrated healthcare system. In the examination of friction, values and potential ethical issues arising from trade-offs between them are explicitly considered. With regards to human behavior, the study aims to characterize the engagement and responses of patients and relatives associated with genomics-integrated healthcare. Based on the goals of this exploratory study, two research questions have been formulated.

RQ1: *Which (value-) frictions exist within or between different stakeholders, and what are the obstacles they pose for the implementation of personalized healthcare?*

RQ2: *What are the reactions and behaviors exhibited by patients and relatives in relation to the process of genetic testing in healthcare, and which factors have influenced them?*

As the transition towards a genomics-integrated healthcare system is a novel and evolving phenomenon, the availability of studies on this topic is limited. Although reports are available on the developments and progress of individual parties and stakeholders, a holistic characterization across interdependent stakeholders is currently lacking. Through an exploratory study using an ecosystems approach, employing the empirical method of expert interviews with ecosystem participants, this project aims to provide such a characterization.

5.1 Summary of results

Thematic analysis of the empirical data resulted in the generation of themes and sub-themes relating to the research question. The following section will provide a concise summary of the main findings for each of the overarching themes.

Figure 6 *The four overarching themes identified in the data*

A multitude of loci at which friction occurs in the ecosystem have been identified. These can be divided into two kinds of friction. The first is predominantly value-based friction (but includes some process, operational, relational and regulatory friction), in which diverging values, value-priorities, or interests result in friction between interdependent stakeholders. Lacking homologation of appropriate standards of evidence for personalized medicines is a challenge to their incorporation into healthcare. Particular interests and responsibilities in data sharing causes friction as stakeholders struggle to reconcile their interest in data-exchange with their interests or responsibilities with regards to shielding that data. Furthermore, there is friction in attempts to reconcile stakeholder specific interests, such as commercial or academic interests, with the broader interests of public health. Financial considerations cause friction as some stakeholders aim to maximize treatment efficacy on an individual level whilst others are tasked with maximizing collective public health impact. Another locus of friction concerns the essentiality of genomic data in realizing improved public health outcomes, and concerns with regards to the proportionality of the resources required in relation to the outcomes realized. Establishing trust amongst stakeholders is essential for facilitating collaboration and furthering the innovation process yet is particularly difficult to establish in the early phases of the innovation lifecycle. Friction is also observed with regards to defining privacy and the potential for conflicting notions to hamper collaboration between stakeholders. Friction is present concerning conservative versus progressive policy, and concerning what policy framework would be fit to deal with the unique characteristics of a personalized healthcare system.

The second kind of friction is more practical in nature, and concerns loci of instrumental, organizational, and regulatory friction without the presence of significant value conflict. These are referred to as instrumental barriers. Inadequate cooperation between stakeholders poses a challenge to overcoming knowledge and skill fragmentation, and correspondingly hampers synergistic value creation. Inadequate infrastructure and standards for data-exchange make it such that data, whilst present in the ecosystem, cannot be effectively employed by stakeholders to meet the challenges they face. Inadequate interoperability of activities and artefacts poses a barrier to the effective implementation of personalized medicine and disrupts the circular manner in which the system of personalized care is supposed to operate. The lack of a clear and comprehensive legal framework for genomics-based personalized care creates uncertainty and increases risk for stakeholders, whilst other parties might employ existing legal ambiguity to subvert policies generally deemed applicable. In addition to lacking unified frameworks and infrastructure, issues are raised with regard to the extent to which the workforce across the

healthcare sector would be able to meet the additional requirements placed on it by a transition to a genomics-integrated healthcare system.

In addition to value friction, based on other observed value trade-offs, the ethical issues associated with a transition to a genomics integrated healthcare system can be characterized. Ethical issues surrounding accessibility relate to both trade-offs in the distribution of healthcare resources between personalized and general care, and equitable access to personalized healthcare between individuals with different socio-economic backgrounds. The issue of beneficence highlights that personalized healthcare efforts cannot simply be assumed to be an effective way of benefiting patients overall, nor can they be expected to be an efficient way to create such benefits. Ethical issues also arise in the challenges posed by personalized medicine to traditional models of consent. Firstly, traditional models of consent are ill equipped to deal with the dynamic and iterative nature of genomics-integrated personalized care. Second, the nature of genetic data gives rise to situations in which decisions have to be made for individuals that have not been able to provide consent. With regards to fairness, whilst personalized care by definition involves unequal treatment of individuals, access to an equal quality of care can be promoted through increased personalization of that care. Fair distribution of benefits between individuals is also cited as an ethical issue, especially when such benefits are obtained through the contributions of said individuals. Lastly, ethical issues surrounding fears of reductionism relate to how, through increased medicalization and the potential for genetic discrimination, increased use of genetic data would come to affect society.

Based on the contributions of healthcare professionals, several relevant aspects of the interplay between personalized medicine and human behavior have been identified. In addition to attaining personal benefit, solidarity motives are indicated as influencing individuals' willingness to engage in genetic data sharing behaviors. Participants perceived a general positive attitude towards data sharing amongst their patients as long as preconditions such as privacy are guaranteed. Both the availability of genetic information as well as availability of options for health-directed behaviors, however, are not perceived as strong drivers of positive health-directed lifestyle changes in individuals. Similarly, providing at-risk relatives with information about genetic testing is not perceived to be strongly associated with follow-up behaviors. Rather, as the experts note, individuals' willingness and ability to engage with health directed behaviors is affected by what they prioritize at a specific point in time, contingent upon socio-economic determinants. A related factor is the fact that low genetic literacy in

society influences both the extent to which individuals can engage with personalized care and participate in a societal debate regarding the issues surrounding personalized care.

Another valuable aspect of human behavior characterized through the contributions of healthcare professionals are the reactions displayed by patients throughout the process of genetic testing. Not all patients can be expected to be open to engaging with genetic testing, some might prioritize other (philosophical or religious) considerations over the potential benefits of genetic testing. Genetic testing often induces concerns in patients about the future. These extend beyond health-related effects to ramifications for other aspects of life, such as fears of a reduction in opportunities. Such fears are, however, indicated as being secondary to concerns about the health risks faced by oneself and one's relatives. Concerns about the implications of having passed on a condition to their children might consist of both a component of worry for the other person as well as a feeling of responsibility or guilt. Whether results are positive or negative, return of result can also provide some comfort to patients by resolving uncertainty associated with ignorance. It is warned however that some patients might obtain comfort from testing results to the extent that they inspire unhealthy behaviors. One very specific initial reaction indicated is information seeking with regards to treatment options or other ways of mitigating the onset of a detected condition.

5.2 Interpretation of results

The results obtained are extensive and diverse and so far, have been presented as organized into four overarching themes and a multitude of sub-themes. There is however significant commonality between different themes, that is deemed associated with several common issues. The current section will discuss and interpret the results on the basis of four key insights. These insights bring together distinct themes that, when taken together, represent a common issue with regards to the transition to a genomics-integrated healthcare system.

Insight 1: Genetic data from WGS in a genomics-integrated healthcare system is not expected to be a strong driver of behavioral change, nor is a focus on genetics deemed to be the most appropriate means to the end of improving public health.

One of the most valuable insights obtained is that genetic data is not expected to be a strong driver of health-directed behavioral change. One of the promises of a genomics-integrated healthcare system is that it would enable patients to exert increased control over their (long-term) health through the provision of information that would enable targeted health-directed

behavioral change. Healthcare professionals, however, argue that there are plenty of options for evidence-based health-directed behaviors available, yet these options are not broadly exploited by the public. Such options include widely known beneficial behaviors, such as dietary changes or ceasing the consumption of alcohol and tobacco products. Recommendations could even be personalized based on easily obtainable diagnostic information (such as BMI, heart rate, and blood pressure). Nevertheless, such healthy behaviors are not adopted across society. They also indicate that even in cases of provision of specific genetic information and the explicit recommendation to act upon that information, such as in the case of the family letter, follow-up behavior by relatives is low. This is consistent with earlier findings by Hodgson & Gaff (2013). Failure to engage in health-directed behaviors cannot simply be attributed to a lack of willingness to engage in such behaviors, but also to other factors. This mirrors observations made with regards to the value-action gap, relating to individual's environmentally conscious consumer behavior (Gupta & Ogden, 2006; Farjam et al., 2019), and relation to individuals' intentions and actions in relation to personal privacy (Kokolakis, 2017; Gerber et al., 2018). Commonality between these cases is that a positive attitude towards certain behaviors is not the determining factor in whether an individual will engage in such behaviors. Factors such as social and economic determinants are argued to have a much stronger effect on health directed behaviors than information provision, e.g. one of the proposed reasons for low follow up on family letters is the costs associated with genetic testing.

The strong influence of social and economic determinants on health-directed behaviors might be related to the construal-levels at which processing of health-related information takes place. The amount of psychological distance that is experienced in relation to an issue influences perception and judgement (Trope et al., 2007). Causality between genetic makeup and health is generally not part of an individual's lived experience. Genomics' microscopic scale and complex, uncertain, indirect, and interactive effects are all conducive to increased psychological distance for genomic information. Difficulty in relating to potential future adverse health effects might also increase the perceived psychological distance, leading to processing on a higher level more concerned with abstraction and meaning. Personal circumstances, such as children, professional responsibilities, and ensuring sustenance and housing, are much more likely to be represented at lower construal levels, and representations are therefore more concerned with actionable or goal-directed details (Wakslak et al., 2006). This could be an explanation for how social and economic determinants might lead individuals

to prioritize other actions over health-directed behaviors. More appropriate methods of behavioral research should be employed to explore such dynamics.

The influence of these determinants is also associated with a potential increase in inequality. The individuals most likely to be in a position to capitalize on the opportunities afforded by personalized care are argued to be those for which other preconditions for a healthy life are comfortably met, and thus health directed behavioral change is expected to provide only marginal improvements. Similarly, those that could benefit the most might be forced to prioritize other actions. In addition, there are significant individual difference in genomic or health literacy, and the resources individuals are able to expend to inform themselves, meaning that engaging with healthcare resources can be much more difficult for some than for others. These findings confirm concerns voiced by Zimani et al. (2021) for the need to keep target groups adequately informed, in order to ensure their ability to access this new generation of healthcare. Patient reactions to genetic testing show that, although health related concerns are still primary, individuals are very much aware of the non-health related ramifications genetic testing results can have on their life, worrying about insurance and job security.

The link between availability of information and options and actual behavior is complex. It is deemed unlikely by most interviewed experts that investments into widespread genetic screening will elicit health directed behavioral change without considering the other factors that influence an individual's ability to engage in such behaviors. Based on these observations, the essentiality and proportionality of investments in widespread and broad genetic screen as a means to promote public health is questionable. Rather, experts argue, it is much more fruitful to engage in research and initiatives to promote public health through the facilitation of known, evidence-based, and easily accessible lifestyle changes.

Insight 2: The innovation ecosystem concerned with the transition to a genomics-integrated healthcare system in The Netherlands experiences significant friction between stakeholders.

Results indicate several loci of significant value-friction between stakeholders in the innovation ecosystem. One important source of value friction is found in insufficient reconciliation between personalized medicine and collective approaches to public health. Stakeholders have diverging views regarding the most appropriate way to approach healthcare, and the most appropriate distribution of resources between general and personalized healthcare initiatives. Whilst some stakeholders point to the potential benefits of personalized care, others emphasize

the potential harm caused by diverting resources away from collective approaches. The latter views mirror the concerns voiced by Clarke (2014b) on how to focus on the individual genetic basis of disease diverts attention away from public health measures. An emphasis on genetics with regards to health is in line with the traditional medical model but is at odds with contemporary biopsychosocial approaches to public health, which emphasize the influence of a wide range of individual, socioeconomic, and environmental contextual factors on individual and collective health. Solutions to such clear value-conflict must be sought in debate and compromise with regards to balancing individual and collective needs.

