Bringing personalized medicine to people

Isabelle Budin Ljøsne

Centre for Medical Ethics, Institute of Health and Society

Faculty of Medicine, University of Oslo

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-210-4

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

ABSTRACT

Background: Personalized medicine (PM) aims to adapt prevention, diagnosis and treatment to the molecular and genetic characteristics of the individual patient and the disease. The Responsible Research and Innovation (RRI) framework of the European Union encourages stakeholders to discuss societal and ethical challenges associated with new scientific innovations such as PM, and indicate potential courses of action to address those challenges. The overarching aim of this thesis is to explore the perspectives of key groups of stakeholders regarding the four following themes of relevance to PM: (1) the feedback of genetic research results of potential health utility to research participants, (2) the endorsement of PM by citizens, (3) challenges to the realization of PM, and (4) the use of dynamic consent in PM research. The specific stakeholder groups and themes that were studied include PM researchers (themes 1 and 4), policymakers (theme 2) and patient and interest organizations (theme 3). The research addressing these themes was conducted in four distinct but interrelated studies that form the basis of this thesis. This thesis also provides a synthesis of main challenges and strategies raised in the four studies.

Methods: The themes addressed in the four studies emerged from discussions within the Norwegian Cancer Genomics Consortium (NCGC) and the COST Action CHIP ME IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives". Both projects recognized the importance of the RRI framework and aimed to adopt a "bottom-up" approach when exploring the four themes. The methods used for data collection in this thesis include an email survey, two international workshops, semi-structured telephone interviews, and a literature review. The data in each study were analysed using a conventional content analysis. The synthesis of main challenges and strategies across the studies was conducted using a similar method of analysis.

Results: Financial, organizational, regulatory, ethical and societal challenges that may negatively affect the provision of PM to patients and citizens were identified in the studies. The stakeholders discussed many strategies to address these challenges, which include the development of sustainable funding mechanisms for PM, the design of concrete tools and modern organizational structures for PM, and increased education and engagement of stakeholders in PM. Particular emphasis was placed on the importance of developing PM in a responsible and sustainable way. Our findings show that PM researchers, policymakers, and patient and interest organizations share common views regarding many of the strategies to adopt to move the PM agenda forward, with some exceptions. For instance, views vary regarding the design of educational strategies for patients, citizens, and health care professionals.

Conclusions: The work conducted in this thesis provides new insight into the types of real-life challenges that may be encountered "on the ground" in the implementation of PM. To facilitate the transition to PM, more effort should be directed towards developing PM in a way that is congruent with European values of health care. This will require continuing the discussions with PM stakeholders and conducting more research, for instance, to explore ways to develop the tools and strategies discussed in this thesis. Working collaboratively at an international level will be useful, as challenges to the realization of PM seem to be largely similar across countries.

ACKNOWLEDGMENTS

I would like to thank the Norwegian Cancer Genomics Consortium for funding this PhD thesis, and the Centre for Medical Ethics, University of Oslo, for warmly welcoming me and offering me the opportunity to explore the exciting field of personalized medicine.

Jan Helge Solbakk introduced me to the field of research ethics thirteen years ago, and was the first to encourage me to develop my interest in it. Jan Helge was my main supervisor on this PhD project. I would like to thank him for giving me the freedom I needed to conduct my work and generously sharing his extraordinary expertise and knowledge of bioethics with me. He was always there to support my choices, and cheered me up when I needed it. His friendship is extremely valuable to me.

Jennifer Harris has been my mentor and friend for many years. She rightfully encouraged me to take formal education in research ethics, and relentlessly challenged me to learn more. She taught me how to write scientific papers, and helped me develop a critical mind. As my co-supervisor, she was always available when I needed her. She spent an exhaustive amount of time helping me to develop and organize my thoughts, and improve my work. It really made a difference to know that I could always count on her. I can never thank her enough!

Ola Myklebost warmly welcomed me to take part in such an important project as the Norwegian Cancer Genomics Consortium. As my co-supervisor, he did not hesitate to spend his valuable time to guide me through the complex and innovative field of personalized medicine, and keep me updated about latest developments. I would like to thank him for his generosity and for always providing me his expert advice whenever I needed it.

Jane Kaye has been a great colleague and friend during this last decade. She and her team generously welcomed me at the University of Oxford in 2015. Thanks for their support and friendliness! During these last three years, I have worked closely with Heidi Beate Bentzen. Her legal expertise has been very valuable in this work. Heidi must be one of the most energetic people I know. Thanks for being such a good friend and thanks for great trips together! I would also like to thank Deborah Mascalzoni for being such a knowledgeable colleague and friend, for taking so good care of me in Oxford, and for being so fun to work with.

Many thanks to Søren Holm, Berge Solberg, and Øivind Mikkelsen for coming to my rescue in difficult times. I really appreciated your help. Thanks to Åsa L'Abbée-Lund, Gun Peggy Knudsen, and my colleagues at the Norwegian Institute of Public Health, for being so supportive. Many thanks to Anita Lakshmi Iyer and Benedikte Lindskog for being so helpful, wise and reflected, and Viva Combs Thomsen for her useful comments on my work and our therapeutic chats! Thanks to my colleagues in the COST Action IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives". It has been extremely enriching and inspiring to work with them and be part of the CHIP ME community.

None of this would have been possible without the support of my beloved husband Knut Tore. Thank you for always believing in me and giving me the space I needed to work, even in very busy times. Thank you Martin and Anna for your patience! I am lucky to have you. Finally, thanks to my assistant Buster (our cat) who conscientiously helped me to editfjvlsahghasgfhgklhljm the text of this thesis with his paws.

TABLE OF CONTENTS

LIST OF PAPERS

I. Budin-Ljøsne I, Mascalzoni D, Soini S, Machado S, Kaye J, Bentzen HB, Rial-Sebbag E, D'Abramo F, Witt M, Schamps G, Katić V, Krajnovic D, Working Group 1 COST Action CHIP ME IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives", Harris JR. Feedback of individual genetic results to research participants: Is it feasible in Europe? Biopreservation and Biobanking. 2016 Jun;14(3):241-8.

II. Budin-Ljøsne I, Harris JR. Ask not what PM can do for you -- ask what you can do for PM. Public Health Genomics. 2015;18(3):131-8.

III. Budin-Ljøsne I, Harris JR. Patient and interest organizations' views on PM: a qualitative study. BMC Med Ethics. 2016 May 13;17(1):28.

IV. Budin-Ljøsne I, Teare HJA, Kaye J, Beck S, Bentzen HB, Caenazzo L, Collett C, D'Abramo F, Felzmann H, Finlay T, Javaid MK, Jones E, Katić V, Simpson A, Mascalzoni D. Dynamic Consent: a potential solution to some of the challenges of modern biomedical research. BMC Med Ethics. 2017 Jan 25;18(1):4.

ABBREVIATIONS AND DEFINITIONS

ACMG: American College of Medical Genetics and Genomics

Biobank: An organized collection of human biological material and associated information stored for one or more research purposes (Source: P^3G Biobank lexicon)

BRCA1/BRCA2: genes associated with increased risk of breast and ovarian cancer

CHIP ME: Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives

COST: European cooperation in science and technology

DNA: Deoxyribonucleic acid

EHR: Electronic Health Record

ELSA: Ethical, legal and societal aspects

EMA: European Medicines Agency

EPF: European Patients Forum

GeCIP: Genomics England Clinical Interpretation Partnerships

Genome: An organism’s complete set of DNA, including all of its genes (Source: NIH Genetics Home Reference)

GINA: Genetic Information Nondiscrimination Act

HeLEX: Centre for Health, Law and Emerging Technologies

HER2: gene that can play a role in the development of breast cancer (Source: breastcancer.org)

NHS: National Health Service in the United Kingdom

NCGC: Norwegian Cancer Genomics Consortium

NoSarc: National study on gene mutations in sarcoma

NoSarc ELSA: A sub-study of NoSarc focusing on the ethical, legal, socio-economic, and anthropological aspects of genomic research

OST: Open Space Technology

Personalized medicine (PM): An emerging practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease (Source: NIH Talking Glossary of Terms)

PIOs: Patient and interest organizations

Pharmacogenomics: The study of how genetic variants affect a patient's response to drug treatment

Precision medicine: The use of genomic, epigenomic exposure and other data to define individual patterns of disease, potentially leading to better individual treatment (Source: National Academy of sciences)

P4 medicine: The clinical application of the tools and strategies of systems biology and medicine to quantify wellness and demystify disease for the well-being of an individual. (Hood, 2008)

RRI: Responsible Research and Innovation. The ongoing process of aligning research and innovation to the values, needs and expectations of society (Source: Rome Declaration on Responsible Research and Innovation in Europe)

Stratified medicine: The grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques (Source: The Academy of Medical Sciences)

VUS: Variant of uncertain significance

1.0. INTRODUCTION

Personalized medicine (PM) is a new medical approach that aims to tailor prevention and treatment to the individual patient [1]. By using information about the patient's molecular and genetic make-up in combination with clinical, lifestyle and environmental exposures, physicians may increase treatment effectiveness and reduce side effects [2]. This is important given that the efficacy rate of prescribed drugs today is largely unsatisfactory [3], and adverse drug reactions occur frequently, incurring thousands of hospitalizations and preventable deaths each year [4] as well as considerable costs to health care systems [5]. PM is progressively becoming possible as genome sequencing technologies are more affordable and our ability to translate molecular and genetic data into information of practical utility for clinicians and patients improves.

Numerous steps are being taken in Europe and worldwide to accelerate the transition to PM [1, 6, 7]. For instance, data and research infrastructures are developed to support big data and data sharing [8]. Large-scale biobanks are established to enhance access to data and biospecimens needed to fuel knowledge development within PM [9]. In parallel, ethical and regulatory instruments are being modified to adapt to the data sharing needs of today's science [10, 11]. While great effort has been dedicated to developing technologies and infrastructures in support of PM, limited attention has focused on how to integrate PM into health care in a way that complies with larger societal concerns and expectations [12]. Primary among these concerns are equitable access to health care and fair distribution of resources among patient groups [13]. PM will also create new demands on patients and citizens to take greater responsibility for their own health [14] and to share their sensitive health data more broadly with researchers [15]. In parallel, PM will create new responsibilities for researchers to collaborate with health care professionals in the use of

genetic and genomic research results for health care purposes [16]. Learning more about the perspectives of those who may be affected by PM, or may play an important role in enabling PM, is critical to identify potential challenges, obstacles and concerns "on the ground", and develop concrete guidance regarding how to address these challenges [17].

The overarching aim of this thesis is to explore the perspectives of key groups of stakeholders regarding the four following themes of relevance to PM: (1) the feedback of genetic research results of potential health utility to research participants, (2) the endorsement of PM by citizens, (3) challenges to the realization of PM, and (4) the use of dynamic consent in PM research. The specific stakeholder groups and themes that were studied include PM researchers (themes 1 and 4), policymakers (theme 2) and patient and interest organizations (theme 3). The focus of this thesis emerged from work conducted in two projects in which I was involved as a researcher. The first project is the Norwegian Cancer Genomics Consortium (NCGC), a national platform that aimed to explore new clinical practices for cancer treatment using sequencing technologies [18]. The second project is the COST Action CHIP ME, a European network that brought together experts within a variety of disciplines such as genomics, ethics and law, with the objective to analyse ethical and legal challenges related to genomics and PM [19].

The approach taken in this thesis is couched, both conceptually and methodologically, within the Responsible Research and Innovation (RRI) framework of the European Union [20]. The RRI framework encourages stakeholders to discuss societal and ethical challenges that new scientific and technological innovations such as PM may bring, and identify concrete strategies to address these challenges [17]. Both the NCGC and the COST Action CHIP ME aimed to engage with stakeholders, using consultative and qualitative approaches as

recommended by the RRI framework. In this thesis, the four themes identified in the projects were explored using such methods in four distinct, but interrelated studies. This thesis presents results from these studies and provides a synthesis across these studies of information pertaining to the challenges that may affect the provision of PM to people, and potential strategies to address these challenges. This thesis consists of a Background section, followed by a description of Methods and Results, a Discussion section, and Conclusions. Finally, suggestions for further research are outlined.

2.0. BACKGROUND

The work was conducted while I was a researcher in the Norwegian Cancer Genomics Consortium (NCGC) [18], a national consortium established with the objective to develop PM strategies for cancer care in Norway, and the COST Action CHIP ME, a European network of experts involved in the field of genomics [19].

2.1. Background projects

2.1.1. The Norwegian Cancer Genomics Consortium (NCGC)

In 2012, the Research Council of Norway [21] financed a national platform for personalized cancer medicine through its KREFT [22] and BIOTEK2021 programmes [23] – the Norwegian Cancer Genomics Consortium (hereafter "the NCGC") [18]. This project was the first in Norway to explore new clinical practises for cancer treatment by using tumour sequencing technologies. The project included all Norwegian Health Regions and medical faculties, the Norwegian Cancer Registry [24], the Biotechnology Advisory Board [25], and Oslo Cancer Cluster [26]. During the 6 years of project funding, the detailed complete sequences of all genes in specific sets of approximately one thousand matched pairs of tumour and normal samples were to be produced to identify tumour mutations that could guide treatment choices or predict disease characteristics. Although the primary focus was on investigating tumour mutations, the analysis process also determined the normal germ line sequence, and thus germ line sequence variation in all genes. Central objectives of the project were to identify new treatments which target specific mutated cancer proteins, use such information to provide personalized cancer care to patients, and establish a tumour mutation database that could serve as a national resource for research. In recognition of the ethical,

legal, and societal considerations that a project like the NCGC must address, it included an "Ethical, Legal and Societal Aspects (ELSA)" work package (WP5). The main objectives of this work package were to explore ethical and societal challenges related to the production, use and dissemination of genetic and genomic data. Particular focus was placed on exploring issues related to the feedback of genetic research results to research participants, and investigating potential overall challenges to the realization of PM. The methods to use to explore these themes were not described in details in the project description of the NCGC, although one objective was to collect empirical data from the stakeholders of the consortium. The present PhD project, as well as one PhD project in health economics and one in law, is linked to this work package. A senior researcher with background in social anthropology also joined the work package.

2.1.2. The COST Action CHIP ME

In 2013, the COST Action CHIP ME IS 1303 (Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives) [19] was established by the COST programme of the European Union [27]. The COST Action CHIP ME (hereafter "the COST Action") is a network of researchers and stakeholders involved in the field of genomics and with an interest in PM. The network members have expertise in a broad range of disciplines such as bioethics, social studies of science and technology, genetic technology, information and communication technology, and stakeholder deliberation. As described in its Memorandum of Understanding, the COST Action aimed to "(…) improve the state of the art by creating a community of researchers and stakeholders and linking existing initiatives which bring critical expertise in bioethics, social studies of science and technology, genetic technology, information and communication technology (ICT), stakeholder deliberation, and

patient centred initiatives (PCI) with a new focus on new public-private interactions and consumer genetic testing" [28]. Using deliberative processes such as workshops and meetings, the Action aimed to "(…) provide guidance and coordination to researchers, opinion leaders, public officials and experts involved in the drafting or application of regulations, recommendations, and best practices guidelines in the field of genetic testing and biobanking" [28]. The Action was organized into three working groups: 1) WG1 "Research ethics" focused on the ethical and legal issues of research biobanks and genomic research; 2) WG2 "2.0 genomics and markets: stakeholder perspectives" focused on mapping techno-scientific innovations and applications of genomics and Direct-to-Consumer genetic testing; and 3) WG3 "Science and values" investigated the ethical status of genetic testing and genomics research.

As of 2013, the COST Action included 95 experts from 25 European countries [19]. In the period of 2014-2015, I acted as the chair of the Action's working group on Research Ethics (WG1) and continued as co-chair in 2016 and 2017 [29]. The specific questions to be addressed by the Research Ethics working group throughout the duration of the Action were outlined in the Action's Memorandum of Understanding and related to the feedback of genetic information to patients and research participants, the governance of informed consent (with particular focus on technological solutions for dynamic consent), and governance models and legal frameworks for ensuring data security [19].

2.2. What is new with PM?

PM represents a novel approach on two fronts:

- First, **PM aims to re-classify diseases** on the basis of their underlying molecular profile rather than upon observation of physical manifestation of symptoms, and then

tailor treatment to those profiles [6]. For instance, cancers, which previously were classified according to a site-specific category of disease, are being re-classified into different subgroups defined by tumour and genetic profiles. Fine-tuning the classification of disease in this manner enables more precise and accurate diagnosis and treatment because molecular testing can potentially be used to identify and confirm disease sub-types, and determine whether a patient may or may not benefit from a particular therapeutic intervention [30]. As an illustration, breast cancer patients with abnormally high levels of the HER2 protein, which leads to a rapid proliferation of cancer cells, can now be prescribed a molecularly targeted therapy designed to "shut off " the HER2 gene and make cancer cells grow more slowly [31]. This strategy, also known as pharmacogenomics (i.e. the study of how genetic variants affect a patient's response to drug treatment) may enable better drug selection and dosage of medication, and reduction of toxicity [32]. Re-classifying disease according to underlying molecular profiles may also be useful to understand chronic diseases such as inflammatory disorders that often share common aetiologies but have different clinical presentations across individuals [33].

- Second, **PM aims to detect disease long before symptom occurrence**. Early detection of genetic variants may enable earlier initiation of prevention and intervention measures. For instance, women with certain BRCA1 or BRCA2 gene variations have a significantly increased lifetime risk of developing breast or ovarian cancer compared with the general female population. Genetic testing can be informative for preventative measures such as the frequency of mammography screening or prophylactic surgery [34]. Individuals with an increased genetic risk of developing diseases such as familial hypercholesterolemia or cardiovascular disease

may also receive early guidance regarding life style modifications that could help delay or avoid disease development.

Genetic and molecular information about patients can be used early and in a targeted way to offer better outcomes to patients and reduce the frequency of side effects. Such opportunities have led promoters of PM to argue that PM represents a paradigm shift that will "revolutionize" health care and radically change the way we understand and deal with health and disease [35]. Meanwhile, others are more cautious and believe that PM may, at best, help "categorize patients into more defined subgroups according to their genotypic markers or risk for a specific disease" [36]. In general, PM can be described as "work in progress". As stated in a workshop report from the Health Research Directorate of the European Commission: "PM, like any other research field, is characterised by not one or two ground-breaking developments, but rather by a series of important but iterative steps forward, usually one disease at the time" [37]. This is best illustrated in the field of oncology where a whole range of targeted therapies that act on specific molecular targets associated with cancer cell growth and survival have been developed for various cancers including breast cancer, colorectal cancer, lung cancer, leukaemia, prostate cancer and melanoma [38]. In addition to cancer, PM research is also progressing in other areas of medicine such as cardiology, HIV/AIDS, mental health and infectious diseases, and some applications are under development in the field of organ transplantation [39]. Initiatives are also progressively being started to investigate whether PM could contribute to providing better treatment to patients suffering from Alzheimer's disease [40] and diabetes [41], the causes of which remain largely unknown even though many genetic variants associated with these diseases have been discovered during the last decade [42]. Finally, PM could also potentially help patients with rare diseases who often

remain undiagnosed for years due to a lack of good genetic tests, thus limiting any possibility to identify adequate treatment for them.

Several terms have been applied, sometimes interchangeably, to name PM [33]. While "personalized medicine" is frequently used in Europe, "precision medicine" is preferred in the United States to describe "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle" [43]. It emphasizes that treatment cannot literally be designed for each individual but rather for groups of patients sharing the same genetic and disease characteristics [6]. In practice, precision medicine aims to improve the precision with which patients are categorized and treated [44]. The British Academy of Sciences uses the terms "stratified medicine" to describe "the grouping of patients according to disease risk or likely treatment response, as determined by diagnostic tests, to determine the course of care" [45]. Thus, the concept of stratification is preferred to the concept of "personalization" [44]. "P4 medicine" is also a label in use [46]. Despite these diverse labels and definitions of PM in the literature [47], PM can be broadly understood as a medical innovation that utilizes genetic and molecular information to improve health care.

2.3. Potential impact of PM

Since its introduction at the turn of this century, PM has generated a range of debates and reactions regarding how it may potentially change the way in which societies approach and understand health and disease [44]. Three widely discussed issues are:

- PM's ability to empower patients and citizens. PM aims to provide patients and citizens with precise and detailed information about their present and potential future health (based on genetic risk predisposition estimates). It is argued that such an approach will empower patients and citizens to use this information to monitor their own health and prevent disease occurrence in partnership with their health care provider [33]. However, questions have been raised whether receiving information about genetic risk predisposition will really lead to empowerment, particularly because at our current state of knowledge, genetic risk information has limited validity and utility for many types of diseases [48]. Currently, few high-penetrance actionable pathogenic or likely pathogenic variants have been discovered, and for many of these variants, specific interventions often do not exist beyond standard advice to maintain a healthy life style [49, 50]. However, new knowledge is changing this landscape continuously [51]. Genetic risk predisposition estimates may not be sufficient to inform decisions regarding most common diseases in which genetic and molecular factors play a limited role [52]. Focusing solely on "omics" information may be too narrow-sighted [53]. It has also been argued that, even if the genetic information is reliable and of potential high impact, there is no guarantee that people actually want to be empowered. To illustrate this point, a recent review study shows that individuals who were informed about their DNA based risk estimates did not change their life-style [54]. There are also concerns that PM, rather than empowering people, may create unnecessary anxiety and distress among otherwise healthy and asymptomatic individuals who may feel guilty if they are "unable or unwilling" to behave rightly as expected on the basis of their genetic profile and risk for developing future illness (that may never materialize) [55, 56]. The argument has also been made that increased focus on an individual's genetic profile may have unwanted side effects. For instance, individuals who are informed that they have a low risk of developing heart disease may use such information to justify unhealthy diet or life-style choices [14]. It has also been argued

that focus on an individual's genetic profile may lead to genetic determinism, i.e. the belief that a person's health and behaviour is determined by her genes [57]. Thus, the opposite of personal empowerment may become the result.

- PM's potential impact on solidarity in health. Under PM, health care becomes "personalized", "tailor-made", and focuses on the single person rather than populations. This represents a shift in focus from traditional public health under which combating disease requires a collective approach on the basis that "(…) disease can target anyone, that risks are spread across a population and therefore must be tackled at this level" [48]. Increased focus on the individual, and personal responsibility for one's own health, has generated concerns that the well-established view (at least in European welfare systems) that health is a matter of solidarity and shared responsibility, may be threatened. This could in practice mean that the traditional "responsibility free" access to health care may be challenged, in particular if governments in the future consider sanctioning those individuals who do not comply with the rules of healthy lifestyle that are considered suitable for their genetic profile [55]. Further, increased focus on personal responsibility may lead those who are at low risk of developing a disease to reconsider whether they are willing to pay taxes to finance the health care of others who are at high risk, or whether they would prefer private insurance [48]. If such preferences were to develop, how would this affect our health care systems that currently rely upon principles of universal and equitable access to health care? Concerns regarding solidarity in health have also been expressed which extend beyond national borders. For instance, there is a risk that PM, like many other health technologies, may become only available to patients in the wealthy parts of the world because of the financial investments it requires. Thereby, there are concerns that PM might increase the health divide between rich and poor countries [58].

- PM's potential impact on privacy. PM relies heavily on the production and sharing, for research and health care purposes, of sensitive information about individuals, including genetic and molecular information. Such information, although medically valuable, could potentially be misused to discriminate against some people, for instance, by denying them access to employment if they have a high risk of developing a rare and incurable disease [59, 60]. Despite efforts to develop secure data handling mechanisms, sensitive data always present some level of risk. Recent cases have demonstrated that genetic datasets, which were believed to be sufficiently anonymised, could be re-identified under specific circumstances by combining them with other publicly available datasets [61, 62], thus raising the question whether safe anonymization of genetic data is possible. This has led to concerns that PM may translate into the end of privacy, or at least may represent a significant threat to genetic privacy [60]. If these concerns materialize and genetic privacy actually is threatened by PM, this could have a significant impact on society knowing that genetic information cannot be considered to be strictly individual as it also provides information about blood relatives [63]. Technical, legal and organizational solutions have been proposed to address privacy concerns. For instance, legislators in some countries have adopted specific legislation on genetic discrimination [59, 64]. The U.S. Genetic Information Non-discrimination Act of 2008 (GINA) is one example of such a regulation that prohibits discrimination from health insurers and employers [64]. Another approach has been to argue that since privacy cannot be fully protected, openness and "explicit communication of risks to those whose data are being used" is more appropriate [65]. However, one may question whether such a strategy solves the issue or instead puts all responsibility on the shoulders of those individuals whose privacy should be protected. Questions regarding how privacy issues under PM should be handled, what impact PM will have on the concept of privacy (e.g. should privacy be re-defined or

abandoned?), and who should take responsibility for reducing privacy risks, continue to be at the centre of intense debate [65].