Another related cause of friction is the insufficient homologation of appropriate standards of evidence. Traditional standards of evidence based on collectivity are not well suited to evaluate personalized interventions, and thus delay or prevent the integration of personalized interventions into healthcare. A major challenge for stakeholders is thus to balance stakeholder specific interests with the broader need to maintain a strong public health system.

Although all stakeholders recognize the need to engage in data exchange in order to realize synergistic value creation at the ecosystem level, there is significant value friction with regards to the sharing of data. This friction is caused by the diverging interests and responsibilities stakeholders have with regard to their data. Misalignment of goals between collaborating stakeholders is a strong source of friction in the cooperation. Another cause of friction is a perceived insufficient proportionality of reciprocity in relation to the interests' stakeholders have in keeping their data shielded. This is consistent with findings that awareness of the value of their data leads stakeholders to engage in data shielding (Ormond & Cho, 2014). Although not indicated in the data, this could be related to biases that lead stakeholders to overestimate the value of their contribution and underestimate the value of other's (Tversky & Kahneman, 1974). Results show that aversion to data sharing is related to a lack of sense of control when engaging in data exchange, amplified by the lack of safeguards (and trust between stakeholders) in these early stages of ecosystem development. This trust is often based on fears of a lack of commitment from other stakeholders. Data sharing comes with a certain expectation of stewardship, and stakeholders want assurances against data being used in ways deemed undesirable by the sharing party, or parties suddenly abandoning a collaborative effort. Possible solutions to this value-friction can be sought in collaborative agreements between stakeholders, and frameworks for data governance with mechanisms for accountability.

Whilst privacy is recognized as an important value for genomic-integrated healthcare, no consensus is present amongst ecosystem participants in defining the relevant aspects of privacy, and what the subsequent implications for the design of the system are. Some deem issues of privacy to be the responsibility of regulators and have not formulated requirements about this themselves. Whilst aspects of personalized medicine are framed as detrimental to personal privacy, it is promising that ensuring control, and focusing on solidarity and common interests, might be a way to reconcile between privacy and other system requirements. Solutions to this value conflict must be sought in debate and compromise between stakeholders.

Another source of friction is found in the policies that govern the actions of stakeholder participants. Whilst the importance of diligence in a transition to a genomics-integrated healthcare system is recognized, overly precautious policies are deemed by some stakeholders to unnecessarily delay innovation. In addition, stakeholders feel constrained by policies that are unfit to deal with the circular dynamics of a personalized healthcare system. This new dynamic implies the blending of healthcare with research and development and requires new modes of cooperation between stakeholders to be enabled. In establishing such new modes, hospitals, academia, and pharmaceutical companies experience friction with regards to the division of roles and responsibilities. Consistent with literature, there is a strong need for coordination in order to ensure ecosystem success (e.g. Ginsburg, 2014). The need for adequate and comprehensive governance frameworks is recognized in the European and Dutch initiatives (European Commission, 2018; Nationaal Groeifonds, 2021). Nevertheless, stakeholders still feel insufficiently empowered by whatever progress has been made with regards to policy frameworks. Whilst regulatory reform might be a way to resolve the regulatory friction that is experienced, debate and compromise is needed to resolve the value-based friction and to align stakeholders with regards to new modes of cooperation.

Insight 3: The transition to a genomics-integrated healthcare system in The Netherlands experiences instrumental barriers as general preconditions for effective ecosystem operations are insufficiently met.

Many of the general preconditions for effective innovation ecosystems are insufficiently met. Stakeholders experience inadequate cooperation and synergistic value creation in the ecosystem, signal too much fragmentation of knowledge and expertise, and point to insufficient technology transfer between academia and industry. These barriers are consistent with those identified in a European context by Horgan et al. (2017). In addition, a barrier is posed by

inadequate infrastructure and standardization for data-exchange. This leads to stakeholders not being able to access or employ relevant data required for innovation. EU and Dutch initiatives explicitly aimed to overcome these barriers, emphasizing facilitation of collaboration between stakeholders and the creation of unified infrastructure and governance frameworks (European Commission, 2018; Nationaal Groeifonds, 2021). These barriers are yet insufficiently addressed. In addition, stakeholders indicate that, especially with regards to the creation of unified and standardized data infrastructure, ambiguity remains as to who exactly will take responsibility for this, and who will bear the financial costs. In addition to the lack of standardization of data, insufficient coordination between stakeholders leads to inadequate interoperability between activities and artifacts throughout the system. This system's failure poses a barrier to capturing value at the aggregate level, consistent with expectations based on the ecosystems approach (Granstrand & Holgersson, 2020). These instrumental and operational frictions can be solved through effective collaboration between stakeholders, although the ecosystem might benefit from a stronger presence of coordinating actors, which can take a leading role in standard setting and the defragmentation of expertise.

Another cited barrier to ecosystem success is the lack of a comprehensive, clear, and fit-for-purpose legal framework for personalized healthcare. As the current framework is insufficiently suited to this new generation of healthcare, the need for a more consistent and comprehensive policy and regulatory framework has been voiced repeatedly (ESPON, 2019). Lack of clear policy results in increased risk and uncertainty for stakeholders and enables some parties to act in ways deemed undesirable by regulators. As this is yet insufficient address, the implications of the barrier posed by this only increase. Whilst recognizing the potential of personalized medicines, the governmental agencies tasked with regulating them are bound by insufficiently applicable standards of evidence. Whilst there is a multitude of DTC services employing legal ambiguity to provide services to Dutch consumers, healthcare professionals are still not allowed to perform genetic testing inside the Netherlands without indication. There is a role for regulatory bodies in resolving this regulatory friction, by ensuring the presence of adequate and clear legal, policy, and regulatory frameworks.

Results suggest that the healthcare labor force will have insufficient capacity to meet the demands placed on them by increased scale of genetic testing, as well as the additional requirements placed on healthcare professionals through *datafication*. The latter relates to the importance of generating and exchanging data, for example, through the standardization and

expansion of data registry protocols to ensure compatibility throughout the system. These issues mirror the issues identified previously with regards to the challenge posed by a disorganized state of data systems in establishing a learning healthcare system (McGinnis, 2009; Kierkegaard, 2011). However, whilst not fundamentally different from infrastructure for the registry and exchange of other health data, the volume and complexity of genomic data in a genomics-integrated healthcare system can be expected to pose an even greater challenge to the integration and implementation of this data throughout healthcare (Chute & Kohane, 2013).

Additional labor force challenges result from the increased demand for genetic counseling resources associated with the widespread integration of genetic testing into healthcare. Such resources are necessary for the effective integration of genetic testing, but since current availability is already deemed insufficient, it is unlikely that a decent standard of care can be maintained in the face of increased demand. These results are consistent with earlier predictions that traditional service delivery models would be insufficient (Stoll et al., 2018). Results also indicate that individuals do indeed appeal to healthcare professionals for assistance based on results obtained through DTC testing, also consistent with previous findings (Brett et al., 2012). It is argued in literature that the integration of genetic data into care for diagnostics could empower healthcare professionals to focus more on those aspects of care that require human interaction (Snape et al., 2019). However, whatever task relieve integration of genetic data will bring, it is deemed unlikely that this by itself would result in the ability to accommodate the increased need for highly specialized genetic counseling professionals. A strong instrumental barrier to ecosystem success is thus the discrepancy between what is required from the healthcare labor force for genomics-integrated healthcare to delivery on its promises, and what can be reasonably provided by that workforce. A successful transition towards a genomics-integrated healthcare system is contingent upon the availability of sufficient amount of adequately trained healthcare professionals. This operational friction could be addressed by increasing the number of counseling professionals, whilst simultaneous evaluating how counseling resources can be most efficiently used to address the challenges posed by a transition to personalized healthcare.

Insight 4: The transition to a genomics-integrated healthcare system in The Netherlands is associated with several ethical issues which should be resolved before widespread integration of genetic testing into healthcare.

The accessibility of the public healthcare system is an ethical issue that is touched upon from several different perspectives. Common between them is the potential for a transition to a genomics-integrated healthcare system to reduce the broad accessibility of the public healthcare system. Although it is recognized that it would be unethical to withhold access to personalized medicines from patients that could benefit from them, making such resources available to individuals might require limiting public health resources that benefit a much larger group, potentially decreasing public health accessibility. Furthermore, a focus on the individual genetic basis of disease in research might reduce funding for research into other important influences. Whilst these findings are consistent with the concerns voiced by Clarke (2014b) and Evangelatos et al. (2017), no reconciliation between individual and collective approaches seems to be happening between stakeholders. A focused on the genetic basis of disease also elicits fears of increased medicalization conditions which are of minor relevance, again reducing the attention afforded to other more relevant determinants of health.

Even when personalized healthcare resources were available to all, it is clear that different individuals would not be equally able to benefit from them. Health-directed behavior in individuals is contingent upon social and economic determinants, which influence which people would be more likely to seek out and benefit from personalized care. Differences in genomic literacy amongst the public only exacerbate the issue of equitable access. In addition, limited genomic literacy also forms a challenge to fair representation in the societal debate concerning personalized healthcare. Although findings by Haga (2013) and Syurina et al. (2011) already emphasized this problem, whilst technological progress has accelerated, ensuring an informed public has seen insufficient progress in this regard. Addressing low levels of genomic literacy will be a challenge, as people tend to lack an intuitive sense in applying concepts of risk and probability (Peters et al., 2006). An additional challenge to equitable treatment of individuals in general is the potential for genetic discrimination or increased stigmatization of specific conditions. This raises the question as to how genomics-integrated healthcare will change our view of the individual, and whether individuals will be treated as equally worthy. These concerns mirror concerns voiced in literature, e.g. Juengst et al. (2012), yet it is unclear if and how stakeholders aim to address these.

One of the most interesting insights from the data is that, whilst ethical issues regarding consent and incidental findings are widely discussed in literature (see Dove et al., 2019), these do not seem to be of major relevance in practice. For example, with regards to informing relatives in traditional genetic testing, healthcare professionals prioritize their *duty of care*, and the general policy is to provide a family letter (with varying degrees of information disclosure) which encourages relatives to seek out further consultation. Although a viable approach in cases of traditional, small scale targeted testing, it's not evident whether this approach is sustainable once broad, untargeted genetic screening is integrated into healthcare. It is clear however that, with respect to the individual patient undergoing screening, current modes of consent are insufficiently suited to the dynamics of personalized healthcare and new modes of consent are required. This is consistent with concerned voice by Bunnik et al. (2013) and Rego et al. (2020). Although new models of consent have been proposed (e.g. Appelbaum et al., 2014), this seems to be more an academic endeavor than something that has found its way to practical implementation. A related issue is what kind of information is even deemed to be suitable for responsible disclosure to patients, in light of the complexity and uncertainty associated with findings from WGS. Both Yu et al. (2013) and Berg at al. (2011) have pointed out that, to maximize the effective use of WGS in personalized healthcare, a high standard must be employed for reporting results. Patients meanwhile indicate a diversity of attitudes towards broad return of results (Clift et al., 2015). Using a lower standard would however require a significant increase of genetic counseling resources or risk a decrease in the quality of counseling patients receive. There is insufficient reconciliation of views between different stakeholders, with some stakeholders advocating for providing patients with broad access to health data. It is also unclear what the long-term effects will be of such a high standard of reporting in healthcare, when the standard employed by DTC testing services is often much lower. This problem is amplified by the fact that currently, consumers often appeal to healthcare professionals for assistance in interpreting such indiscriminate results.

The last ethical issue is that of beneficence. This issue revolved around the question to what extent a transition to a genomics-integrated healthcare system can be expected to be a net positive for the health outcomes of patients. It is clear that whilst in isolation the benefits of personalized care are evident, the systems transition cannot simply be assumed to improve health outcomes across the collective.

5.3 Implications and directions for future research

This important overarching question is to what extent a transition to a genomics-integrated healthcare system can be expected to be a net positive for the health outcomes of patients. Whilst in isolation the benefits of personalized care are evident, the systems transition should not simply be assumed to improve health outcomes across the collective. Applying personalized medicine in a targeted manner, not fundamentally different from how traditional genetic testing is applied, is promising and would not require a systems transition. The results suggest, however, that the benefits of incorporating broad and untargeted screening in healthcare as a means to promote public health should however be critically evaluated. The link between information provision, intent, and behavior is complex, and socio-economic determinants influence which individuals would be most able to capitalize on the opportunities afforded by personalized care. It is imperative to critically reflect on how genomics should be integrated into care in order to offer real and tangible benefits to all patients.