2.4. The pathway towards PM

It is now clear that many medical products will increasingly be based on genetic research, and that new targeted treatments and diagnostic tests will be brought to the market on a regular basis [66]. Extensive work has been conducted by a wide range of actors including governments, funders, medical organizations [6, 33, 45] (hereafter "policymakers"), and the scientific community [67-69] to determine what needs to be done to accelerate the realization of PM [39, 70]. These actors have identified five mains areas of work where particular attention and effort should be focused. These are briefly described as follows:

- **Scientific research needs to be intensified** to map genetic variants, elucidate their role as markers of disease or drug response, and understand gene networks and gene-environment interactions. Cohort studies and biobanks can play a role in providing genotypic and phenotypic information from millions of individuals that can be used for research [9]. Clinical and laboratory research is also important to understand the implications of structural and regulatory variants in relevant genes and investigate how the patients' genetic profile may impact response to treatment [71].

- **Solid data sharing infrastructures need to be developed** to support the collection, analysis, linkage and sharing at reasonable cost of comprehensive and interoperable datasets [33, 45], following common standards and policies [72]. Efforts are currently being made in pan-European biobank infrastructures [73] and research collaborations [74] to develop such infrastructures and tools. The implementation of electronic health

records (EHR) is also needed to enable the storage of genetic and genomic data with the objective to support the clinical decision-making and open for research at "point-of-care" [6, 75]. Detailed, quality-assured and structured annotation of clinical disease parameters and their disease-specific interpretation must also be established.

- **Robust ethical frameworks are needed** to protect the privacy and confidentiality of individuals when sensitive genetic and molecular information is produced [33]. Safeguards must be developed against potential risks of discrimination based on an individual or an ethnic minority's genetic profile [59, 60]. Emphasis needs to be placed on developing new forms of consent to inform individuals about the risks and benefits associated with the production of individual genetic and genomic information, the possibility that they may be offered access to their genetic research results, and potential future uses of their data by researchers, clinicians, and commercial actors [6, 76].

- **Regulatory frameworks must be modernized** to enable more rapid evaluation and approval of new targeted drugs. Adaptive pathways [77], a fast track model currently piloted by the European Medicines Agency's (EMA) [78], is an example of a tool that can be used to enable a quick conditional approval of treatments in areas of high medical need. Under this program, specific treatments can be approved on the basis of early data that are considered predictive of important clinical outcomes, evidence collected through real-life use, and feedback from patients and health-technology-assessment bodies [77]. It is also recommended that drug approval mechanisms adapt to the conduct of clinical trials including small subsets of patients sharing similar genetic profiles rather than large-scale randomized control trials [79]. In the approval

process, greater emphasis should be put on patient outcomes such as side effects and personal utility of interventions [70].

- **Stakeholders should be educated in PM**. Educational programs targeting health care professionals should be revised to include basic concepts of genetics, molecular biology and clinical informatics, and information about the use of genetic tests [31, 33]. It is also recommended that patients and citizens become familiarized with genetic information and understand genetic risk predisposition [37]. The NHS-funded programme INVOLVE, a British national advisory group aiming to facilitate public involvement in research, is an example of an initiative that helps to increase public awareness and understanding about PM through research festivals, laboratory tours [80], and web-based educational programs [45]. Health care institutions are also encouraged to develop genetic services to provide genetic information to patients in a concise and systematic way [71]. Patient and interest organizations are envisioned to play a role in increasing patient literacy and producing easily understood information about PM [81, 82].

The five areas of work described above – the conduct of scientific research, the development of data sharing infrastructures, the development of ethical frameworks, the modernization of regulatory frameworks, and the education of stakeholders in PM – focus on the development of hands-on technical solutions, tools and infrastructures essential to help integrate PM into our health care systems. The funders and promoters of PM primarily delineated these five areas. This is a "top-down approach": high-level decision makers lay out a roadmap for the realization of PM that other stakeholders of PM are encouraged to follow. However, it is important to explore how well these five areas coincide with what other stakeholders of PM,

for instance, PM researchers and patient groups, see as critically important. This is because these stakeholders work "on the ground", have hands-on experience, and may have a better understanding of real-world issues [83]. They may also be important allies in the realization of PM by providing advice and recommendations for how to move forward. Considering their views may be particularly useful to ensure that PM develops in a way that complies with the expectations and values of society.

2.5. Responsible Research and Innovation: A normative framework for PM in Europe

Developing new scientific, medical, and technological innovations according to values of "universality, access to good quality care, equity, and solidarity" [13] is highly prioritized in Europe [84]. In response to critiques that innovation is often too detached from the needs, values, and expectations of society [85], the European Union developed a normative framework for Responsible Research and Innovation (RRI) [17]. RRI is "an approach that anticipates and assesses potential implications and societal expectations with regard to research and innovation, with the aim to foster the design of inclusive and sustainable research and innovation" [86]. RRI can also be described as "the ongoing process of aligning research and innovation to the values, needs and expectations of society" [84] or as a strategy to move away "(…) from science in society to science for society, with society" [85].

PM, as a medical approach heavily relying on scientific research and innovation, typically falls into this category of innovations encompassed by the RRI framework. It is therefore important to develop PM in a way that aligns with the needs, aspirations, and core values of society. However, realizing PM brings a number of challenges. For instance, in its 2015 note on PM, the Council of the European Union observed that "not all patients have access to innovative methods of better-targeted prevention, diagnosis and treatments" [87]. This is

primarily because PM requires large investments in expensive technology that some European countries may not be able to afford. Targeted treatments are also often highly priced, as illustrated by cancer drugs, which frequently cost above $100,000 per year of treatment [88]. If European health care systems cannot handle such additional costs, the principle of equitable access to health care becomes threatened, leading to a situation that is quite contrary to the expectations of society [89]. As described in section 2.3, PM may also require that patients and citizens take greater responsibility for their health. However, we know relatively little regarding how realistic and desirable this requirement is, and what its impact may be across different socio-economic groups.

Discussing how to bring innovations such as PM to society in a way that complies with its needs, values, and expectations is the recommended strategy of the RRI framework. The EU Framework Programme for Research and Innovation [86] states that:

> "Responsible Research and Innovation (RRI) implies that societal actors (researchers, citizens, policy makers, business, third sector organisations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society." (The EU Framework Programme for Research and Innovation) [20]

Although the framework does not outline clear rules and regulations, but rather is a "learning process with no fixed answers" [90], it encourages " (…) all stakeholders including civil society [to be] responsive to each other and take shared responsibility for the processes and outcomes of research and innovation" [84]. This translates into an engagement of key stakeholders in consultations and deliberative processes that are transparent, encourage

interdisciplinarity, and are open to all those who may be involved in, or affected by, a research and innovation process [90]. Under the RRI framework, stakeholders are invited to discuss the implications of new innovations and "define an implementation plan for the responsible development" of these innovations [85]. In particular, stakeholders are encouraged to discuss "the direction of travel for science and innovation – from the outset – opening up opportunities for these to be directed towards socially desirable ends" [85]. RRI invites to "collective deliberation through processes of dialogue, engagement and debate" to learn more about the perspectives of different stakeholders [85]. Such processes are seen as useful to "provide continual input and substance to new governance practices" [90] and ensure that technological developments align with the values and aspirations of society [91]. Another benefit of this approach is that it provides a voice to stakeholders and give them more visibility [92].

Deliberative processes involving a range of stakeholders, spanning from researchers to patient groups and civil society, have been rather limited in number within the context of PM, at least in Europe. As explained earlier in section 2.4, the primary focus has been on developing a roadmap for PM consisting of action points or work areas to develop, and discussing the risks and benefits of using genomic technologies [83]. Understanding the views and perspectives of stakeholders in PM has received comparatively less attention. Studies targeting the public [93, 94], ethnic groups [95, 96], patients [97-100], physicians [101, 102], clinicians and researchers [103, 104] have been recently published, but these were primarily conducted in North America. To date, the number of studies (published in English) exploring the views of European stakeholders of PM on specific questions of relevance for PM remains limited, although this is progressively changing [67, 105-108]. This is problematic knowing that PM is developing rapidly in Europe. This thesis aims to help partly fill this knowledge gap by

investigating the views of key groups of European stakeholders of PM on specific themes of relevance for the PM agenda, following the principles of the RRI framework. Adopting such approach may help anticipate key challenges encountered by PM stakeholders at "the ground level", and contribute to identify societal needs and social values that are relevant in the context of PM [91].

2.6. Design and structure of this thesis

Figure 1 depicts the design and structure of this thesis as a visual image showing the relationship between the RRI, the NCGC and COST Action, and the research papers comprising the thesis work. As represented by the thick band in Figure 1, the RRI encourages activities that enable stakeholders to anticipate potential key issues that may arise in connection to innovations such as PM, identify ways to address these issues, and delineate potential courses of action, for instance, in the form of governance mechanisms. Towards this end, the RRI framework defines six main groups of stakeholders for which these activities are important (Figure 1): the research community, policymakers, civil society organizations (e.g. patient and interest organizations), business and industry, patients, and the education community [17]. These six groups of stakeholders were identified early on in both the NCGC and the COST Action projects as important to engage to achieve the project aims.

Both projects recognized the importance of the RRI framework and adopted its approach for achieving their project goals. Furthermore, there was great complimentary across the projects regarding a number of thematic issues to be explored including the feedback of genetic research results to research participants, the use of dynamic consent in research projects, and the endorsement of PM by patients and citizens.

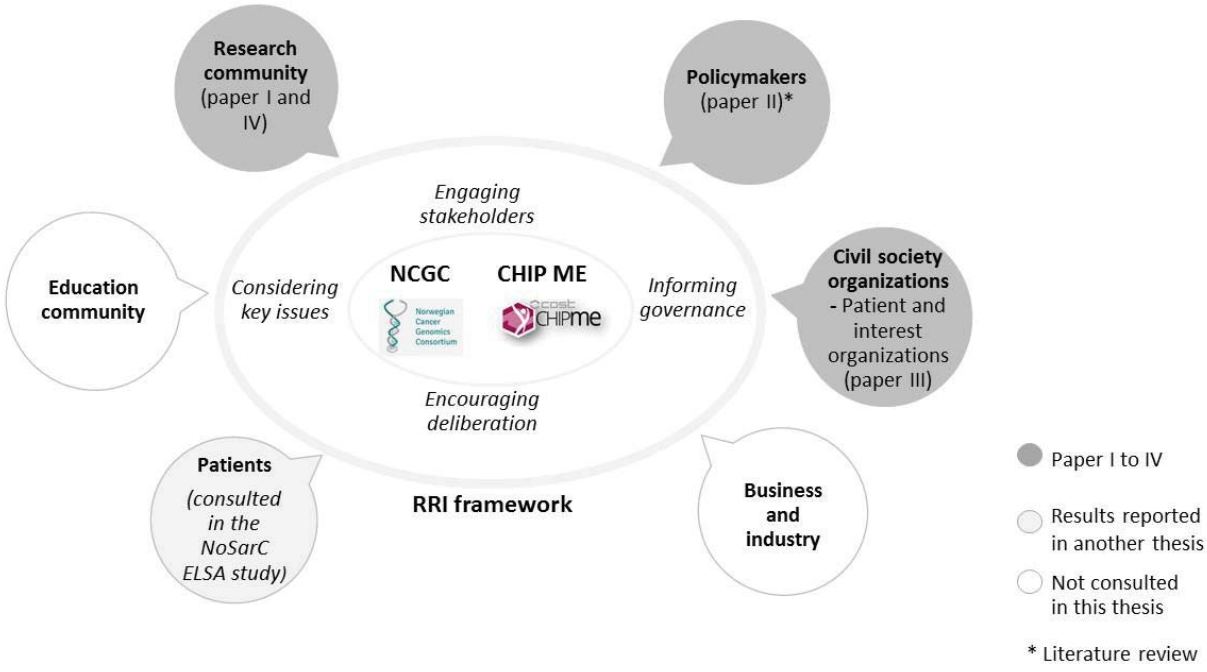


Figure 1: Relationship between the RRI, the NCGC and COST Action

The projects also aimed at engaging with patient and interest organizations to discuss PM and identify ways to collaborate with them to move the PM agenda forward. Thus, the RRI framework provided a unifying framework for the body of work comprising this thesis. Following the advice of the RRI framework to engage with stakeholders, this thesis investigates the views of three of the six main groups of stakeholders listed in Figure 1: the research community, policymakers, and patient and interest organizations. Results from this work are outlined in four studies (papers I to IV - dark grey circles in Figure 1).

Views from stakeholders representing business and industry or the education community were not directly investigated in this thesis, although scholars and academics did participate in the COST Action. In addition to my thesis work, my colleagues in the NCGC ELSA work package and I conducted a joint study (the NoSarC ELSA study) to investigate the views of

patients and health care professionals on specific aspects of PM. The results from that study will be reported in another PhD-thesis in the process of being developed.

2.6.1. Development of the studies

The NCGC and the COST Action broadly aimed to explore overall themes of relevance for PM including the feedback of genetic research results to research participants, the governance of informed consent, and potential overall challenges to the realization of PM. How to explore these themes was not outlined in details in the project descriptions, although recommendation was made to use deliberative processes to engage stakeholders. The studies included in this thesis primarily developed through discussions within the projects and in partnership with my colleagues in the NCGC and the COST Action. These discussions enabled us to map out key considerations on the horizon and identify specific areas we could explore, and ways to explore these areas, that would help inform the development of the PM agenda. The approach we undertook within the projects to develop the studies is, I believe, in line with the principles of the RRI framework which recommends that stakeholders and societal actors "work together during the whole research and innovation process" to identify societal concerns and challenges [109]. Thus, both the design of the studies, as well as the methods used to investigate the views of stakeholders, adopted the RRI approach. The sections below provide a more detailed description of how each of the four studies (papers I to IV) were developed.

Study 1 (paper I)

The NCGC comprised several sub-studies, including the NoSarC study, a national study on gene mutations in sarcoma (a rare form of cancer that grows in tissue or bone) [110]. The researchers associated with this study expected to produce findings that would be particularly important for the participants, including information about their individual predisposition for

cancer. Thus, the NoSarC study provided an "in-vivo" opportunity to investigate how to provide such information to research participants. This was a main research goal of the NCGC ELSA work package in which I participated. In parallel, the COST Action aimed to explore whether the right conditions are in place in Europe for enabling the feedback of results of potential health utility to research participants [28]. The need to find ways to feedback information to participants in the NCGC, and the prominence of feedback issues in Europe, led us to engage with PM researchers in the COST Action to explore their views regarding **challenges that may arise when research projects plan to feedback genetic research results to research participants, and potential strategies to address these challenges**. Doing so was considered useful knowing that research projects such as the NCGC are often multi-site projects, and that practical issues may be similar across countries (e.g. which exact results to provide, how, according to which criteria). Results from this work are reported in paper I.

Study 2 (paper II)

The NCGC also aimed to explore how patients such as those participating in the NoSarc study [110] may react when being offered the possibility to learn about their genetic risk predisposition. Currently, little is known regarding how patients and citizens may behave when they receive genetic risk information, for instance, whether they worry more about their health or actively use such information to monitor their health [54]. In parallel, the COST Action was interested in exploring how patients and citizens may behave when individual risk information, and individualized prevention and treatment, become more available. The Action planned to conduct public hearings at the end of the Action period to investigate the views of the public regarding the use of genetic tests [19]. In the NCGC ELSA work package, we decided to explore this topic in two ways. First, we conducted a study to identify **the types of**

new behaviours that patients and citizens may endorse under PM. Recent reports (listed in paper II) produced by policymakers extensively describe these behaviours. We reviewed these reports to explore whether the endorsement of these new behaviours is realistic. Results from this work are presented in paper II.

Second, we conducted interviews among research participants in the NoSarC study during the fall of 2015 and spring 2016 to investigate their interest in their individual genetic research results, and potential use of such results. We also investigated the views of health care professionals on this same topic. This work was designed as a joint study – the NoSarC ELSA study - between the researchers participating in the ELSA work package. Due to the timeline of this study, and because its design was particularly fit to address the research questions to be explored by the health economist in our work package, it was decided that the results would be integrated in the PhD thesis in health economics that will be finalized in 2018. The results are currently being analysed and will be described in a scientific paper that is under preparation (personal reference: Iyer AL, Bentzen HB, Budin-Ljøsne I, Lindskog B. Sarcoma patient's and health care professionals' perspectives on the production and use of individual genetic research results: An ethical legal, health economics and anthropological study -- NoSarC – ELSA).

Study 3 (paper III)

Both the NCGC and the COST Action aimed to understand how to integrate PM in health care systems in a way that is compatible with the needs and aspirations of patients. Patient and interest organizations (PIOs) have close contact with patients and their families and may provide qualified insight into what patients consider as most critical in terms of health care [6]. The NCGC already had some established collaborations with PIOs such as the Norwegian

Cancer Society [111] and the Norwegian patient organization for sarcoma patients [112]. The COST Action also aimed to engage with PIOs [19]. We therefore decided that it would be useful to engage with PIOs to investigate their views regarding **challenges to the realization of PM, and potential strategies to address these challenges,** knowing that, currently, few empirical studies exist to document such views [67, 113]. Making use of our contacts in the NCGC, and in order to get a broad understanding of how PIOS view PM, we contacted PIOs working within a variety of disease areas, nationally and internationally. Results from this work are described in paper III.

Study 4 (paper IV)

The NCGC aimed to investigate how to best design informed consent to inform research participants in the NoSarC study about the possibility of receiving genetic risk information. The NCGC researchers experienced that traditional forms of consent were ill-adapted to provide complex information to participants in an open, understandable, and transparent way [114]. Simultaneously, the COST Action aimed to investigate how dynamic consent, a concept describing the use of online platforms for consent collection, may facilitate an ongoing and interactive consent process [115]. Although some projects have tested the use of dynamic consent [116, 117], and the pros and cons of dynamic consent have been thoroughly discussed [115, 118], still little is known regarding **how dynamic consent can help address the types of challenges that researchers usually encounter in PM research** such as research involving the use of genome sequencing technologies. We therefore decided to explore the views of PM researchers on this topic, using the network of the COST Action. Results from this work are reported in paper IV.

By conducting the four studies above, we hoped to gain new insight into the types of issues and concerns that key stakeholders of PM have, and potential strategies they propose to address these issues. However, it is important to mention that these four studies do not aim to identify all potential challenges that may arise when developing PM. Rather, they provide an indication of what key stakeholders consider important at a certain point in time regarding specific aspects of PM. The approach described below was used to conduct the studies.

2.6.2. Choice of method

The work conducted for this thesis is primarily empirical and relies on the use of qualitative methods. The RRI framework supports the use of such methods to develop a "contextual understanding" of real-life issues [91, 92] and gain insight into what stakeholders experience at the "ground level"; something that is difficult to achieve if research questions are explored solely at a conceptual level [92]. Information collected through such empirical work can, at least in principle, also be used "to inform moral discourses and the formulation of policy, regulation and legislation" [119]; something that is in line with the objectives of the COST Action [19] and those of the NCGC [18]. It should be noted that results from qualitative studies may have limited normative value, in particular if the sample size used to conduct the research is very small [119]. Furthermore, the views and values of stakeholders may be influenced by the context in which they work. However, the stakeholders are also affected by normative decisions and policies made at higher level. Exploring their opinions in an inclusive and transparent way therefore seems reasonable [92]. The RRI framework does not provide detailed guidance regarding which deliberative, consultative methods to use [90], thus suggesting that a pragmatic approach regarding the choice of working methods is appropriate.

The methodology used to develop the four papers included in this thesis, and synthesize results, is described in section 4.0.

3.0. AIMS AND RESEARCH QUESTIONS

The overall aim of this thesis is to investigate the views of key stakeholders of PM regarding specific themes of relevance for PM. The themes are explored through the following research questions addressed in four distinct, but interrelated studies (papers I to IV):

- Study I: What challenges may European research projects encounter when planning to provide genetic research results of potential health utility to research participants? What steps could be taken to facilitate such provision? *(As seen from the perspective of PM researchers)*

- Study II: What new behaviours and practices are required from citizens to support the realization of PM? What is needed in order for citizens to fulfil these expectations? *(As seen from the perspective of policymakers)*

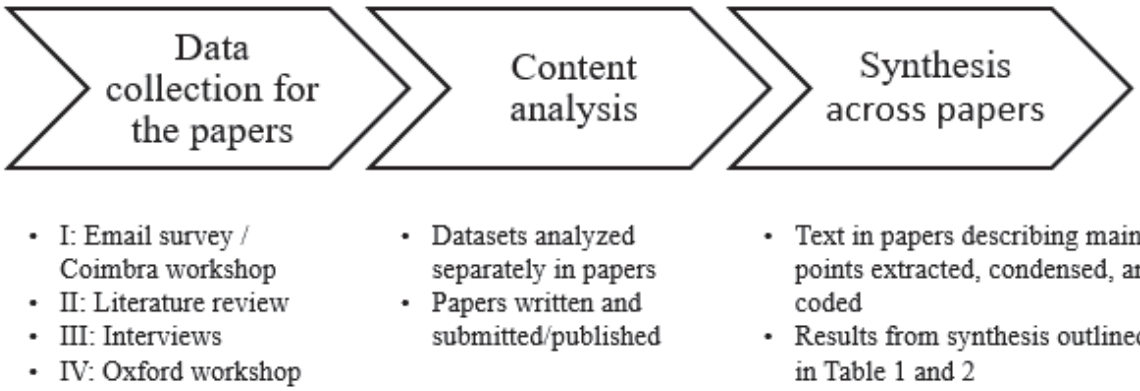
- Study III: What potential challenges may impede or delay the realization of PM? What solutions may help address those challenges? How may patient and interest organizations contribute to PM? *(As seen from the perspective of patient and interest organizations)*

- Study IV: How can dynamic consent, an online consent and engagement tool, help address some of the challenges of research related to participant recruitment and retention, and consent collection and management? *(As seen from the perspective of PM researchers)*

4.0. MATERIAL AND METHODS

The work in this thesis was conducted in two steps. First, data were collected for the four studies addressing the specific research questions. This work took place between October 2013 and October 2015. Qualitative methods were used to collect the data including an email survey, two international workshops, semi-structured telephone interviews, and a literature review. For each study, a justification of the choice of method is provided below. The same conventional qualitative content analysis approach was applied to analyse the data in each study [120]. Second, after the research papers generated from these studies were submitted to journals and/or had been published, a synthesis of the collective findings was conducted to extract main themes and points raised pertaining to challenges identified, and solutions proposed. The text describing main points was extracted from the papers, integrated into a matrix, condensed, and analysed, following a qualitative content analysis approach as described in section 4.2. Results from this work are provided in Tables 1 and 2 in the Results section of this thesis. Figure 2 depicts the steps for data collection, data analysis, and synthesis.

Figure 2: Data collection and analysis processes



4.1. Data collection procedures for the four papers

4.1.1. Paper I - Email survey and Coimbra workshop

Paper I aimed to investigate the views of PM researchers involved in the COST Action regarding potential challenges to the feedback of genetic research results to research participants in Europe, and solutions to address these challenges. The method selected to investigate this issue was guided by a requirement of the Action in its Memorandum of Understanding [19] to hold an annual workshop among its members on this topic, and produce a working paper (paper I). The workshop was planned to take place in October 2014.