The findings in this report are based on expert interviews, and no direct examination of patient behavior has occurred. Through the use of appropriate behavioral research methods, future research should focus on better understanding the value-action gap with regards to health-directed behaviors. It is important to uncover the factors of influence and gain a better understanding of the role played by specific social and economic determinants in the context of personalized care. It is also imperative to understand the role played by construal levels and characterize the way the different kinds of information in personalized care are perceived and processed by individuals. The goal should be able to characterize how personalized care can be employed to actually empower individuals to engage in health-directed behaviors. Further research could also focus on accounting for the influence of construal levels and genomic literacy in initiatives for public participation surrounding this healthcare transition.

Whilst technology has progressed over the past decade, other relevant aspects of the transition are lagging behind. Experts indicate insufficient reconciliation between the opportunities of personalized medicine and the current healthcare system, which is strongly grounded in principles of collectivity throughout. This study demonstrates the challenges that exist regarding the desire to capitalize on personalized medicine on the one side, and the responsibilities of maintaining a strong and accessible public healthcare system on the other.

Current legal and governance frameworks are deemed unfit by stakeholders to deal with the particularities and circular dynamics of a personalized healthcare system. Whilst clear policy

can be a facilitator of innovation, the shortcomings of current frameworks contribute to risk and uncertainty for stakeholders, both with regards to their particular activities as well as in the collaborative efforts between stakeholders. Adequate and comprehensive legal, policy, and governance frameworks are needed to facilitate the activities of stakeholders in the ecosystem and need to account for the circular nature of data sharing in personalized healthcare.

Value creation at the ecosystem level is hindered by a strong emphasis of stakeholders on their own interests. While the common goal is clear, stakeholders indicate that there is insufficient progress in reconciling misaligned interests between them, especially when responsibilities towards patients and their data are involved. Frameworks and modes of cooperation that facilitate collaboration and information exchange between stakeholders are required. Although partly an ecosystem issue, it is also contingent upon the legal frameworks to which stakeholders are bound. The building of relations and trust in the ecosystem can be facilitated by appropriate governance frameworks with mechanisms for transparency and accountability.

Next to ecosystem friction, stakeholders also point to the existence of significant instrumental barriers. Whilst the preconditions for successful functioning of the innovation ecosystem are clear and have been incorporated in the national and international initiatives for personalized care, stakeholders indicate that there are still insufficiently met. Stakeholders consistently mention inadequate infrastructure, lacking standardization, and inadequate inoperability between activities and artefacts. Inadequate fulfillment of these preconditions forms a barrier to synergistic value creation between stakeholders.

Future research should focus on understanding what ecosystem stakeholders and participants require from specific preconditions. In this, research efforts should be mindful of both the value- and instrumental dimensions. One important question is what would facilitate data exchange between stakeholders, and subsequently, how a unified infrastructure can be designed to support these requirements. Research will need to explore how new modes of cooperation can be established that integrate the concepts of stewardship and responsibility with regards to data. In addition, addressing instrumental barriers that result from regulatory friction will require some form of regulatory reform.

Another relevant question is what different stakeholders require for their operations, and how activities and artefacts can be designed in an interoperable way. Standardization will play a significant role in ensuring ecosystem success, but only if all stakeholder requirements are adequately represented. There is significant ambiguity with regards to the division of roles and

responsibilities in the ecosystem. Coordinating actors, such as two of the interviewed stakeholders, should take a more dominant role in creating alignment between different stakeholders and their activities the ecosystem. It is however important to examine whether actors that fulfill a coordinating role in the ecosystem, especially those not mandated by the government, have enough power and resources to effectively fulfill their role, and whether there are other factors that form a barrier to effective coordination. Coordinating actors in the ecosystem should focus on the preconditions most relevant early in the innovation lifecycle, such as building trust between stakeholders and employing forms of governance to make sure appropriate safeguards (through governance frameworks) are in place.

There are significant unresolved ethical issues surrounding the implementation of genomic-integrated personalized care. Current modes of consent are insufficiently suited to the dynamics of personalized healthcare. Several models of consent more appropriate for a genomic healthcare paradigm have been proposed, taking a more dynamic approach to consent (e.g. Yu et al., 2013; Mascalzoni et al., 2022; Wiertz & Boldt, 2022). Such models aim to promote self-determination by providing granular choices and the ability to adjust consent over time. Although proposals for new modes of consent are promising, research is needed to assess their viability in practice. For example, it is unclear how dynamic consent could be applied and guaranteed once data has been shared and incorporated amongst a large group of stakeholders.

Assessment of new modes of consent also needs to incorporate the associated counseling requirements need to guarantee informed and autonomous decision making. A transition to a genomics integrated healthcare system will place additional demands on a healthcare labor force already stressed by an aging population. Broad integration of genomics into healthcare will require significant increases in trained professionals in the area of genetic counseling. This requires an assessment of which modes of counseling are appropriate for this new paradigm.

Ethical research can also be of value in reconciliation of individual and collective approaches to care. However, trade-offs between collective and personalized approaches are also political endeavor and should be informed by public debate. Ethics studies, in combination with behavioral research, might be of value in assessing how exactly counseling resources can be employed to enable informed and autonomous decision-making with regards to consent, and ensure fair representation in the public debate.

5.5 Limitations

Whilst effort has been expended to ensure rigor throughout the current project, the research is not without its limitations. The current section serves to recognize the limitations of the project and highlight areas of improvement for future research. This discussion of limitations will include four common criteria for validation of qualitative research: credibility, transferability, dependability, and confirmability (Anney, 2014).

The limited number of concrete studies into the Dutch genomics innovation ecosystem makes it a valuable subject for an exploratory study. Nevertheless, although deemed an appropriate approach for the analysis and characterization of the topic at hand at this specific point in its lifecycle, the exploratory design of this research implies several limitations. Exploratory research sacrifices depth for breadth; aiming to expose a broad range of relevant aspects inevitably entails limiting the depth at which each of those aspects can be explored.

Another limitation is the non-exhaustive nature of exploratory research. Whilst care has been taken to, within the scope of the research questions, explore a multitude of facets of the topic at hand, there are still potential blind spots that both the literature and the empirical study might have failed to address. The risk of this having obtained obsolete information is deemed to be low, as the participants in the empirical research are active participants and stakeholders in the ecosystem of interest. Whilst the exploratory design has enabled this project to formulate a better understanding of the issues at hand, the results cannot be assumed to be conclusive. Whilst the results can be effective in informing subsequent research into the exposed issues, the strength of the conclusions of this single study is limited and should be explored in depth in order to facilitate effective decision-making.

An additional limitation resulting from research-design is that expert interviews do not allow for the direct examination of behavior or assessment of psychological states of patients. The results do thus not allow for direct conclusions to be drawn with respect to the effect of the attitude-behavior gap, or the role played by construal levels in human behavior in regard to personalized medicine. Such issues should be addressed in follow up research using appropriate behavioral research methods. Nevertheless, the chosen methodology has been able to expose how aspects of the issue at hand could be better understood through behavioral research with a focus on the influence of attitudes and construal levels in health directed behavior.

Another limiting factor is the relatively low number of participants in the expert interviews, considering the diversity of the included stakeholder groups. This is caused by a lower-than-

expected willingness to participate amongst the approached parties. Representation for some stakeholder groups is limited to a single participant. A major mitigating factor in this is that in all such cases, those participants were representatives for (professional) associations or other institutions tasked with representing the views and interests of the broader stakeholder group. This strengthens the credibility of their contributions. Some bias might have been introduced as such organizations proved much more willing to participate than individuals, potentially due to particular interests or simply because of available resources. Speaking to individual genetic counselors proved very difficult, as they either did not have any availability or did not deem their expertise to be relevant.

Although genetic counselors have been included through their professional association, no individual patients that underwent genetic testing and genetic counseling have been included in the sample, as individual patients did not fit the sampling frame for the expert interview methodology. This might have resulted in blind spots with regards to information obtained regarding this group. Subsequent research should employ appropriate methods to explore their interests and experiences more specifically.

As discussed in section 3.1 on researcher reflexivity, another limiting factor is the fact that, due to the constraints of the project, the current research has been predominantly designed and executed by a single researcher. This potentially resulted in the assumptions and biases of this individual influencing the process and subsequently the results of this study. With regards to confirmability, it should be emphasized that a strategy to mitigate the influence of researcher subjectivity has been formulated a priori and executed rigorously throughout.

With regards to transferability, the scope of the project is limited to the innovation ecosystem in the Netherlands, which itself is situated in a larger European collaborative effort. Although this focus on a single ecosystem is advantageous with regards to specificity, it comes with the limitation of low generalizability of the results. Whilst some of the issues are representative of the broader situation in Europe, the results cannot be assumed to be applicable to developments outside of Europe. However, precisely the contrasts with the developments in the USA and China (for example) make it valuable to study the Dutch (and European) approach.

6. Conclusion

Currently a convergence of several key trends is enabling a *genomic revolution* in healthcare. This means transitioning from a system of reactive and generalized care to a system of *predictive*, *preventative*, *participatory*, and highly *personalized* medicine. This project set out to examine the transition to a genomics-integrated healthcare system in The Netherlands, focusing both on friction between eco-system participants and on human behavior. In this, the project merges perspectives from the Innovation Sciences and Human-Technology Interaction disciplines. The primary objectives of this research are twofold. First, this research aims to explore and identify the (value-) frictions that exist within or between the various stakeholders involved in the implementation of genomics-integrated healthcare, and to determine the obstacles these frictions pose to the coherent realization of a personalized healthcare system. Second, this research aims to examine the engagement and responses exhibited by patients and their relatives in relation to the process of genetic testing in healthcare. By characterizing these behaviors and their implications, the research aims to provide insights into how patient behavior can impact the integration of genomics into a highly personalized healthcare system. The objectives were pursued through semi-structured expert interviews involving a diverse set of active ecosystem stakeholders, ensuring that findings are grounded in the actual experiences and interactions of those involved in the transformation of the Dutch healthcare system. Participants generally cited a consistent set of issues, each providing their particular perspective, allowing for a rich and nuanced characterization of such frictions.

Results indicate a multitude of loci where value frictions occur between stakeholders in the ecosystem. Value friction occurs with regards to standards of evidence, data sharing, and balancing commercial, academic, and public health interests. Financial considerations, trust establishment, conceptions of privacy, and differing views on policy conservatism versus policy progressiveness further contribute to these frictions, complicating effective collaboration. An important locus of value-based friction concerns the essentiality of genomic data in realizing improved public health outcomes, and concerns with regards to the proportionality of the resources required in relation to the health outcomes realized. In addition, there are several loci of instrumental, operational, and regulatory friction, referred to as instrumental barriers, that hinder collaborative success in the ecosystem. These barriers are inadequate cooperation and infrastructure for data exchange, insufficient interoperability of activities, lack of a clear legal framework, and concerns regarding the healthcare workforce's

capacity to meet the demands of a genomics-integrated healthcare system. Friction is also present in the form of issues more explicitly ethical in nature. These ethical issues involve questions about trade-offs in resource distribution and equitable access, highlighting accessibility concerns for people from different socio-economic backgrounds. Other ethical challenges include the efficacy and efficiency of personalized care, inadequacies in traditional consent models, fairness in treatment quality and benefit distribution, fears of societal impact from increased medicalization, and concerns about potential genetic discrimination.

Healthcare professionals identified several relevant aspects of human behavior in relation to personalized healthcare. While personal benefit and solidarity motives encourage genetic data sharing, privacy concerns remain. Positive attitudes towards data sharing are common, but genetic information and availability of health-directed behaviors do not strongly drive lifestyle changes or follow-up actions. Engagement with health-directed behaviors depends on individual priorities and socio-economic factors. Additionally, low genetic literacy may limit engagement with personalized care and participation in societal debates about its implications. Not all patients are open to genetic testing, some people prioritize philosophical or religious beliefs over potential benefits. Genetic testing can prompt concerns about the future, including fears of reduced opportunities, though health risks to oneself and relatives are primary concerns. Patients may experience feelings of worry, responsibility, or guilt about passing on conditions to their children. Regardless of the results, receiving them can provide comfort by resolving uncertainty, though it might also inspire unhealthy behaviors. Initial information seeking is focused on treatment options or ways to mitigate detected conditions.

This study demonstrates the challenges that exist between the desire to capitalize on personalized medicine on the one side, and the responsibility of maintaining a strong and accessible public healthcare system on the other. Whilst individual stakeholders are working hard to contribute to a personalized medicine transition, there is currently insufficient alignment between ecosystem participants. Regulatory reform, increased investment in standardization and infrastructure for information exchange, and frameworks for accountability and commitment in collaboration can be employed to address regulatory, instrumental, and operational friction. The results also suggest that, while personalized medicine shows promise in targeted applications, broad and untargeted screening requires careful consideration. The value-based frictions and ethical challenges that surround this issue are much harder to address, and will require debate, compromise, and collaboration between stakeholders, including the public, to be resolved. The complex link between information provision, intent, behavior, and

socio-economic factors means that it is imperative to reflect critically on how genomics can be integrated into healthcare to provide tangible benefits for all patients.

The current research has taken an exploratory approach to examining and mapping the issues at hand. Whilst care has been taken to obtain a representative overview of the issues surrounding the transition in the Netherlands, the results are not exhaustive. Whilst this broad overview of friction in the ecosystem is a useful starting point, additional research is needed to provide a deeper characterization. Future research should explore new governance frameworks and modes of cooperation, which integrate the concepts of stewardship and responsibility, to facilitate collaboration and information exchange between stakeholders in the ecosystem. Furthermore, future research should focus on understanding in detail what ecosystem stakeholders and participants require from specific preconditions.

Although the method of expert interviews has been useful in exploring relevant issues with regards to human behavior, more appropriate research methods are needed to characterize such issues and their underlying factors in greater detail. Future research should use behavioral research methods to understand the value-action gap in health-directed behaviors, and the influence of attitudes and construal levels, considering social and economic determinants. It is crucial to explore how different types of information in personalized care are perceived and processed by individuals to empower them to engage in health-directed behaviors. Ethics studies, combined with behavioral research, might be of value in assessing how counseling resources can be employed to enable informed and autonomous decision-making with regards to consent, and ensure fair representation in the public debate.

The innovation ecosystem experiences significant value-based, instrumental, operational, and regulatory friction, as well as significant ethical issues, that form barriers to synergistic value creation. More important, however, is that genetic data from whole-genome sequencing in a genomics-integrated healthcare system is not expected by experts to be a strong driver of behavioral change, nor is a focus on genetics deemed to be the most appropriate means to the end of improving public health. While it is clear that personalized medicine has the potential to be of immense value to healthcare, it is recommended to critically examine in which instances and contexts personalized medicine can be most efficiently and effectively applied to create greater societal benefit than possible through traditional means. To achieve a meaningful and equitable impact, a comprehensive, multidisciplinary approach is essential for integrating personalized medicine into the broader healthcare system.

References

Abbing, H. R. (2009). Humane biotechnologie en recht, preadviezen van de Nederlandse Juristen Vereniging. *Tijdschrift voor Gezondheidsrecht, 33*, 531-537. https://doi.org/10.1007/BF03081656

Adams, W. C. (2015). Conducting semi-structured interviews. *Handbook of practical program evaluation*, 492-505. https://doi.org/10.1002/9781119171386.ch19

Andorno, R. (2004). The right not to know: an autonomy based approach. *Journal of medical ethics, 30*(5), 435-439. https://doi.org/ 10.1136/jme.2002.001578

Andrejevic, M. (2014). The big data divide. *International Journal of Communication, 8*(1), 1673–1689.

Anney, V. N. (2014). Ensuring the quality of the findings of qualitative research: Looking at trustworthiness criteria. *Journal of Emerging Trends in Educational Research and Policy Studies, 5*(2), 272-281.

Appelbaum, P. S., Parens, E., Waldman, C. R., Klitzman, R., Fyer, A., Martinez, J., W. N. Price & Chung, W. K. (2014). Models of consent to return of incidental findings in genomic research. *Hastings Center Report, 44*(4), 22-32. https://doi.org/10.1002/hast.328

Arts, J. W., Frambach, R. T., & Bijmolt, T. H. (2011). Generalizations on consumer innovation adoption: A meta-analysis on drivers of intention and behavior. *International Journal of Research in Marketing, 28(*2), 134-144. https://doi.org/10.1016/j.ijresmar.2010.11.002

Athens, B. A., Caldwell, S. L., Umstead, K. L., Connors, P. D., Brenna, E., & Biesecker, B. B. (2017). A systematic review of randomized controlled trials to assess outcomes of genetic counseling. *Journal of Genetic Counseling, 26*(5), 902-933. https://doi.org/10.1007/s10897-017-0082-y

Bar-Anan, Y., Liberman, N., & Trope, Y. (2006). The association between psychological distance and construal level: Evidence from an implicit association test. Journal of Experimental Psychology: General, 135(4), 609–622. https://doi.org/10.1037/0096-3445.135.4.609

Bauer, D. C., Gaff, C., Dinger, M. E., Caramins, M., Buske, F. A., Fenech, M., ... & Cobiac, L. (2014). Genomics and personalised whole-of-life healthcare. *Trends in molecular medicine, 20(*9), 479-486. https://doi.org/10.1016/j.molmed.2014.04.001

Belliger, A., Krieger, D.J. (2018). The Digital Transformation of Healthcare. In: North, K., Maier, R., Haas, O. (eds) *Knowledge Management in Digital Change. Progress in IS* (pp. 311-326). Springer, Cham. https://doi.org/10.1007/978-3-319-73546-7_19

Berg, J. S., Khoury, M. J., & Evans, J. P. (2011). Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. *Genetics in medicine, 13(*6), 499-504. https://doi.org/10.1097/GIM.0b013e318220aaba

Berger, M. F., & Mardis, E. R. (2018). The emerging clinical relevance of genomics in cancer medicine. Nature reviews. *Clinical oncology, 15*(6), 353–365. https://doi.org/10.1038/s41571-018-0002-6

Biesecker, L. G., Burke, W., Kohane, I., Plon, S. E., & Zimmern, R. (2012). Next-generation sequencing in the clinic: are we ready?. *Nature Reviews Genetics, 13*(11), 818-824. https://doi.org/10.1038/nrg3357

Blumenthal, D., Campbell, E. G., Anderson, M. S., Causino, N., & Louis, K. S. (1997). Withholding research results in academic life science: evidence from a national survey of faculty. *Jama, 277*(15), 1224-1228. https://doi.org/10.1001/jama.1997.03540390054035

Bogaert, P., & Van Oyen, H. (2017). An integrated and sustainable EU health information system: national public health institutes' needs and possible benefits. *Archives of Public Health, 75*(1), 1-5. https://doi.org/10.1186/s13690-016-0171-7

Boulstridge, E., & Carrigan, M. (2000). Do consumers really care about corporate responsibility? Highlighting the attitude—behaviour gap. *Journal of Communication Management, 4*(4), 355–368. https://doi.org/10.1108/eb023532

Boyd, D., & Crawford, K. (2012). Critical questions for big data: Provocations for a cultural, technological, and scholarly phenomenon. *Information, communication & society, 15*(5), 662-679. https://doi.org/10.1080/1369118X.2012.678878

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology, 3*(2), 77-101. https://doi.org/10.1191/1478088706qp063oa

Brett, G. R., Metcalfe, S. A., Amor, D. J., & Halliday, J. L. (2012). An exploration of genetic health professionals' experience with direct-to-consumer genetic testing in their clinical practice. *European Journal of Human Genetics, 20*(8), 825-830. https://doi.org/10.1038/ejhg.2012.13

Brinkmann, S., & Kvale, S. (2015). *Interviews: Learning the craft of qualitative research interviewing* (3rd ed.). Thousand Oaks, CA: Sage. https://doi.org/10.1002/nha3.20251

Brinkmann, S., & Kvale, S. (2018). *Doing interviews.* SAGE Publications Ltd, https://doi.org/10.4135/9781529716665

Brittain, H. K., Scott, R., & Thomas, E. (2017). The rise of the genome and personalized medicine. *Clinical medicine, 17*(6), 545–551. https://doi.org/10.7861/clinmedicine.17-6-545

Bunnik, E. M., de Jong, A., Nijsingh, N., & de Wert, G. M. (2013). The new genetics and informed consent: differentiating choice to preserve autonomy. *Bioethics, 27*(6), 348-355. https://doi.org/10.1111/bioe.12030

Bunnik, E. M., Schermer, M. H., & Janssens, A. C. J. (2011). Personal genome testing: test characteristics to clarify the discourse on ethical, legal and societal issues. *BMC medical ethics, 12*, 1-13. https://doi.org/10.1186/1472-6939-12-11

Büschel, I., Mehdi, R., Cammilleri, A., Marzouki, Y., & Elger, B. (2014). Protecting human health and security in digital Europe: how to deal with the "privacy paradox"?. *Science and engineering ethics, 20*(3), 639-658. https://doi.org/10.1007/s11948-013-9511-y

Castillo-Montoya, M. (2016). Preparing for interview research: The interview protocol refinement framework. *Qualitative report, 21*(5), 811-831. https://doi.org/10.46743/2160-3715/2016.2337

Caulfield, T., Burningham, S., Joly, Y., Master, Z., Shabani, M., Borry, P., Becker, A., Burgess, M., Calder, K., Critchley, C., Edwards, K., Fullerton, S. M., Gottweis, H., Hyde-Lay, R., Illes, J., Isasi, R., Kato, K., Kaye, J., Knoppers, B., Lynch, J., … Zawati, M. H. (2014). A review of the key issues associated with the commercialization of biobanks. *Journal of law and the biosciences, 1*(1), 94–110. https://doi.org/10.1093/jlb/lst004

Chesbrough, H. (2003). The logic of open innovation: managing intellectual property. *California management review, 45*(3), 33-58. https://doi.org/10.1177/0008125603045003

Cho, M. K., Illangasekare, S., Weaver, M. A., Leonard, D. G., & Merz, J. F. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *The Journal of molecular diagnostics, 5*(1), 3-8. https://doi.org/10.1016/S1525-1578(10)60444-8

Chrystoja, C. C., & Diamandis, E. P. (2013). Whole Genome Sequencing as a Diagnostic Test: Challenges and Opportunities. *Clinical Chemistry, 60*(5), 724–733. https://doi.org/10.1373/clinchem.2013.209213

Chute, C. G., & Kohane, I. S. (2013). Genomic Medicine, Health Information Technology, and Patient Care. *JAMA, 309*(14), 1467. https://doi.org/10.1001/jama.2013.1414

Clarke, A. E. (2014a). Biomedicalization. In Clarke, A. E., Mamo, L., Fosket, J. R., Fishman, J. R., Shim, J. K. (Eds.), *The Wiley Blackwell Encyclopedia of Health, Illness, Behavior, and Society* (pp. 137–142). Wiley. https://doi.org/10.1002/9781118410868.wbehibs083

Clarke, A. E., Shim, J. K., Mamo, L., Fosket, J. R., & Fishman, J. R. (2003). Biomedicalization: Technoscientific transformations of health, illness, and US biomedicine. *American Sociological Review, 68*, 161-194. https://doi.org/10.2307/1519765

Clarke, A. J. (2014b). Managing the ethical challenges of next-generation sequencing in genomic medicine. *British Medical Bulletin, 111*(1), 17-30. https://doi.org/10.1093/bmb/ldu017