To lay the ground for discussions among workshop participants, we decided to collect data prior to the workshop (in July 2014) by sending an email survey to the Action members in the 25 participating countries. The survey consisted of an open-ended questionnaire inquiring about challenges and practical issues that the Action members could encounter related to providing feedback of genetic research results to research participants (Appendix A). The questionnaire also asked for suggestions to address these challenges. The survey respondents were asked, whenever possible, to coordinate responses within their country. In total, 19 questionnaires were collected through the email survey, and they provided information from 14 of the 25 COST Action countries.

In October 2014, the Research Ethics working group (WG1) of the Action organized a one-day workshop at the University of Coimbra, Portugal. The workshop gathered 43 Action members from 21 European countries and was designed as an open space technology (OST) meeting. OST meetings do not require a specific detailed agenda but are rather conducted as open forums where discussions on a few broadly defined topics are encouraged. The

workshop was moderated by a COST Action member with expertise in leading OST events. To facilitate discussions, a case study (Appendix B) was used requiring workshop participants to anticipate how they would organize the feedback of individual genetic research results to research participants at their home institution, the challenges they expected to encounter, and the types of solutions that would be needed to address these challenges. Notes were taken by appointed participants during the workshop and collected by the working group chairs at the end of the day. The data collected through the survey questionnaire (sent out in July 2014), and notes from the workshop, were gathered and analysed using a qualitative content analysis approach as described later in section 4.2. These data formed the basis for paper I.

4.1.2. Paper II - Literature review

Paper II aimed to investigate the perspectives of policymakers regarding the types of behaviours and practices expected of citizens to support the realization of PM. During recent years, policymakers have published several reports that detail the steps required for the realization of PM, and the kind of behaviours and practices that are expected from patients and citizens to support PM. It was therefore decided that a systematic review of these reports would be useful to gain insight into 1) the types of roles and responsibilities that patients and citizens are envisioned to endorse under PM, 2) the implications of these expectations for citizens, and 3) potential barriers that exist, which may prevent citizens from endorsing these roles. To our knowledge, this review would be the first to focus specifically on how the reports describe new behaviours of patients and citizens under PM. The benefit of conducting such review is that it provides good insight into what policymakers in different countries expect from patients and citizens. An Internet search was conducted using Google and the following search terms: [‘personalized medicine’] and/or [personalised medicine] and/or [‘stratified medicine’] and/or [‘precision medicine’] combined with [report] and [pdf]. In

total, 18 publicly available reports published between 2008 and 2013 and written in English were selected and reviewed to identify sections of text addressing envisaged behaviours and/or practices of patients and/or citizens. These reports are listed in the paper [121]. The sections describing behaviours and/or practices of patients and/or citizens were extracted and compiled into a list of verbatim texts. The data collected were analysed using a qualitative content analysis approach as described later in section 4.2.

4.1.3. Paper III - Interviews

Paper III aimed to investigate the views of patient and interest organizations (PIOs) regarding potential challenges to the realization of PM, and strategies to address these challenges. We decided to engage directly with the PIOs by approaching their leading representatives and inviting them to discuss PM in individual interviews. First, an e-mail invitation was sent to the leading representatives of a small number of PIOs that co-operate with the NCGC. The invitation provided an outline of the study objectives and a description of what participation in the study entailed[1]. Those who accepted our invitation helped to identify other PIO representatives that might want to participate in the study. Such snowball sampling enabled the recruitment of representatives from 8 PIOs concerned with one specific disease or disease area. Second, the same e-mail invitation was sent to 20 leaders of disease-specific PIOs members of the European Patients' Forum (EPF), an umbrella organization that works with patient groups and health advocacy organizations across Europe [122]. This further enabled the recruitment of 5 PIO representatives. Between July 2014 and January 2015, semi-structured individual telephone interviews were conducted with 10 organizational leaders (e.g. CEO, secretary general, and director) and 3 senior managers, representing in total 13 PIOs.

[1] In the information provided to representatives, we used the acronym PAOs (patient advocacy organizations) to describe patient groups. Later, after we had conducted the interviews, we changed the acronym to PIOs to reflect more accurately the way the organizations defined themselves.

The PIOs worked within the following areas: cancer (4), hereditary and genetic disorders (3), mental health (1), diabetes (1), psoriasis (1), AIDS (1), lupus (1), and primary immunodeficiencies (1). All participants signed an informed consent form (Appendix C) and the study was approved by the Norwegian Social Science Data Services (Appendix D and E). The interviews were conducted using an interview guide (Appendix F) which included open-ended questions about the PIOs' perspectives regarding PM, PM-related activities, perceived challenges with regard to the realization of PM, recommendations for the adoption of PM, and the potential roles the PIOs may play in the realization of PM. The interviews lasted, on average, 40 minutes and were audio recorded and transcribed verbatim in English and Norwegian for data analysis using a qualitative content analysis approach as described in section 4.2.

4.1.4. Paper IV - Oxford workshop

Paper IV aimed to investigate the views of PM researchers regarding how dynamic consent may help address some of the challenges usually encountered in PM-friendly research. Both the NCGC and the COST Action had an interest in investigating dynamic consent approaches. The Action called for "coordination of analysis of ICT solutions for dynamic consent and research subject participation" and the production of a working paper [19]. It was therefore decided to organize a workshop (the preferred method of consultation in the Action, following the principles of the RRI framework). In October 2015, the Research Ethics working group (WG1) of the Action and the Centre for Health, Law and Emerging Technologies (HeLEX) at the University of Oxford jointly organized an interdisciplinary two-day workshop gathering PM researchers experienced in the use of dynamic consent solutions [123]. The workshop brought together ethicists, lawyers, clinicians, medical researchers, research nurses and research participants to discuss how dynamic consent approaches may facilitate the conduct

of biomedical research. During the workshop, the participants mapped a process flowchart describing main tasks and goals for recruiting, enrolling, and maintaining participants in research studies and identified challenges usually encountered when carrying out these tasks. Then, they discussed how dynamic consent may facilitate the conduct of these tasks and attainment of the goals. Input from researchers involved in the design of dynamic consent solutions for their projects were central to the discussions. Appointed participants took notes during the workshop, and the workshop organizers gathered these notes, summarised their content, and analysed the data using a content analysis approach as described below.

4.2. Data analysis

4.2.1. Analysis of the data collected for the four papers

The same data analysis method was applied across all four studies. Each paper describes the analytical procedure in more detail. Briefly, the objective was to adopt a simple, straightforward and systematic method of data analysis that could help identify results of practical utility. All datasets were analysed using a qualitative content analysis approach. Consequently, the coding categories were derived directly from data through open and unrestricted coding [120, 124]. Each dataset was read several times and analysed manually to gain an in-depth understanding of its content.

Although the same method of qualitative content analysis was applied to all datasets, slight variation exists in the way coding and categorization was conducted between datasets. For paper I, III, and IV, the datasets already had some preliminary structure as specific questions/themes had been asked or discussed, thus providing a first indication of overarching themes. For these datasets, the substantive content of the text was extracted, coded and categorized according to overarching themes. If new codes were identified, the coding frame

was updated accordingly. Then, the text pertaining to each of these themes was condensed to reflect main points raised by the study participants. To confirm findings in paper I, the coding was conducted by several researchers. To confirm findings in paper III and IV, a short report/preliminary paper providing an overview of findings was sent to the study participants for comments, and their comments were integrated in new versions of the papers.

The dataset generated through the literature review (paper II) did not have a basic structure; some work was therefore needed to identify relevant pieces of text, and then code and categorize them according to overarching themes that had to be defined. I then reviewed the dataset to identify the type of behaviours and practices it described. These behaviours were coded and then further examined to identify overarching categories under which they could be grouped. Each category of behaviour and/or practice was then analysed in light of current knowledge regarding citizen and/or patient involvement in health care to determine the extent to which citizens and/or patients may realistically adopt, wholly or partly, such behaviours and practices.

4.2.2. Synthesis of main points raised in the papers

The four papers comprising this thesis were published and/or submitted in the time period 2015-2016. In 2016, I began to review the papers to extract main points raised in the papers, with a particular focus on points describing challenges and strategies. The objective was to identify higher-order, crosscutting themes that may need to be addressed to facilitate the realization of PM. The same conventional qualitative content analysis approach was used to conduct this work. Text from each paper describing challenges and strategies was extracted and entered into a matrix document comprising four columns (one per paper) and two rows (one for “challenges”, one for “strategies”). The text was categorized under “challenges” and

"strategies" depending on its content. Then, the text was coded and condensed. If the same challenges and strategies were mentioned in several papers and coded, the codes were merged into one code. Codes were further examined to identify overarching categories describing similar and interrelated ideas that could be set up under "challenges" and "strategies". Results from this work are provided in Table 1 (challenges) and Table 2 (strategies) in the Results section of the thesis.

5.0. SUMMARY OF RESULTS

5.1. Paper I

Budin-Ljøsne I, Mascalzoni D, Soini S, Machado S, Kaye J, Bentzen HB, Rial-Sebbag E, D'Abramo F, Witt M, Schamps G, Katić V, Krajnovic D, Working Group 1 COST Action CHIP ME IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives", Harris JR. **Feedback of individual genetic results to research participants: Is it feasible in Europe?** *Biopreservation and Biobanking*. 2016 Jun;14(3):241-8.

We investigated the views of PM researchers and experts who are members of the European COST Action regarding challenges to the feedback of individual genetic results to research participants in Europe, and potential strategies to address these challenges. To do so, we organized an email survey and an international workshop.

The members reported that many financial, organizational, and societal challenges exist that may jeopardize the feedback process and render participant access to results of potential health utility unfeasible. They explained that resources are largely missing to enable the feedback of individual genetic results to research participants in a professional way, and that legal frameworks supporting such feedback are unclear. The members identified a number of strategies to facilitate feedback processes. These strategies include the clarification of legal requirements applying to the feedback of results, the allocation of specific funds to the feedback process, the development of harmonized European best practices, the promotion of interdisciplinary and cross-institutional collaboration, the design of educational programs and IT-based platforms, collaboration with ethics committees, and the documentation of the health benefits and risks of feedback.

5.2. Paper II

Budin-Ljøsne I, Harris JR. **Ask not what PM can do for you--ask what you can do for PM.** *Public Health Genomics*. 2015;18(3):131-8.

We investigated the views of policymakers regarding the types of behaviors and practices that they envision citizens to adopt under PM. To do so, we reviewed 18 reports on PM published in English between 2008 and 2013. We examined the behaviors described in the reports in light of current knowledge regarding citizen involvement in health care.

We found that policymakers expect citizens to have a high level of health literacy and engage extensively in their own health care. For instance, they envision that citizens use electronic devices to monitor own health on a regular basis, or purchase genetic services and participate in the choice and validation of new diagnostics and therapeutics. Policymakers also expect citizens to contribute to the research endeavor to a greater extent than currently practiced, for instance by joining citizen-led networks and data sharing initiatives. Further, they envision that citizens engage in the design of PM, for instance through participation in public consultations and debates, or representation in health technology assessment bodies. Public engagement from ethnic groups and minorities, which traditionally have been underrepresented, is seen as particularly important.

Policymakers put large emphasis on educating citizens in PM, and increasing genetic awareness and interest in health management. They also envision that citizens may be involved in the design and development of educational tools to inform diverse publics about genetics and PM.

5.3. Paper III

Budin-Ljøsne I, Harris JR. **Patient and interest organizations' views on PM: a qualitative study.** *BMC Med Ethics*. 2016 May 13;17(1):28.

We investigated the views and perspectives of PIO representatives on PM, the challenges they perceived for the realization of PM, and the strategies they proposed to advance the PM agenda. To do so, we conducted semi-structured telephone interviews with leading representatives of 13 PIOs located in Europe and North America.

We found that the PIO representatives supported PM but feared that many financial and organizational challenges may delay its realization. They expressed particular concerns regarding the cost of PM, and feared that PM may be available only to the socio-economically advantaged. They also worried that increased focus on technology may be detrimental to the patient-doctor relationship. They encouraged the adoption of strategies that aim to modernize drug-licensing mechanisms, the development of research and data sharing infrastructures, and the education of health care professionals in PM. Notably, they emphasized the importance of developing principles and criteria for equitable access to PM, and taking into consideration the patients' needs, values and personal situation.