Clift, K. E., Halverson, C. M., Fiksdal, A. S., Kumbamu, A., Sharp, R. R., & McCormick, J. B. (2015). Patients' views on incidental findings from clinical exome sequencing. *Applied & Translational Genomics, 4*, 38-43. https://doi.org/10.1016/j.atg.2015.02.005

Conroy, M. C., Lacey, B., Bešević, J., Omiyale, W., Feng, Q., Effingham, M., Sellers, J., Sheard, S., Pancholi, M., Gregory, G., Busby, J., Collins, R., & Allen, N. E. (2023). UK Biobank: a globally important resource for cancer research. *British Journal of Cancer, 128*(4), 519–527. https://doi.org/10.1038/s41416-022-02053-5

Cumming, D., Hervé, F., Manthé, E., & Schwienbacher, A. (2022). Testing-the-waters policy with hypothetical investment: Evidence from equity crowdfunding. *Entrepreneurship Theory and Practice, 46*(4), 1019-1053. https://doi.org/10.1177/1042258720932522

Demir, E., & Stamhuis, E. (2023). Patenting human biological materials and data: balancing the reward of innovation with the ordre public and morality exception. *Journal of Intellectual Property Law and Practice, 8*(7), 546–553. https://doi.org/10.1093/jiplp/jpad052

Dove, E. S., Chico, V., Fay, M., Laurie, G., Lucassen, A. M., & Postan, E. (2019). Familial genetic risks: how can we better navigate patient confidentiality and appropriate risk disclosure to relatives?. *Journal of Medical Ethics, 45*(8), 504-507. https://doi.org/10.1136/medethics-2018-105229

Elias, S., & Annas, G. J. (1994). Generic Consent for Genetic Screening. *New England Journal of Medicine, 330*(22), 1611–1613. https://doi.org/10.1056/nejm199406023302213

Elliott, R., Fischer, C. T., & Rennie, D. L. (1999). Evolving guidelines for publication of qualitative research studies in psychology and related fields. *British Journal of Clinical Psychology, 38(*3), 215–229. https://doi.org/10.1348/014466599162782

Evangelatos, N., Satyamoorthy, K., & Brand, A. (2018). Personalized health in a public health perspective. *International journal of public health, 63*(4), 433-434. https://doi.org/10.1007/s00038-017-1055-5

Evans, J. P., & Khoury, M. J. (2013). The arrival of genomic medicine to the clinic is only the beginning of the journey. *Genetics in Medicine, 15*(4), 268-269. https://doi.org/10.1038/gim.2012.133

Farjam, M., Nikolaychuk, O., & Bravo, G. (2019). Experimental evidence of an environmental attitude-behavior gap in high-cost situations. *Ecological Economics, 166*, 106434. https://doi.org/10.1016/j.ecolecon.2019.106434

Feero, W. G. (2020). Bioinformatics, Sequencing Accuracy, and the Credibility of Clinical Genomics. *JAMA, 324*(19), 1945–1947. https://doi.org/10.1001/jama.2020.19939

Firth, L., & Mellor, D. (1999). The impact of regulation on innovation. *European Journal of Law and economics, 8*(3), 199-205. https://doi.org/10.1023/A:1008743308935

Flores, M., Glusman, G., Brogaard, K., Price, N. D., & Hood, L. (2013). P4 Medicine: How Systems Medicine Will Transform the Healthcare Sector and Society. *Personalized Medicine, 10*(6), 565–576. https://doi.org/10.2217/pme.13.57

Flynn, R., Bellaby, P., & Ricci, M. (2009). The 'value-action gap'in public attitudes towards sustainable energy: the case of hydrogen energy. *The Sociological Review, 57*(2_suppl), 159-180. https://doi.org/10.1111/j.1467-954X.2010.0189

Gaff, C. L., M. Winship, I., M. Forrest, S., P. Hansen, D., Clark, J., M. Waring, P., South, M., & H. Sinclair, A. (2017). Preparing for genomic medicine: A real world demonstration of health system change. *NPJ Genomic Medicine, 2*(1). https://doi.org/10.1038/s41525-017-0017-4

Gambardella, A. (2023). Private and social functions of patents: Innovation, markets, and new firms. *Research Policy, 52*(7), 104806. https://doi.org/10.1016/j.respol.2023.104806

Garrett, J. R., Lantos, J. D., Biesecker, L. G., Childerhose, J. E., Chung, W. K., Holm, I. A., Koenig, B.A., McEwen, J. E., Wilfond, B. S. & Brothers, K. (2019). Rethinking the "open future" argument against predictive genetic testing of children. *Genetics in Medicine, 21*(10), 2190-2198. https://doi.org/10.1038/s41436-019-0483-4

Geanta, M., Boata, A., Brand, A., Cioroboiu, C., Cucos, B. (2022). Personalized Medicine Literacy. In Hasanzad, M. (eds) *Precision Medicine in Clinical Practice*. Springer, Singapore. https://doi.org/10.1007/978-981-19-5082-7_12

Gerber, N., Gerber, P., & Volkamer, M. (2018). Explaining the privacy paradox: A systematic review of literature investigating privacy attitude and behavior. *Computers & security, 77*, 226-261. https://doi.org/10.1016/j.cose.2018.04.002

Ginsburg, G. (2014). Medical genomics: Gather and use genetic data in health care. *Nature, 508*(7497), 451-453. https://doi.org/10.1038/508451a

Ginsburg, G. S. (2013). Realizing the opportunities of genomics in health care. *Jama, 309*(14), 1463-1464. https://doi.org/10.1001/jama.2013.1465

Golubnitschaja, O., Kinkorova, J., & Costigliola, V. (2014). Predictive, preventive and personalised medicine as the hardcore of 'Horizon 2020': EPMA position paper. *EPMA Journal, 5*(1), 1-29. https://doi.org/10.1186/1878-5085-5-6

Goodwin, S., McPherson, J. D., & McCombie, W. R. (2016). *Coming of age: ten years of next-generation sequencing technologies. Nature Reviews Genetics, 17*(6), 333–351. https://doi.org/10.1038/nrg.2016.49

Granstrand, O., & Holgersson, M. (2020). Innovation ecosystems: A conceptual review and a new definition. *Technovation, 90*, 102098. https://doi.org/10.1016/j.technovation.2019.102098

Greely, H. T. (2019). CRISPR'd babies: human germline genome editing in the 'He Jiankui affair'*. *Journal of Law and the Biosciences, 6*(1), 111–183. https://doi.org/10.1093/jlb/lsz010/

Gupta, S., & Ogden, D. (2006). The attitude-behavior gap in environmental consumerism. *APUBEF Proceedings, 3*(1), 199-206.

Gymrek, M., McGuire, A. L., Golan, D., Halperin, E., & Erlich, Y. (2013). Identifying personal genomes by surname inference. *Science, 339*(6117), 321-324. https://doi.org/10.1126/science.1229566

Haga, S. B., Barry, W. T., Mills, R., Ginsburg, G. S., Svetkey, L., Sullivan, J., & Willard, H. F. (2013). Public knowledge of and attitudes toward genetics and genetic testing. *Genetic testing and molecular biomarkers, 17*(4), 327-335. https://doi.org/10.1089/gtmb.2012.0350

Hamilton, A. B., Oishi, S., Yano, E. M., Gammage, C. E., Marshall, N. J., & Scheuner, M. T. (2014). Factors influencing organizational adoption and implementation of clinical genetic services. *Genetics in Medicine, 16*(3), 238-245. https://doi.org/10.1038/gim.2013.101

Hansson, M. G. (2010). Taking the patient's side: the ethics of pharmacogenetics. *Personalized Medicine, 7*(1), 75-85. https://doi.org/10.2217/pme.09.47

Hassan, L. M., Shiu, E., & Shaw, D. (2016). Who says there is an intention–behaviour gap? Assessing the empirical evidence of an intention–behaviour gap in ethical consumption. *Journal of Business Ethics, 136*(2), 219-236. https://doi.org/10.1007/s10551-014-2440-0

Hassan, M., Awan, F. M., Naz, A., deAndrés-Galiana, E. J., Alvarez, O., Cernea, A., ... & Kloczkowski, A. (2022). Innovations in Genomics and Big Data Analytics for Personalized Medicine and Health Care: A Review. *International Journal of Molecular Sciences, 23*(9), 4645. https://doi.org/10.3390/ijms23094645

Hayden, E. C. (2013). Geneticists push for global data-sharing: international organization aims to promote exchange and linking of DNA sequences and clinical information. *Nature, 498(*7452), 16-18. https://doi.org/10.1038/498017a

Heller, M. A., & Eisenberg, R. S. (1998). Can patents deter innovation? The anticommons in biomedical research. *Science, 280*(5364), 698-701. https://doi.org/10.1126/science.280.5364.698

Hodgson, J., & Gaff, C. (2013). Enhancing family communication about genetics: ethical and professional dilemmas. *Journal of genetic counseling, 22(1),* 16-21. https://doi.org/10.1007/s10897-012-9514-x

Hogarth, S., Javitt, G., & Melzer, D. (2008). The current landscape for direct-to-consumer genetic testing: legal, ethical, and policy issues. *Annual Review of Genomics and Human Genetics, 9*, 161-182. https://doi.org/10.1146/annurev.genom.9.081307.164319

Horgan, D., Lawler, M., & Brand, A. (2015). Getting Personal. *Public Health Genomics, 18*(6), 325-328. https://doi.org/10.1159/000441554

Horgan, D., Romao, M., & Hastings, R. (2017). Pulling the strands together: MEGA steps to drive European genomics and personalised medicine. *Biomedicine hub, 2*(Suppl. 1), 1-11. https://doi.org/10.1159/000481300

Huxley, A. (1932). *Brave New World.* New York: Harper Brothers.

Jakka, S., & Rossbach, M. (2013). An economic perspective on personalized medicine. *The HUGO Journal, 7*(1), 1. doi:10.1186/1877-6566-7-1

Jimenez-Sanchez, G. (2015). Genomics innovation: transforming healthcare, business, and the global economy. *Genome, 58*(12), 511–517. doi:10.1139/gen-2015-0121

Jinek, M., Chylinski, K., Fonfara, I., Hauer, M., Doudna, J. A., & Charpentier, E. (2012). A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science, 337*(6096), 816–821. https://doi.org/10.1126/science.1225829

Josephs, K. S., Berner, A., George, A., Scott, R. H., Firth, H. V., & Tatton-Brown, K. (2019). Genomics: the power, potential and pitfalls of the new technologies and how they are transforming healthcare. *Clinical Medicine, 19*(4), 269. https://doi.org/10.7861/clinmedicine.19-4-269

Juengst, E. T., Settersten, R. A., Fishman, J. R., & McGowan, M. L. (2012). After the revolution? Ethical and social challenges in "personalized genomic medicine." *Personalized Medicine, 9(*4), 429–439. https://doi.org/10.2217/pme.12.37

Kaiser, F. G., Oerke, B., & Bogner, F. X. (2007). Behavior-based environmental attitude: Development of an instrument for adolescents. *Journal of Environmental Psychology*, *27*(3), 242–251. https://doi.org/10.1016/j.jenvp.2007.06.004

Kaye, J., Heeney, C., Hawkins, N., De Vries, J., & Boddington, P. (2009). Data sharing in genomics—re-shaping scientific practice. *Nature Reviews Genetics, 10*(5), 331-335. https://doi.org/10.1038/nrg2573

Kennedy, H., Poell, T., & van Dijck, J. (2015). Data and agency. *Big Data & Society, 2*(2). https://doi.org/10.1177/2053951715621569

Keren, G., & Roelofsma, P. (1995). Immediacy and certainty in intertemporal choice. Organizational Behavior and Human Decision Processes, 63(3), 287–297. https://doi.org/10.1006/obhd.1995.1080

Kesselheim, A. S., Cook-Deegan, R. M., Winickoff, D. E., & Mello, M. M. (2013). Gene patenting—the Supreme Court finally speaks. *The New England journal of medicine, 369*(9), 869-875. https://doi.org/10.1056/NEJMhle1308199

Kessler, S. (1997). Psychological aspects of genetic counseling. IX. Teaching and counseling. *Journal of Genetic Counseling, 6*, 287-295. https://doi.org/10.1023/A:1025676205440

Kierkegaard, P. (2011). Electronic health record: Wiring Europe's Healthcare. *Computer Law & Security Review, 27(*5), 503–515. https://doi.org/10.1016/j.clsr.2011.07.013

Koboldt, D. C., Steinberg, K. M., Larson, D. E., Wilson, R. K., & Mardis, E. R. (2013). The Next-Generation Sequencing Revolution and Its Impact on Genomics. *Cell, 155*(1), 27–38. https://doi.org/10.1016/j.cell.2013.09.006

Kokolakis, S. (2017). Privacy attitudes and privacy behaviour: A review of current research on the privacy paradox phenomenon. *Computers & security, 64*, 122-134. https://doi.org/10.1016/j.cose.2015.07.002

Lander, E. S., Baylis, F., Zhang, F., Charpentier, E., Berg, P., Bourgain, C., Friedrich, B., Joung, J. K., Li, J., Liu, D., Naldini, L., Nie, J.-B., Qiu, R., Schoene-Seifert, B., Shao, F., Terry, S., Wei, W., & Winnacker, E.-L. (2019). Adopt a moratorium on heritable genome editing. *Nature, 567*(7747), 165–168. https://doi.org/10.1038/d41586-019-00726-5

Lesko, L. J. (2007). Personalized medicine: elusive dream or imminent reality?. *Clinical Pharmacology & Therapeutics, 81*(6), 807-816. https://doi.org/10.1038/sj.clpt.6100204

Lezaun, J. (2010). Bioethics and the risk regulation of 'frontier research': the case of gene therapy. In Hutter, B. (Ed.). *Anticipating Risks and Organising Risk Regulation* (pp. 208–230). Cambridge University Press. https://doi.org/10.1017/cbo9780511761553.011

Liao, W.-L., & Tsai, F.-J. (2013). *Personalized medicine: A paradigm shift in healthcare. BioMedicine,* 3(2), 66–72. https://doi.org/10.1016/j.biomed.2012.12.005

Liberman, N., & Trope, Y. (1998). The role of feasibility and desirability considerations in near and distant future decisions: A test of temporal construal theory. *Journal of Personality and Social Psychology, 75*(1), 5–18. https://doi.org/10.1037/0022-3514.75.1.5

Liberman, N., Trope, Y., McCrea, S. M., & Sherman, S. J. (2007). The effect of level of construal on the temporal distance of activity enactment. *Journal of Experimental Social Psychology, 43*(1), 143–149. https://doi.org/10.1016/j.jesp.2005.12.009

Lock, M. (1993). Cultivating the Body: Anthropology and Epistemologies of Bodily Practice and Knowledge. *Annual Review of Anthropology, 22*(1), pp. 133–155). https://doi.org/10.1146/annurev.an.22.100193.001025

Lohn, Z., Adam, S., Birch, P. H., & Friedman, J. M. (2014). Incidental findings from clinical genome-wide sequencing: a review. *Journal of Genetic Counseling, 23,* 463-473. https://doi.org/10.1007/s10897-013-9604-4

Lwoff, L. (2009). Council of Europe adopts protocol on genetic testing for health purposes. *European Journal of Human Genetics, 17*(11), 1374-1377. https://doi.org/10.1038/ejhg.2009.84

Madlensky, L., Trepanier, A. M., Cragun, D., Lerner, B., Shannon, K. M., & Zierhut, H. (2017). A rapid systematic review of outcomes studies in genetic counseling. *Journal of genetic counseling, 26*(3), 361-378. https://doi.org/10.1007/s10897-017-0067-x

Magaldi, D., & Berler, M. (2020). Semi-structured interviews. *Encyclopedia of personality and individual differences*, 4825-4830. https://doi.org/10.1007/978-3-319-24612-3_857

Manolio, T. A., Abramowicz, M., Al-Mulla, F., Anderson, W., Balling, R., Berger, A. C., Bleyl, S., Chakravarti, A., Chantratita, W., Chisholm, R. L., Dissanayake, V. H., Dunn, M., Dzau, V. J., Han, B. G., Hubbard, T., Kolbe, A., Korf, B., Kubo, M., Lasko, P., Leego, E., … Ginsburg, G. S. (2015). Global implementation of genomic medicine: We are not alone. *Science translational medicine, 7(*290), 290ps13. https://doi.org/10.1126/scitranslmed.aab0194

Manolio, T. A., Chisholm, R. L., Ozenberger, B., Roden, D. M., Williams, M. S., Wilson, R., ... & Ginsburg, G. S. (2013). Implementing genomic medicine in the clinic: the future is here. *Genetics in Medicine, 15*(4), 258-267. https://doi.org/10.1038/gim.2012.157

Manyika, J., Chui, M., Bughin, J., Dobbs, R., Bisson, P., & Marrs, A. (2013). *Disruptive technologies: Advances that will transform life, business, and the global economy* (Vol. 180, pp. 17-21). San Francisco, CA: McKinsey Global Institute.

Mårtensson, E. (2017). Construal level theory and moral judgments: How thinking abstractly modifies morality. *Journal of European Psychology Students, 8*(1), 30-40. https://doi.org/10.5334/jeps.413

Mascalzoni, D., Melotti, R., Pattaro, C., Pramstaller, P. P., Gögele, M., De Grandi, A., & Biasiotto, R. (2022). Ten years of dynamic consent in the CHRIS study: informed consent as a dynamic process. *European Journal of Human Genetics, 30*(12), 1391-1397. https://doi.org/10.1038/s41431-022-01160-4

Matthijs, G., Souche, E., Alders, M., Corveleyn, A., Eck, S., Feenstra, I., Race, V., Sistermans, E., Sturm, M., Weiss, M., Yntema, H., Bakker, E., Scheffer, H. & Bauer, P. (2016). Guidelines for diagnostic next-generation sequencing. *European Journal of Human Genetics, 24*(1), 2-5. https://doi.org/10.1038/ejhg.2015.226

Mayer-Schönberger, V. & Cukier, K. (2013). *Big Data: A Revolution That Will Transform How We Live, Work, and Think*. Boston: Houghton Mifflin Harcourt.

McGinnis, J. M. (2009). Evidence-based medicine. *Information Knowledge Systems Management, 8*(1-4), 145-157. https://doi.org/10.3233/IKS-2009-0156

Metzl, J. F., & Martin, E. (2019). *Hacking Darwin: Genetic engineering and the future of humanity.* Naperville, IL: Sourcebooks.

Middleton, A., Mendes, Á., Benjamin, C. M., & Howard, H. C. (2017). Direct-to-consumer genetic testing: where and how does genetic counseling fit?. *Personalized medicine, 14*(3), 249-257. https://doi.org/10.2217/pme-2017-0001

Murdoch, C. J., & Caulfield, T. (2009). Commercialization, patenting, and genomics: researcher perspectives. *Genome Medicine, 1*, 1-5. https://doi.org/10.1186/gm22

Nafus D, Neff G (2016). Self-Tracking. Cambridge, MA: MIT Press. https://doi.org/10.7551/mitpress/10421.001.0001

Najafzadeh, M., Lynd, L. D., Davis, J. C., Bryan, S., Anis, A., Marra, M., & Marra, C. A. (2012). Barriers to integrating personalized medicine into clinical practice: a best–worst scaling choice experiment. *Genetics in medicine, 14*(5), 520-526. https://doi.org/10.1038/gim.2011.26

Niccol, A. (Director). (1997). *Gattaca* [Film]. Columbia Pictures, Jersey Films.

Nussbaum, S., Trope, Y., & Liberman, N. (2003). Creeping dispositionism: The temporal dynamics of behavior prediction. *Journal of Personality and Social Psychology, 84*(3), 485–497. https://doi.org/10.1037/0022-3514.84.3.485

Ormond, K. E., & Cho, M. K. (2014). Translating personalized medicine using new genetic technologies in clinical practice: the ethical issues. *Personalized medicine, 11*(2), 211-222. https://doi.org/10.2217/pme.13.104

Ormond, K. E., Wheeler, M. T., Hudgins, L., Klein, T. E., Butte, A. J., Altman, R. B., Ashley, E. A. & Greely, H. T. (2010). Challenges in the clinical application of whole-genome sequencing. *The Lancet, 375*(9727), 1749-1751. https://doi.org/10.1016/S0140-6736(10)60599-5

Paradise, J., Andrews, L., & Holbrook, T. (2005). Patents on human genes: an analysis of scope and claims. *Science, 307*(5715), 1566-1567. https://doi.org/10.1126/science.1105162

Perez, C. (2004). Technological revolutions, paradigm shifts and socio-institutional change. Reinert, E. S. (Ed.) *Globalization, economic development and inequality: An alternative perspective* (pp. 217-242). Edward Elgar Publishing. https://doi.org/10.4337/9781845421625

Peters, E., Västfjäll, D., Slovic, P., Mertz, C. K., Mazzocco, K., & Dickert, S. (2006). Numeracy and decision making. *Psychological Science, 17*(5), 407-413. https://doi.org/10.1111/j.1467-9280.2006.01720.x

Pingo, Z., & Narayan, B. (2019). "My smartwatch told me to see a sleep doctor": A study of activity tracker use. *Online Information Review, 44*(2), 503-519.

Prelec, D., & Loewenstein, G. (1991). Decision making over time and under uncertainty: A common approach. *Management science, 37*(7), 770-786. https://doi.org/10.1287/mnsc.37.7.770

Rachlin, H., Raineri, A., & Cross, D. (1991). Subjective probability and delay. *Journal of the experimental analysis of behavior, 55*(2), 233-244. https://doi.org/10.1901/jeab.1991.55-233

Ramos E. (2020). Genetic Counseling, Personalized Medicine, and Precision Health. C*old Spring Harbor perspectives in medicine, 10*(9), a036699. https://doi.org/10.1101/cshperspect.a036699

Rego, S., Grove, M. E., Cho, M. K., & Ormond, K. E. (2020). Informed consent in the genomics era. *Cold Spring Harbor Perspectives in Medicine, 10*(8), a036582. https://doi.org/10.1101/cshperspect.a036582

Rhodes, R., & Holzman, I. R. (2014). Is the Best Interest Standard Good for Pediatrics? *Pediatrics, 134(*Issue Supplement_2), S121–S129. https://doi.org/10.1542/peds.2014-1394H

Rising, C. J., Gaysynsky, A., Blake, K. D., Jensen, R. E., & Oh, A. (2021). Willingness to Share Data From Wearable Health and Activity Trackers: Analysis of the 2019 Health Information National Trends Survey Data. *JMIR mHealth and uHealth*, *9*(12), e29190. https://doi.org/10.2196/29190

Ritala, P. & Thomas, L.D.W. (2023). *Innovation ecosystems.* In Eriksson P., Montonen, T., Laine, P-M., & Hannula A. (Eds.) *Elgar Encyclopedia of Innovation Management.* Edward Elgar. https://doi.org/10.4337/9781035306459

Roberts, J. A. F., & Pembrey, M. E. (1963). *An introduction to medical genetics*. London: Oxford University Press.

Roberts, R. E. (2020). Qualitative Interview Questions: Guidance for Novice Researchers. *Qualitative Report, 25*(9), 3185-3203. https://doi.org/10.46743/2160-3715/2020.4640

Rose, N. (2006). *The politics of life itself: Biomedicine, power and subjectivity in the twenty-first century*. Princeton, NJ: Princeton University Press.