We also found that despite their varying levels of awareness regarding PM, the PIO representatives expressed willingness to engage in the PM agenda and recommended that PIOs work closely with policymakers to design PM in a way that truly addresses the needs and concerns of patients.

5.4. Paper IV

Budin-Ljøsne I, Teare HJA, Kaye J, Beck S, Bentzen HB, Caenazzo L, Collett C, D'Abramo F, Felzmann H, Finlay T, Javaid MK, Jones E, Katić V, Simpson A, Mascalzoni D. **Dynamic Consent: a potential solution to some of the challenges of modern biomedical research.** *BMC Med Ethics*. 2017 Jan 25;18(1):4.

We investigated the views of PM researchers regarding how dynamic consent may help address some of the challenges researchers encounter when they invite individuals to participate in PM-friendly research. To do so, we organized a workshop hosted by the University of Oxford, which gathered clinicians, medical researchers, ethicists, lawyers, research participants, and patient representatives with an experience in the development of dynamic consent solutions. The workshop participants discussed their use of dynamic consent, and explored in which way it may facilitate the conduct of specific research tasks.

We found that dynamic consent may provide practical and flexible solutions to challenges related to participant recruitment, the collection of informed consent, participant retention and consent management. For instance, it facilitates the recruitment of participants from different geographical regions, it enables researchers to tailor information to the participants' needs and level of health literacy, and it provides a solution for electronic storage of consents. The use of dynamic consent may be particularly useful to support research designs in which researchers need to collect updated health data from participants. Dynamic consent may also provide some flexibility in the management of regulatory changes.

5.5. Table 1 - Main challenges discussed in the four papers

Financial challenges

Lack of clarity regarding the funding of genetic tests and targeted treatments

- "Most [PIO] representatives feared that PM may be too expensive for many health care systems which are currently dealing with significant financial constraints. They experienced that patient access to conventional treatment is increasingly restrained due to cost issues (…)" [125]. (paper III)

- "Even in countries where health care is publicly funded, public payers may decide not to cover additional costs of targeted drugs and require that the patients cover such costs themselves. To illustrate our point, we refer to ongoing plans in the UK to modify pricing systems with the objective to increase prices for targeted drugs and allow drug producers to achieve sufficient return on investment. For the time being, it is still unclear who will cover potential additional costs related to the use of targeted drugs" [121]. (paper II)

Lack of funding to support the feedback of genetic research results to participants

- "Currently, there is no specific financing dedicated to support the feedback process. (…) Funding schemes for research normally do not encompass the cost of feedback. Similarly, it is unclear whether healthcare systems are willing to finance the feedback of genetic results that are not produced in a clinical setting and do not comply with clinical standards" [126]. (paper I)

Lack of clarity regarding the funding of PM infrastructures

- "(…) [The PIO representatives] expected PM to require significant up-front capital investments in equipment and infrastructures that most countries cannot afford" [125] (paper III).

- *Quote from PIO representative*: "I think that for PM we will need to develop another system because it is unrealistic that the government will have enough money to cover everything, (…), they have a problem with the financing". (raw data paper III)

Limited financial ability of some groups of patients and citizens to endorse PM

- "Most [PIO] representatives (…) observed that new targeted drugs that are launched on the market are so highly-priced that patients can hardly afford them unless their cost is fully covered by payers". [125] (paper III)

Organizational and regulatory challenges

Lack of good frameworks and tools to support the feedback of research results

- "Professional guidelines and best practices for the feedback of results to research participants are largely missing in Europe, with the exception of a few countries such as the United Kingdom and Norway. Where guidelines do exist, they are often general and do not offer guidance regarding the specific genetic variants for which feedback of results should be provided to participants". [126] (paper I)

- "Providing genetic results to research participants within a qualified professional framework may be difficult as there are few genetic counselors and clinical geneticists in Europe, in particular in rural regions. Furthermore, the qualifications of genetic counselors often vary due to the lack of standard training requirements" [126] (paper I).

- *Quote from CHIP ME representative*: "The [feedback of results] may be more feasible for clinical biobanks that already operate closely in hospital districts, but is much more challenging for research biobanks [due to] lack of doctor-patient relationship, clinical laboratories, and health care facilities". (raw data paper I)

Lack of flexible tools for inviting and retaining participants in research

- "(…) Research participants often do not understand the content of the information sheet or the consent form for the study, particularly if the consent form is lengthy and includes complex terminology". (…) "If new research needs arise that were not foreseen and included in the original consent document, collecting new consent from research participants may be expensive and burdensome, particularly if additional consent requires face-to-face interaction or the mailing of paper consent forms. If multiple consents are collected over time, keeping records of these consents can be complicated, particularly in cohort studies, or in projects spanning several years and multiple iterations where paper consent forms are stored in several institutions". [127] (paper IV)

Lack of efficient drug approval policies

- *Quote from PIO representative*: "Understanding from an end-user perspective the value of a novel intervention is something that systems are very bad at and again we've been working to persuade [approval] bodies of the necessity of broadening their approach to the concept of value". (Raw data paper III)

Limited knowledge of PM among health care professionals

- "Several PIO representatives also explained that general practitioners often do not understand the specificities of disease, and suspected that many are insufficiently trained in genetics to use PM strategies in their medical practice". [125] (paper III)

Ethical and societal challenges

Limited health and technology literacy of patients and citizens

- "Empirical data show that individuals who receive information about their personal genetic risk predisposition often fail to interpret it, either overestimating or minimizing it (…)". [121] (paper II)

- *Quote from PIO representative*: "People do not understand information well enough, this is where we see a big job for the patient organizations and patient groups in each of the countries in Europe, (…) educate, bring awareness of how important (…) the different kinds of medications are, when they are supposed to be used and for what, (…) there is a reason why it has been prescribed (…). There is a huge communication aspect that we have just picked up" [125]. (Raw data paper III).

Varying engagement of stakeholders in PM/awareness of PM

- "Paradoxically, groups of population who are given the opportunity to contribute to the scientific endeavor may not be willing to do so. For instance, 44% of Europeans are not willing to provide personal information to a biobank, and 67% prefer being asked to consent to every new piece of research instead of consenting only once to a broad range of research uses". [121] (paper II)

- "(…) Several [PIO] representatives confessed that PM was a topic that had not been thoroughly discussed in their organization. Most PIOs did not use the terms PM and did not specifically mention PM in their strategic documents with the exception of some cancer PIOs". [125] (paper III)

- "In most established research projects, the participants are not aware that genetic results may be provided to them, as this possibility was not mentioned in the original informed consent".[126] (paper I)

Underrepresentation in research of some groups of patients and citizens

- "(…) Ethnic groups and minorities are often excluded from research and deprived of the opportunity to contribute and benefit from medical progress. As an illustration, 9 out of 10 genome-wide association studies are reported to be conducted on populations of European descent, unveiled gene-disease correlations therefore primarily applying to Caucasians". [121] (paper II)

Patient values and circumstances insufficiently taken into consideration in health care

- *Quote from PIO representative*: "I think it is essential that the patient remains at the center and that he doesn't become a data or an entity; it's really a patient and a face

and the [health care professionals] need to treat that patient, that's the main goal". [125] (Raw data paper III)

Risk that important non-genetic research may be neglected

- "(…) One [PIO] representative worried that priority may be given to genetic research, not because it may lead to the most useful results, but because it is technologically exciting and may benefit the commercial interests of pharmaceutical companies. This representative emphasized the importance of also conducting other types of research such as social and behavioral research". [125] (paper III)

Risk of genetic discrimination

- *Quote from PIO representative*: "If we, sometime in the future, find genes that you would like to have and genes you would prefer not having, it is clear that it may contribute to creating A-people and B-people. From the moment our genes become a question of value, it may create differences between people. Some people may be worth more than others and then we are back to the 30's, so from a historical point of view, this is important". [125] (Raw data paper III)

5.6. Table 2 - Main strategies discussed in the four papers

Development of sustainable funding mechanisms for PM

Allocate specific funding to PM-related activities

- "Funding schemes should include specific funding that can be granted to researchers and healthcare services that establish collaboration to provide results to participants. The expected cost of the feedback process should be determined as early as possible in research projects and specified in research applications". [126] (paper I)

- "The [PIO] representatives also recommended allocating specific funding to the implementation of PM, for instance to develop necessary biobanks and data sharing infrastructures". [125] (paper III)

- "A budget for the development or use of [dynamic consent] should be included in research funding applications. [127] (paper IV)

Implement mechanisms to limit drug prices

- "Limitations may also be put on the pricing of targeted drugs. Such limitations, albeit controversial, can be more acceptable for pharmaceutical companies if financial incentives are offered, for instance through internationally financed funds, for the development of targeted drugs that benefit large numbers of people, such as drugs used for the treatment of infectious diseases and cancer" . [121] (paper II)

Implement PM gradually through pilot projects including the neediest patients

- *Quote from PIO representative*: "We thought that for patients in phase I or II for whom there is no established treatment option anymore, that they could receive personalized treatment through sequencing, DNA and molecular profiling (…). We want it to be a personal offer, not just random patients here and there, but that all patients in Phase I or II situations who wish such treatment. This is something we've discussed". (Raw data paper III)

Aim for equitable patient access to PM

- *Quote from PIO representative*: "I think that [there are] human rights issues, key populations are at this moment having difficulties in getting a good standard of care (…). We should make sure that those in need get access and not only those who have the financial capacity to do so". (Raw data paper III)

- *Quote from PIO representative*: "If you prioritize individualized medicine, then I suspect that it will be for the few rich [people] and not for all (…). (Raw data paper III)

- "(…) Systematically mapping disparities in the access and use of genetic tests and targeted therapies and making the results publicly available may motivate changes in policy in areas where disparities are the most striking". [121] (paper II)

Develop low-cost programs to broaden patient and citizen access to PM

- "Such programs may, for instance, consist of publicly funded annual health check including mapping of genetic risk predisposition and lifestyle intervention provided free of charge. In general, low-cost solutions should be preferred to expensive solutions. For instance, health-care providers may prioritize investment in wireless medicine, which is cheaper than traditional technology and offers the possibility to perform medical tests remotely and at reduced cost while simultaneously limiting the number of medical consultations". [121] (paper II)

Design of modern tools and organizational structures for PM

Explore and develop dynamic consent tools

- "Participants' preferences regarding the use of interactive and cost-efficient IT-based tools such as dynamic consent and web-based and telephone-based platforms for access to genetic results should be explored" [126] (paper I).