Rosenfeld, J. A., & Mason, C. E. (2013). Pervasive sequence patents cover the entire human genome. *Genome medicine, 5*(3), 1-8. https://doi.org/10.1186/gm431

Ross, L. F., Saal, H. M., David, K. L., & Anderson, R. R. (2013). Technical report: ethical and policy issues in genetic testing and screening of children. *Genetics in medicine, 15*(3), 234-245. https://doi.org/10.1038/gim.2012.176

Ruckenstein, M., & Schüll, N. D. (2017). The datafication of health. *Annual review of anthropology, 46*, 261-278. https://doi.org/10.1146/annurev-anthro-102116-041244

Sagristano, M. D., Trope, Y., & Liberman, N. (2002). Time-dependent gambling: Odds now, money later. *Journal of Experimental Psychology: General, 131*(3), 364–376. https://doi.org/10.1037/0096-3445.131.3.364

Salari, P., & Larijani, B. (2017). Ethical issues surrounding personalized medicine: a literature review. *Acta Medica Iranica*, *55*(3), 209-217.

Sampat, B., & Williams, H. L. (2019). How do patents affect follow-on innovation? Evidence from the human genome. *American Economic Review, 109*(1), 203-236. https://doi.org/10.1257/aer.20151398

Schutte, P. (1999). Complemation: An alternative to automation. *Journal of Information Technology Impact, 1(*3), 113-118.

Seidman, I. (2013). *Interviewing as qualitative research: A guide for researchers in education & the social sciences* (4th ed.). New York: Teachers College Press.

Shashi, V., McConkie-Rosell, A., Rosell, B., Schoch, K., Vellore, K., McDonald, M., Jiang, Y.-H., Xie, P., Need, A., & Goldstein, D. B. (2014). The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. *Genetics in Medicine, 16*(2), 176-182. https://doi.org/10.1038/gim.2013.99

Sheeran, P. and Webb, T.L. (2016) The Intention–Behavior Gap. *Social and Personality Psychology Compass, 10*(9). pp. 503-518. https://doi.org/10.1111/spc3.12265

Simpson, J. L., Kuliev, A., & Rechitsky, S. (2019). Overview of preimplantation genetic diagnosis (PGD): historical perspective and future direction. *Prenatal Diagnosis,* 23-43. https://doi.org/10.1007/978-1-4939-8889-1_2

Skirton, H., Goldsmith, L., Jackson, L., & Tibben, A. (2013). Quality in genetic counselling for presymptomatic testing—clinical guidelines for practice across the range of genetic conditions. *European Journal of Human Genetics, 21*(3), 256-260. https://doi.org/10.1038/ejhg.2012.174

Smerecnik, C. M., Mesters, I., Verweij, E., de Vries, N. K., & de Vries, H. (2009). A systematic review of the impact of genetic counseling on risk perception accuracy. *Journal of genetic counseling, 18,* 217-228. https://doi.org/10.1007/s10897-008-9210-z

Snape, K., Wedderburn, S., & Barwell, J. (2019). The new genomic medicine service and implications for patients. *Clinical Medicine, 19*(4), 273-277. https://doi.org/10.7861/clinmedicine.19-4-273

So, D., Sladek, R., & Joly, Y. (2021). Assessing public opinions on the likelihood and permissibility of gene editing through construal level theory. *New Genetics and Society, 40(*4), 473-497. https://doi.org/10.1080/14636778.2020.1868985

Soderberg, C. K., Callahan, S. P., Kochersberger, A. O., Amit, E., & Ledgerwood, A. (2015). The effects of psychological distance on abstraction: Two meta-analyses. *Psychological bulletin, 141*(3), 525. https://doi.org/10.1037/bul0000005

Spence, A., Poortinga, W., & Pidgeon, N. (2012). The psychological distance of climate change. *Risk Analysis: An International Journal, 32*(6), 957-972. https://doi.org/10.1111/j.1539-6924.2011.01695.x

Steinbock, B. (2008). Designer babies: choosing our children's genes. *The Lancet, 372*(9646), 1294-1295. https://doi.org/10.1016/s0140-6736(08)61538-x

Stoeklé, H. C., Mamzer-Bruneel, M. F., Vogt, G., & Hervé, C. (2016). 23andMe: a new two-sided data-banking market model. *BMC medical ethics, 17,* 1-11. https://doi.org/10.1186/s12910-016-0101-9

Stoll, K., Kubendran, S., & Cohen, S. A. (2018). The past, present and future of service delivery in genetic counseling: Keeping up in the era of precision medicine. *American Journal of*

Medical Genetics Part C: Seminars in Medical Genetics, 178(1), 24–37. https://doi.org/10.1002/ajmg.c.31602

Swen, J. J., van der Wouden, C. H., Manson, L. E., Abdullah-Koolmees, H., Blagec, K., Blagus, T., Böhringer, S., Cambon-Thomsen, A., Cecchin, E., Cheung, K.-C., Deneer, V. H., Dupui, M., Ingelman-Sundberg, M., Jonsson, S., Joefield-Roka, C., Just, K. S., Karlsson, M. O., Konta, L., Koopmann, R., … Rajasingam, A. (2023). A 12-gene pharmacogenetic panel to prevent adverse drug reactions: an open-label, multicentre, controlled, cluster-randomised crossover implementation study. *The Lancet, 401*(10374), pp. 347–356). https://doi.org/10.1016/s0140-6736(22)01841-4

Syurina, E. V., Brankovic, I., Probst-Hensch, N., & Brand, A. (2011). Genome-based health literacy: a new challenge for public health genomics. *Public Health Genomics, 14*(4-5), 201-210. https://doi.org/10.1159/000324238

Todorov, A., Goren, A., & Trope, Y. (2007). Probability as a psychological distance: Construal and preferences. *Journal of Experimental Social Psychology, 43*(3), 473–482. https://doi.org/10.1016/j.jesp.2006.04.002

Trope, Y., & Liberman, N. (2003). Temporal construal. *Psychological review, 110*(3), 403. https://psycnet.apa.org/doi/10.1037/a0018963

Trope, Y., & Liberman, N. (2010). Construal-level theory of psychological distance. Psychological Review, 117(2), 440–463. https://doi.org/10.1037/a0018963

Trope, Y., Liberman, N., & Wakslak, C. (2007). Construal levels and psychological distance: Effects on representation, prediction, evaluation, and behavior. *Journal of consumer psychology, 17*(2), 83-95. https://doi.org/10.1016/S1057-7408(07)70013-X

Tversky, A., & Kahneman, D. (1974). Judgment under Uncertainty: Heuristics and Biases. *Science, 185*(4157), 1124–1131. https://doi.org/10.1126/science.185.4157.1124

Van Dijck, J., & Poell, T. (2016). Understanding the promises and premises of online health platforms. *Big Data & Society, 3*(1). https://doi.org/10.1177/2053951716654173

Varelius, J. (2006). The value of autonomy in medical ethics. *Medicine, Health Care and Philosophy, 9*, 377-388. https://doi.org/10.1007/s11019-006-9000-z

Verbeek, P.-P. (2008). Obstetric Ultrasound and the Technological Mediation of Morality: A Postphenomenological Analysis. *Human Studies, 31(*1), 11–26. https://doi.org/10.1007/s10746-007-9079-0

Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012). Five years of GWAS discovery. *The American Journal of Human Genetics, 90*(1), 7-24. https://doi.org/10.1016/j.ajhg.2011.11.029

Wakslak, C. J., Trope, Y., Liberman, N., & Alony, R. (2006). Seeing the forest when entry is unlikely: Probability and the mental representation of events. *Journal of Experimental Psychology: General, 135*(4), 641–653. https://doi.org/10.1037/0096-3445.135.4.641

Wang, C., Lei, L., & Wu, B. (2017). The attitude–behavior gap of ethical consumers: From the perspective of construal level. *Advances in Psychological Science, 25*(3), 511. https://doi.org/10.3724/SP.J.1042.2017.00511

Wang, S., Hurlstone, M. J., Leviston, Z., Walker, I., & Lawrence, C. (2019). Climate change from a distance: An analysis of construal level and psychological distance from climate change. *Frontiers in psychology, 10*, 230. https://doi.org/10.3389/fpsyg.2019.00230

Weber, E. U. (2016). What shapes perceptions of climate change? New research since 2010. *Wiley Interdisciplinary Reviews: Climate Change, 7*(1), 125-134. https://doi.org/10.1002/wcc.377

Weston, A. D., & Hood, L. (2004). Systems Biology, Proteomics, and the Future of Health Care: Toward Predictive, Preventative, and Personalized Medicine. *Journal of Proteome Research, 3(*2), 179–196. https://doi.org/10.1021/pr0499693

Wiertz, S., & Boldt, J. (2022). Evaluating models of consent in changing health research environments. *Medicine, Health Care and Philosophy, 25*(2), 269-280. https://doi.org/10.1007/s11019-022-10074-3

Williams, H. L. (2013). Intellectual property rights and innovation: Evidence from the human genome. *Journal of Political Economy, 121*(1), 1-27. https://doi.org/10.1086/669706

Winner, L. (1980). Do Artifacts Have Politics? *Daedalus, 109*(1), 121–136. https://www.jstor.org/stable/20024652

Yu, J. H., Jamal, S. M., Tabor, H. K., & Bamshad, M. J. (2013). Self-guided management of exome and whole-genome sequencing results: changing the results return model. *Genetics in Medicine, 15(*9), 684-690. https://doi.org/10.1038/gim.2013.35

Yudell, M., & DeSalle, R. (2002*). The Genomic Revolution: Unveiling the Unity of Life.* Washington, DC: Joseph Henry Press. https://doi.org/10.17226/10125

Yuen, J., Lee, S. Y., Courtney, E., Lim, J., Soh, H., Li, S. T., Chen, Y., McAllister, M., Fenwick, E. K., & Ngeow, J. (2020). Evaluating empowerment in genetic counseling using patient-reported outcomes. *Clinical genetics, 97*(2), 246–256. https://doi.org/10.1111/cge.13646

Žeželj, I. L., & Jokić, B. R. (2014). Replication of experiments evaluating impact of psychological distance on moral judgment (Eyal et al., 2008; Gong & Medin, 2012). *Social Psychology, 45*(3), 223–231. https://doi.org/10.1027/a000001

Zhu, M., Wu, C., Huang, S., Zheng, K., Young, S. D., Yan, X., & Yuan, Q. (2021). Privacy paradox in mHealth applications: An integrated elaboration likelihood model incorporating privacy calculus and privacy fatigue. *Telematics and Informatics, 61*, 101601. https://doi.org/10.1016/j.tele.2021.101601

Zimani, A. N., Peterlin, B., & Kovanda, A. (2021). Increasing genomic literacy through national genomic projects. *Frontiers in Genetics, 12*, 693253. https://doi.org/10.3389/fgene.2021.693253

Other references

Atlas.TI (2023). *Atlas.TI for Windows, version 23.2.3.27778* [software]. Atlas.TI. https://atlasti.com/atlas-ti-desktop

Cyranoski, D. (2020, January 03). *What CRISPR-baby prison sentences mean for research*. Nature. https://www.nature.com/articles/d41586-020-00001-y

Deming, D. (2021, February 19). *Balancing privacy with data sharing for the public good.* The New York Times. https://www.nytimes.com/2021/02/19/business/privacy-open-data-public.html

ESPON (2019). *eHealth – Future Digital Health in the EU*. ESPON. https://www.espon.eu/sites/default/files/attachments/Final%20report.%202019%2003%2025_final%20version_0.pdf

European Commission (2018, April 25). *Communication from the Commission to the European Parliament, The Council, The European Economic and Social Committee and The Committee of the Regions on enabling the digital transformation of heath and care in the Digital Single Market; empowering citizens and building a healthier society, COM(2018) 233*. European Commission. https://digital-strategy.ec.europa.eu/en/library/communication-enabling-digital-transformation-health-and-care-digital-single-market-empowering

European Commission. (2019, April 9). *'Towards access to at least 1 million genomes in the EU by 2022': 1 Year on. Shaping Europe's digital future.* European Commission. https://digital-strategy.ec.europa.eu/en/news/towards-access-least-1-million-genomes-eu-2022-1-year

European Commission. (2022, November 23). *European '1+ million genomes' initiative. Shaping Europe's digital future.* European Commission. https://digital-strategy.ec.europa.eu/en/policies/1-million-genomes

Fox, S. (2012). *Mobile Health. Pew Research Center's Internet and American Life Project 2012*. Pew. www.pewinternet.org/*/media//Files/Reports/2012/PIP_MobileHealth2012.pdf

Frist, B. (2021, January 20). *NIH director dr. Francis Collins: Connecting the dots from the human genome project to the COVID-19 vaccine*. Forbes. https://www.forbes.com/sites/billfrist/2021/01/20/nih-director-dr-francis-collins-connecting-the-dots-from-the-human-genome-project-to-the-covid-19-vaccine/

Helmore, A. (2023, December 5). *Genetic testing firm 23andMe admits hackers accessed DNA data of 7M users*. The Guardian. https://www.theguardian.com/technology/2023/dec/05/23andme-hack-data-breach

Nationaal Groeifonds. (2021). *Health-ri: Een Nationale gezondheidsdata-infrastructuur*. Nationaal Groeifonds. https://www.nationaalgroeifonds.nl/overzicht-lopende-projecten/thema-gezondheid-en-zorg/health-ri

Norris J. (2012). *Self-Tracking May Become Key Element of Personalized Medicine.* UCSF. www.ucsf.edu/news/2012/10/12913/self-tracking-may-become-keyelement-personalized-medicine

OpenAI, (2023). *Whisper, release 20230414* [Software]. OpenAI. https://github.com/openai/whisper

Pelkmans, J., & Renda, A. (2014). *How can EU legislation Enable and/or Disable Innovation*. European Commission. https://ec. europa. eu/futurium/en/system/files/ged/39-how_can_eu_legislation_enable_andor_disable_innovation.pdf.