- *Quote from PIO representative*: "We are going to need new forms of consent that are granular and dynamic and things like that so…PM is not going to be technically very hard, it just need the right components (…)." (Raw data paper III)

- "Establishing a culture of ongoing communication between researchers and research participants is increasingly demanded by patient advocacy groups and research participants who would like to be consulted about third party access to their data and the management of genetic research results". [127] (paper IV)

Develop frameworks for the feedback of genetic research results to research participants

- "European researchers, research funders, research and healthcare institutions, medical societies, and community representatives should collaborate at a European level to develop harmonized European best practices for the feedback of genetic research results to research participants. These discussions should take into consideration the specific needs, contexts, laws, and cultural norms of European research. Recent recommendations for the management of genetic results in research settings (…) and clinical settings may be used to guide such work". [126] (paper I)

- A dynamic consent platform may also enable participants to consent online to the feedback of genetic research results, even years after a project starts. (…) Enabling participants to consent to the feedback of their genetic research results may be useful

in research projects planning to recruit participants in future follow-up studies on the basis of their genotype. [127] (paper IV)

Facilitate stakeholder collaborations

- "Expert networks of clinicians, molecular biologists, bioinformaticians, and geneticists should be established in research projects to facilitate the feedback process". [126] (paper I)

- *Quote from PIO representative*: "We are urging to have much better epidemiology, more consistent research would be nice, it means a lot if you have one country dealing with (…) a rare disease while the neighboring country is not". (Raw data paper III)

- "The [PIO] representatives recommended the development of inter-PIOs collaborations to enable the organizations which are more knowledgeable about PM to help others join the PM endeavor". [125] (paper III)

Develop modern drug licensing mechanisms

- "[The PIO representatives] believed that modernizing drug licensing mechanisms is necessary to enable quicker access to targeted drugs. Adaptive pathways mechanisms were mentioned as a potential approach to improve timely access for patients to new medicines". (paper III)

- *Quote from PIO representative*: "The European Medicines Agency creates a shift in the process by which medicines are brought to the market for authorization by adaptive licensing mechanisms, and that is particularly suited to PM because instead of having to do the traditional large-scale multicenter randomized double blind trial, you could bring medicines to use in patients at an earlier stage of development and in a much more targeted way (…). This approach is absolutely, I think, the right way forward". (Raw data paper III)

Conduct more research

- "(…) Research programs may be developed in close cooperation with local communities to include a wider variety of populations. For instance, clinical trials which focus on genetic variation instead of 'race' or 'ethnicity' could be designed". [121] (paper II)

- "The [PIO] representatives believed that more research should be conducted to understand the causes underlying disease, investigate the mechanisms of side effects, explore the consequences of living a long time with a specific treatment and develop strategies to improve the quality of life of patients". [125] (paper III)

Develop PM infrastructures

- *Quote from PIO representative*: "As an organization we are interested in the development of biobanks because we see that it can promote and create new insights

and knowledge about the causes of [disease]". (Raw data paper III)

- *Quote from PIO representative*: "There needs to be the infrastructural investment in supporting a personalized medicine approach, there needs to be training in re-skilling or bringing new practitioners with the necessary skills and knowledge to apply this new approach, and there needs to be attention to the whole health economics issue to make sure that developing effective drugs for smaller and smaller populations does not just become financially unsustainable". (Raw data paper III)

Education and engagement of key stakeholders in PM

Educate healthcare professionals

- "Educational programs should be developed to enhance genetic knowledge among healthcare professionals such as medical doctors, clinicians, clinical ethicists, psychologists, nutritionists, nurses, biologists, and laboratory geneticists who are strategically placed in the community and may potentially contribute to the feedback process. Such programs could for instance build upon the common set of core competences in genetics recently proposed by the European Society of Human Genetics". [126] (paper I)

Engage citizens in PM

- "Researchers should develop mechanisms to discuss with citizens and research participants the modalities of the feedback of results, for instance through public consultations, debates, and social networks". [126] (paper I)

- "Researchers will benefit from having more engaged, committed and productive participants in their research; such participants are useful as demonstrated by the successful contributions to research made by online communities of patients." [127] (paper IV)

Engage PIOs in PM

- "[The PIO representatives] recommended engaging patients and patient representatives as early as possible in the planning and design of clinical trials (…)" [125] (paper III)

- "The [PIO] representatives envisioned increased collaboration between PIOs and research groups, medical bodies, drug developers and policy-makers, nationally and internationally to encourage the development of PM. They also believed that patients and lay representatives should be more frequently invited to join research ethics committees and drug approval boards". [125] (paper III)

6.0. DISCUSSION

The work in this thesis was conducted through two projects – the NCGC and the COST Action – developed in the wake of the vision for PM. Following the principles of the RRI framework, these projects shared a common interest in exploring stakeholder perspectives on the integration of PM in health care services. Thus, they provided a strong foundation for the work comprising this thesis. We explored the views of key groups of stakeholders – PM researchers, policymakers, and patient and interest organizations – regarding specific themes of relevance for PM with the objective to develop concrete guidance that may inform the PM agenda. This work provides new insight into the variety of challenges that the stakeholders experience "on the ground" and perceive as potential barriers to the development of PM in European health care systems. Our research also highlights the views of PIOs on PM; views which, until now, have hardly been explored. We learned that concerns exist regarding the sustainability and practical feasibility of PM. Our findings also reveal a high degree of consensus among the key groups of stakeholders we targeted regarding strategies needed to foster and facilitate PM, although their views vary on educational strategies targeting patients, citizens, and health care professionals. A more detailed discussion of our main findings is provided below.

6.1. Plethora of challenges

Our research results show that many financial, organizational, regulatory, ethical and societal challenges (summarized in Table 1) exist that may negatively affect the PM agenda. While some of these challenges have been identified in previous studies, others have received limited attention. Research groups have previously raised concerns regarding the lack of funding to support the feedback of genetic research results of potential health results to

research participants[128, 129]. Our research confirms that such issue is expected to be broadly encountered in Europe [126]. Similarly, concerns are regularly raised in the public debate regarding the health care systems' ability to finance the purchase of genetic tests and targeted treatments [88, 130]. These concerns are largely motivated by recent restrictions placed by health care systems on the prescription of new targeted drugs [131], which have provoked heated discussions regarding the reasons for high drug pricing [88], and led to calls for a greater sustainability of drug prices [132]. Our results from paper III show that PIOs largely share these concerns and question the financial sustainability of high drug prices and PM [125].

Our research also reports the existence of organizational issues due to the absence of clear and flexible policies, mechanisms and tools to perform tasks, and a limited culture for collaboration across disciplines. For instance, findings from paper I show that the necessary organizational structures to enable the feedback of results in a professional fashion are often not in place in research projects [129]. Previous studies have reported difficulties in the establishment of collaborations between researchers and clinical genetic services to enable the feedback process [133, 134] due to limited available expertise on genetic testing among health care professionals [103] and some reluctance toward the adoption of genetic tests [101]. Preliminary results from the recently conducted Genetics Clinic of the Future survey seem to support our findings and show that policies for the feedback of results are largely missing in Europe [135]. In addition, organizational challenges exist that are related to the conduct of biomedical research. As discussed in paper IV, established standards for the collection of informed consent and the recruitment and retention of research participants are insufficient and unfit to satisfy the needs of modern and PM-friendly research [127]. Discussions are currently taking place within the scientific community regarding the importance of developing

new and innovative approaches for the collection and management of informed consent that are more efficient and flexible than current practices (see section 2.4).

Our research reports the existence of numerous ethical and societal challenges that may negatively impact PM. A critical challenge relates to the health care professionals', patients', and citizens' ability to endorse PM. In paper III, the PIO representatives explained that health care professionals often do not have the necessary prerequisites to understand the basics of complex or rare diseases [125]. Paper I reported that research participants often are not aware that genetic results may be produced about them, and may not be ready to receive them [126]. Paper II discussed that patients and citizens, contrary to what policymakers and promoters of PM expect, may have limited ability and interest in engaging more strongly in the management of their health, or in participating in PM research [121], an issue that was also discussed with the PIO representatives in paper III [125]. This is in line with results from previous studies which show that patients and citizens' have limited health and technology literacy [136], varying understanding of the meaning of genetic information [137], and insufficient awareness of research [138].

Importantly, our research identified some specific challenges that, until now, have received limited attention. For instance, results from paper III show that PIOs have varying and sometimes limited knowledge of PM [125]. While some PIOs use the concept of PM, and outline strategies for PM in their central documents, others do not have an in-depth knowledge of PM and do not use PM as a concept in their work. This stands in contrast to the assumption of policymakers and promoters of PM; in their PM reports, they often describe PIOs as active players that contribute to, for instance, the development of cutting-edge research projects [6]. Our results suggest that, as I will discuss later, further effort should be

devoted to greater engagement of PIOs in the PM endeavour in order to benefit from their expertise and their networks. Our research results also show that PIOs have concerns, not only regarding the financial and organizational aspects of PM, but also regarding how PM may impact the way one deals with health and disease. More specifically, they fear that increased focus on the genetic and molecular aspects of disease may negatively impact the patient-doctor relationship. This concern is acknowledged in the literature but, to my knowledge, has hardly been addressed in empirical studies on PM.

Concerning many of the challenges discussed in the papers, one could question whether some challenges are more critical than others. For instance, isn't the health care systems' limited ability to purchase genetic tests and targeted treatments (an issue raised by the PIO representatives) a more important challenge than the lack of online communication platforms for interaction between researchers and research participants? Although ranking challenges by order of importance may be necessary, it was not my objective to do so when conducting this work. Rather, I was interested in gaining an overall understanding regarding the diversity of challenges that may affect the realization of PM, directly or indirectly. Furthermore, it would not have been possible to weight or "quantify" challenges based on qualitative studies involving a limited sample of stakeholders. However, I believe that the challenges we identified in our work are all relevant and interrelated. As an illustration, if researchers do not have flexible tools for the conduct of their PM research, this may potentially delay or impede the discovery of new medical treatments and negatively impact people's access to PM over time. This illustrates that focusing on one type of challenges, for instance, financial challenges, may not be enough. Enabling PM requires navigating through a web of challenges, and developing strategies accordingly.

6.2. Variety of strategies

Numerous strategies were discussed in the papers that may contribute to address these challenges. As summarized in Table 2, these strategies are primarily related to the development of long-term, comprehensive, inclusive and sustainable funding mechanisms for PM, the design of concrete tools and modern organizational structures for PM, and the education and engagement of key stakeholders in PM. Similarly to the challenges identified, many of these strategies have already been at the centre of discussions among policymakers and promoters of PM as illustrated earlier in section 2.4. However, several additional lessons can be drawn from our findings as described below.

6.2.1. Convergence of views

Our findings suggest that the groups of stakeholders with whom we engaged share common views regarding many of the strategies to adopt to move the PM agenda forward. As an illustration, the PIO representatives supported initiatives from policymakers to modernize drug approval mechanisms that were experienced to be too burdensome and time consuming [125]. Recently, efforts have been made to simplify bureaucratic requirements for drug approval [139], for instance through the implementation of innovative mechanisms such as adaptive pathways (mentioned in section 2.4), a progressive approach cited by some PIO representatives in paper III. The PIO representatives also called for increased efforts to contain costs of targeted treatments and genetic tests [125]; something that policymakers are trying to achieve by testing new ways to limit drug prices. One example is the use of value-based approaches for drug pricing under which drug reimbursement is tied to the actual value that the drug brings to health care systems [140]. Using such approaches, drugs that offer limited benefit (e.g. overall patient survival of less than one month) are priced lower than

those that offer long-term benefit (e.g. additional years of life). Value-based pricing, an approach also cited by the PIO representatives, is currently being explored in the United Kingdom and may contribute to contain costs of targeted treatments and genetic tests over time [141]. The PIO representatives also largely agreed with policymakers regarding the importance of developing infrastructures and tools for data sharing, and the need for conducting more genetic and epidemiological research [125]; policymakers have continuously encouraged the development of biobanks and research programs during last decades (see section 2.4).

Another area of convergence relates to the development of new and modern approaches for the collection and management of informed consent, and for communication and interface between researchers and research participants. During our consultations for the work presented in papers I, III and IV, PM researchers and PIO representatives repeatedly mentioned dynamic consent as a tool to implement in research projects [125-127]. Dynamic consent is a personalized, online consent and engagement tool which primarily aims to enable research participants to modify their consent preferences over time [115]. In addition, it can be used to establish two-way, ongoing communication between researchers and research participants [142]. For instance, researchers can provide regular updates about research discoveries, invite participants to discuss the research through online forums, and the participants can upload additional health information or fill in health questionnaires whenever needed [127]. As discussed in section 2.4, policymakers have encouraged the development of new forms of consent and communication between researchers and research participants over the last years. This is interesting knowing that, traditionally, there has been some reluctance toward fostering an ongoing researcher-research participant relationship [143]. For instance, in biobank research, the normal practice has been to collect the one-time, paper-based consent

of research participants to the broad use of their biological samples and associated health data within broadly defined research areas. No other forms of communication are usually expected to take place between researchers and research participants after the consent is collected, with the exception of some feedback of general information regarding the research, for instance through a Newsletter or a website. Increased interest in dynamic consent, also among PM researchers involved in biobanking [144], could be explained by a recognition that, in a continuously changing research environment, managing research projects is becoming increasingly difficult if no possibility exists to interact with research participants, for instance, to know whether they support data sharing, or to collect enrichment data. Increased interest in dynamic consent may also be explained by a recognition that research participants have an active role to play in research, and can contribute to improve its quality and relevance [145].