Rigter, T., Jansen, M. E., van Klink-de Kruijff, I. E., & Onstwedder, S. M. (2021). *Kansen en risico's van DNA-zelftesten.* RIVM. https://www.rivm.nl/bibliotheek/rapporten/2020-0196.pdf

The Royal Swedish Academy of Sciences. (2020, October 7). *The Nobel Prize in Chemistry 2020*. Nobel Prize. https://www.nobelprize.org/prizes/chemistry/2020/press-release/

World Economic Forum. *Global Agenda Council on Personalized and Precision Medicine 2012*. WEF. https://www.weforum.org/content/global-agenda-council-personalized-precision-medicine-2012

Appendix A – Interview guide

Interview guide
Expert interview on personalized genomic healthcare

- Encourage the participant to share freely from experience.
- Ask follow-up questions when relevant responses are provided.

Orienting questions

1. How would you describe [organization]'s role in contributing to a system of personalized healthcare?
2. How do [organization]'s activities contribute to accelerating personalized health?
3. How would you describe the relevance of [organization] in the ecosystem?

Main questions

4. To what extent is the approach that [organization] takes value driven, versus values just playing a role in the process?
5. Which values are important in [organization]'s role? Can you provide concrete examples?

6. Which stakeholders do you consider, and what values are important to one and not the other?
7. How were these values uncovered? Where the stakeholders asked directly?

8. If you trade off value [X] against value [Y], who is impacted and in which way?
9. Are there any value conflicts or value friction that you encounter?
10. Are there major changes over time in values that parties bring to the table?

11. How would the values that you hold dear be embodies in advice you give, or how would they be implemented in real world cases?

12. How do you weigh the interests of researchers, citizens, care providers and industry (against each other)?
13. What is the public response towards your activities?

14. What are some major barriers that you see, and what is their nature?
15. How are the collaborations between stakeholders going?

Behavior specific questions

16. What are the dominant subjects about which people seek information in relation to genetic testing?
17. What are the dominant subjects that people express concerns about in relation to genetic testing?

18. How would you characterize the types of reactions patients have when they are initially involved in the process of genetic testing?
19. How would you characterize the types of reactions patients have to the return of results of genetic testing?
20. In the process of genetic testing and return of results, are there any changes over time in the information patients seek or the concerns they express?

21. To what extent does the process of genetic testing and return of results impact health directed behaviors in individuals?

22. In practice, how do healthcare professionals deal with findings that apply to relatives of the patient?

Appendix B – Summary

Currently a convergence of several key trends is enabling a *genomic revolution* in healthcare. This means transitioning from a system of reactive and generalized care to a system of *predictive*, *preventative*, *participatory*, and highly *personalized* medicine (Horgan at al., 2017). Major drivers of this development have been several recent breakthrough developments in the field of genomics, as well as developments in other fields (such as big-data and data-analysis) that converge to enable this radical transformation (Brittain et al., 2017; Horgan et al., 2015). In this new genomics-integrated healthcare paradigm, large-scale genetic screening of individuals will be employed to *"help diagnosis, prevention, and treatment of a health-related condition"* (Salari & Larjani, 2017, p. 209).

The transition towards a genomics-integrated healthcare system is a case in which heterogeneous, interdependent, actors are working to co-create a system-level output, referred to as an innovation ecosystem (Ritala & Thomas, 2023). European and Dutch initiatives regarding this transition emphasize ecosystem building activities in their approaches, including stimulating collaboration between the set of stakeholders and the creation of unified infrastructure and governance frameworks (European Commission, 2018; Nationaal Groeifonds, 2021). Due to its expected impact, personalized healthcare is also associated with a wide range of ethical issues, such as issues relating to equitable treatment of individuals and fair distribution of resources for public health (Clarke, 2014b; Evangelatos et al., 2017).

Although there is significant capacity and willingness to capitalize on the opportunities afforded by the genomic revolution, the incorporation of genomic innovations into clinical care is unlikely to occur by diffusion and instead requires targeted support to be realized (Gaff et al., 2017). Part of this is establishing alignment between the different stakeholders and activities that make up the innovation ecosystem. At loci where elements of the ecosystem are misaligned, friction occurs. It is imperative to understand the values held by stakeholders, and how these translate into system requirements, in order to identify loci of friction that pose barriers to synergistic value-creation in the ecosystem.

Another important factor in the transition towards personalized medicine is the behavior of individuals that are both subject of, as the source of genomic data, and subject to, as patients, genomic medicine. Human engagement with this new system of healthcare will have a critical influence on the successful realization of improved health outcomes for individuals. The study

of human behavior in relation to genomic technologies is, however, complicated by the influence of psychological distance (So et al., 2021). The experienced temporal distance and hypotheticality of genomic medicine influence the experienced psychological distance. The greater the psychological distance, the greater the level of abstraction at which a situation is construed, which in turn affects moral judgements (Trope & Liberman, 2010; Mårtensson, 2017). Representations on lower construal levels are less abstract, and more concerned with actionable or goal-directed details (Wakslak et al., 2006). Psychological distance is expected to be a relevant aspect of studying human attitudes and behavior in relation to personalized medicine. Another complicating factor is the value-action gap, the observation that individuals often behave in ways inconsistent with their stated attitudes or values (Sheeran & Webb, 2016; Farjam et al., 2019). Due to the strong influence of contextual factors, stated attitudes are a poor predictor of in situ behavior. Research does suggest that exhibited behaviors can be a reliable indicator of attitudes (Kaiser et al., 2007). Understanding the complex interactions between cognition, intention, and behavior is imperative if one aims to utilize genetic information to promote and support health directed behaviors in patients.

A holistic characterization of friction across interdependent stakeholders is currently lacking. Through an exploratory study using an ecosystems-approach this project aims to provide such a characterization, focusing on the developing innovation ecosystem in The Netherlands. Furthermore, as a step towards behavioral research that explores relevant behaviors in detail, this study aims to characterize the relevant health-directed behaviors and responses exhibited by patients in relation to the process of genetic testing. The research questions are as follows:

RQ1: Which (value-) frictions exist within or between different stakeholders, and what are the obstacles they pose for the implementation of personalized healthcare?

RQ2: What are the reactions and behaviors exhibited by patients and relatives in relation to the process of genetic testing in healthcare, and which factors have influenced them?

The research questions are pursued through semi-structured expert interviews involving a diverse set of active ecosystem stakeholders, ensuring that findings are grounded in the actual experiences and interactions of those involved in the transformation of the Dutch healthcare system. Six categories of stakeholder groups are identified to be represented in the interviews: *(1) government, (2) industry, (3) academia, (4) healthcare sector, (5) patients, and (6) the public.* The expert contributions of healthcare professionals, such as genetic counselors, are used to characterize relevant engagement and responses of patients in practice.

Subsequent thematic analysis is employed to generate themes from the data that characterize the relevant issues in relation to stakeholder friction, ethical issues, and human behavior. Identified themes can be organized into four distinct overarching themes. These are loci of predominantly value-based friction between ecosystem stakeholders, instrumental and organization fictions that pose barriers to ecosystem success, ethical issues, and themes relating to human engagement with and responses to genetic healthcare.

Figure 7 *The four overarching themes identified in the data*

Value friction occurs with regards to standards of evidence, data sharing, and balancing commercial, academic, and public health interests. Financial considerations, trust establishment, conceptions of privacy, and differing views on policy conservatism versus policy progressiveness further contribute to these frictions, complicating effective collaboration. An important locus of value-based friction concerns the essentiality of genomic data in realizing improved public health outcomes, and concerns with regards to the proportionality of the resources required in relation to the health outcomes realized. The latter also involves tensions between the personalized nature of genomic healthcare and the principles of collectivity in which the Dutch healthcare system is grounded.

There are several loci of instrumental, operational, and regulatory friction, referred to as instrumental barriers, that hinder collaborative success in the ecosystem. These barriers are inadequate cooperation and infrastructure for data exchange, insufficient interoperability of activities, lack of a clear legal framework, and concerns regarding the healthcare workforce's capacity to meet the demands of a genomics-integrated healthcare system. Friction is also present in the form of issues more explicitly ethical in nature. These ethical issues involve questions about trade-offs in resource distribution and equitable access, highlighting accessibility concerns for people from different socio-economic backgrounds. Other ethical challenges include the efficacy and efficiency of personalized care, inadequacies in traditional

consent models, fairness in treatment quality and benefit distribution, fears of societal impact from increased medicalization, and concerns about potential genetic discrimination.

Healthcare professionals have identified several relevant aspects of human behavior in relation to personalized healthcare. While personal benefit and solidarity motives encourage genetic data sharing, privacy concerns remain. Positive attitudes towards data sharing are common, but genetic information and availability of health-directed behaviors do not strongly drive lifestyle changes or follow-up actions. Engagement with health-directed behaviors depends on individual priorities and socio-economic factors. Additionally, low genetic literacy may limit engagement with personalized care and participation in societal debates about its implications. Not all patients are open to genetic testing, some people prioritize philosophical or religious beliefs over potential benefits. Genetic testing can prompt concerns about the future, including fears of reduced opportunities, though health risks to oneself and relatives are primary concerns. Patients may experience feelings of worry, responsibility, or guilt about passing on conditions to their children. Regardless of the results, receiving them can provide comfort by resolving uncertainty, though it might also inspire unhealthy behaviors. Initial information seeking is focused on treatment options or ways to mitigate detected conditions.

These results demonstrate the challenges that exist between the desire to capitalize on personalized medicine on the one side, and the responsibility of maintaining a strong and accessible public healthcare system on the other. The innovation ecosystem experiences significant value-based, instrumental, operational, and regulatory friction, as well as significant ethical issues, that form barriers to synergistic value creation. More important, however, is that genetic data from whole-genome sequencing in a genomics-integrated healthcare system is not expected by experts to be a strong driver of behavioral change, nor is a focus on genetics deemed to be the most appropriate means to the end of improving public health. Future research should explore new governance frameworks and modes of cooperation to facilitate collaboration and resource exchange between stakeholders. Appropriate behavioral research methods should be employed to study the complex link between information provision, intent, behavior, and socio-economic factors. While it is clear that personalized medicine has the potential to be of immense value to healthcare, it is recommended to critically examine in which instances and contexts personalized medicine can be most efficiently and effectively applied to create greater societal benefit than possible through traditional means. To achieve a meaningful and equitable impact, a comprehensive, multidisciplinary approach is essential for integrating personalized medicine into the broader healthcare system.

Appendix C - List of tables and figures