Finally, our findings suggest that there is some consensus among stakeholders regarding the need to facilitate interdisciplinary, cross-milieus collaborations, and challenging the traditional schism between research and health care. As reported in paper III, the PIO representatives explained that health care systems should do more to support and facilitate the recruitment of patients in clinical trials [125]. In paper I, the PM researchers recommended the establishment of expert networks spanning across clinical and research milieus in order to facilitate the feedback of genetic research results to research participants [126]. Policymakers increasingly encourage initiatives to create bridges between clinical and research milieus. As an illustration, in the recently launched Genomics England project [146] which aims to sequence the DNA codes of a 100,000 patients, expert networks similar to those recommended by the COST Action members have recently been implemented. These networks, called Clinical Interpretation Partnerships (GeCIP) [147], enable clinicians and researchers to work together to interpret the genetic and genomic data produced in the

research project and improve the clinical care provided to patients, but also to undertake complementary research [147]. The development of such networks is motivated by the observation that maintaining a clear separation between research and health care, as traditionally practiced, may no longer serve the interests of patients [148, 149]. As stated by Lyon and Segal, "the goal [of research] is increasingly patient-focused and intended to find information of clinical benefit to the participant, indeed blurring the lines between "patient" and "research participant" [148]. Genomic research has the potential to contribute to yield a diagnosis [150] or identify a course of treatment within a clinically actionable time frame [148]. If such applications of genomics are to become common, increased collaboration between research and clinical milieus makes sense. However, as I will discuss later, it may also lead to a number of consequences for patients and research participants that should be considered.

6.2.2. Divergence of views

Although our key groups of stakeholders shared common views regarding many strategies to address challenges, our research also highlighted that there is some divergence of views regarding specific aspects of these strategies. For instance, policymakers seem to put more weight on educating citizens in PM than the PIO representatives do. As explained in paper II and in section 2.4, policymakers largely recommend to educate citizens in PM and basic concepts of genetics [121]. They consider this necessary to enable citizens to engage more strongly in the management of their health and in PM research, for instance by using health monitoring devices and collecting own health measurements [151]. Policymakers emphasize that such engagement is essential for the realization of PM. As stated in a European PM report, "If European citizens are to take advantage of the opportunities provided by PM and become active participants in its continued refinement and implementation, health literacy in

the wider population must be actively promoted" [33]. Our results are based on the review of a limited number of reports, and a review of reports in other languages than English may have provided other results. However, the reports we scrutinized were produced by well-recognized, national and European institutions involved in the realization of PM, thus suggesting that the importance of educating citizens in PM is a view that is widely shared by policymakers.

To educate citizens in PM, policymakers fund a variety of public involvement programs spanning from the dissemination of educational videos and the conduct of laboratory tours, to public forums and science festivals [80]. Interestingly, while the PIO representatives thought that such educational efforts were useful, they did not see them as essential. They rather believed that citizens naturally develop awareness about PM as targeted treatments and genetic tests are becoming more broadly used in health care systems [125]. The PIO representatives also appeared to be less optimistic than policymakers regarding the extent to which patients and citizens can actually engage in PM, and explained that behaviours are not solely a consequence of the individuals' level of health literacy, but also depends on their personal situation, values, and socio-economic background [125]. For instance, patients who have been waiting for a diagnosis for years are usually more motivated to understand genetics than others, who may have a higher level of health literacy, but are not confronted with the same type of health challenges. Our results suggest that the PIO representatives are more supportive of educating patients during the course of health care in a targeted way, i.e. enabling them to "learn by experiencing", rather than conducting large-scale information campaigns targeting citizens and the public. However, this finding would have to be confirmed by further research.

Another potential point of divergence in views between our stakeholder groups concerns the education of health care professionals. In paper III, the PIO representatives explained that health care professionals often do not understand the specificities of disease and have limited knowledge of genetics, and recommended to educate health care professionals in PM [125]. As explained in section 2.4, policymakers have called for increased education of health care professionals in genetics and molecular medicine [6, 45], a point also raised in paper I [126]. Apparently, our stakeholder groups largely agree on this issue. However, the PIO representatives worried that increased focus on genetics in the curricula of health care professionals may negatively impact the patient-doctor relationship if it leads professionals to reduce patients to their genetic profile or to "a bunch of molecules" [152]. The PIO representatives believed that taking the patient's values, beliefs, and preferences into consideration is at least as important as understanding the molecular mechanisms of her disease [125]. This concern has been raised previously in the literature by authors who emphasize that defining an individual's health in "technoscientific, […] quantifiable and controllable" terms may be comprehensive from a biomedical point of view but is too reductionist from a humanistic point of view [53]. Patients are more than the sum of their molecules, and their personal situation and life experiences have to be taken into consideration. The PIO representatives explained that this is an approach to medicine that they have been struggling to put forward for years, with limited success [125]. Although this was not discussed in-depth with the PIO representatives, our findings suggest that more effort should be placed on educating health care professionals in PM in ways that are more nuanced and holistic, taking into consideration all aspects of a patient's health and not just her/his biology.

6.2.3. Calls for the development of hands-on tools and mechanisms

Another finding that emerges from our research is that stakeholders think in very practical terms, and call for the development of a number of concrete, hands-on tools and mechanisms that may facilitate their work, and help advance PM. As an illustration, in paper I, the PM researchers suggested that harmonized European guidelines for the feedback of genetic research results to research participants should be developed [126]. To date, international guidelines exist which primarily recommend the feedback to research participants of clinically actionable research results, i.e. results of potential health utility that clinicians can use to guide prevention or treatment [153-155]. However, most of these guidelines do not provide practical and detailed guidance regarding, for instance, which criteria to use to determine the "actionability" of results, which information about genetic variants to feed back to participants, and how to organize the feedback process [153-155]. Guidelines exist in Europe for reporting genetic results in clinical settings [156-158] but these guidelines encourage researchers to limit the likelihood of detecting clinically useful findings by applying filters when making use of genome sequencing technologies [156-158]. This strategy may be applicable in clinical settings but is not suitable for researchers who aim to discover new gene variants and may want to study as much of the genome as possible; the probability that they "bump into" variants of health utility is therefore higher than in clinical settings. European clinical guidelines also primarily focus on discussing the technicalities of genetic testing but do not explain how to handle, for instance, different types of potentially clinically actionable variants [157].

The guidelines of the American College of Medical Genetics and Genomics (ACMG), published in 2013 and 2016 and developed for use in clinical settings, are one important exception to the general approach adopted in international documents [159, 160]. These

guidelines differ from other guidelines in the sense that they provide a list of pre-determined genetic variants that are known or expected to be pathogenic and that are recommended to be reported to patients undergoing clinical genome sequencing. During our workshop, we did not discuss in details the content of harmonized European guidelines for the feedback of genetic research results to research participants with the PM researchers. However, their request for more guidelines may indicate that concrete and specific guidance is needed at a greater level of granularity than is currently provided in today's documents. This could be interpreted as a demand to develop harmonized European guidelines that are more in line with the ACMG guidelines [159, 160]. If developing a list of reportable variants is what the PM researchers had in mind, this would represent a change with respect to the situation presently prevailing in Europe - pragmatic guidance at a general level. This may, however, prove to be controversial as the ACMG guidelines have been widely criticized for being too top-down and short-sighted, not taking into consideration the patients' situation, and encouraging opportunistic screening [161]. Furthermore, this would contradict results from a recent cross-national study conducted among genetics and genomics experts who, when asked about the type of guidance they would like to receive, agreed that general guidelines are preferable to a list of specific variants to report [162]. As I will discuss later, developing such a list would also generate a number of challenges. For instance, it may be difficult to reach agreement regarding the significance of the variants, and the types of variants to list according to latest scientific developments.

The stakeholders also called for the development of concrete mechanisms for broad and equitable access to PM. In paper I, the PM researchers expressed concerns that if harmonized European guidelines for the feedback of research results to research participants are not in place, situations may arise where "[…] some projects provide results to their participants,

while other similar projects do not provide results or decide to apply different criteria for doing so" [126]. This may lead to inequity in participant access to potentially clinically actionable or lifesaving information. In paper III, the PIO representatives emphasized that equitable access to PM should be the guiding principle for delivering PM to patients and citizens [125]. They experienced that patient access to new diagnostic tests and targeted drugs is fragmented and emphasized that access to PM should not depend on the patients' financial ability to pay for such access but rather take place on the basis of the patients' specific needs [125]. We did not discuss in-depth with the PIO representatives or the PM researchers which mechanisms to put in place to enable broad and equitable access to PM. However, we referred in paper II to some mechanisms that could be developed to adjust for potential disparities in access to PM, and reach out to those populations who normally do not have the prerequisites to benefit from new medical developments [121]. Mechanisms for instance include the implementation of community based participatory research programs, which contribute to inviting communities usually not included in research to participate in research [163], or the development of free and low-cost programs for accessing genetic testing. As an illustration, some public hospitals in the United States offer free BRCA testing and genetic counselling to patients who usually have limited access to health care [164]. Facilitating broad access to genetic testing can not only be done through the development of such mechanisms but also by "creatively delivering genomic risk information" [165]. For instance, mechanisms exist, which were not discussed in our paper but that policymakers are currently considering, that may encourage people to endorse genetics and change behaviour. This for instance includes the delivery of health insurance vouchers upon submitting proof of follow-up with a counsellor [166] or the use of advisory notices accompanying genetic tests to inform that people undergoing similar tests have changed their life-style [165].

Although the mechanisms described above may contribute to facilitate access to PM, enabling PM is expected to raise a number of questions regarding, for instance, prioritization. Many considerations have to be taken when determining who gets access to what and who needs additional support to receive such access: the patients' needs are clearly important but hardly any health care system has the financial resources to address all the needs of all patients without having to set limits and apply criteria for prioritization [167]. Furthermore, principles other than equitable access or addressing the patients' needs, such as the cost-effectiveness of an intervention, may also have to be considered when deciding who gets access to what. Discussing all issues surrounding equitable access to PM requires extensive work. However, a lesson that may be learnt from our consultations is that broad and equitable access to PM seems to be a recurrent concern among stakeholders. This suggests that more discussions are needed, probably at European level, following the principles of the RRI framework, to develop an overall, concrete and clear strategy for such access that aligns with European values for health care.

Finally, our research shows that stakeholders call for the development of concrete mechanisms for the funding of PM. In paper I, the PM researchers recommended to allocate specific funding of research grants to enable researchers and health care services to feedback genetic research results to research participants [126]. In paper III, the PIO representatives called for the allocation of specific funding for the development of PM, including biobanks and data sharing infrastructures, although they suspected that allocating such funding would be challenging [125]. It might not be surprising that central stakeholders of PM think that PM should receive more funding, and PM has already received a lot of attention from funders, including from the European Union. However, such call for funding raises an interesting question: what is sufficient funding to support the realization of PM? This was not discussed

in details in our consultations. One observation is that the funding of PM research and PM infrastructures, although existing, at least, in some European countries, is often fragmented and short-sighted. As an illustration, genomics research is generally funded through programs spanning three to five years. The same applies to the funding of biobank and data sharing infrastructures. This short-sightedness with regard to funding may have negative side effects as experienced by large-scale research projects which have been hindered to exploit valuable research data after project end because financial resources were lacking [168]. Generally, possible strategies pertaining to long-term funding of PM need to receive more attention in the public debate [169]. Until recently, the promoters of PM have primarily discussed practical tools and infrastructures to develop to enable PM, and shown limited interest in discussing the financial sustainability of PM. This could be because PM is assumed to reduce health care costs as the quality of treatment increases and less money is spent on developing drugs that do not work [170]. However, to achieve such savings, large investments must be made upfront. The feedback we received during our consultations is that significant concerns exist regarding how such investments may be secured in the future, and which areas of PM should be given priority in a context where health care systems are increasingly struggling to finance their core activities.

6.2.4. Feasibility and potential implications of strategies

In paper I-IV, many different strategies were discussed. Due to our choice of work method, the papers did not provide an opportunity to explore each of these strategies in-depth. However, it is interesting to look more closely at the specific strategies that were discussed and question their feasibility and potential implications.

Development of harmonized guidelines for the feedback of genetic research results to research participants

Conducting a 1-day workshop to discuss the feedback of genetic research results to research participants with PM researchers did not give us enough time to discuss how to develop such guidelines. However, a number of practical challenges are expected to arise if, as suggested earlier, more detailed guidelines than those currently existing were to be developed. For instance, which genetic variants or categories of variants, if they were to be listed, should be included in such guidelines? Currently, there is no established consensus regarding which variants are actionable and should be fed back to research participants [162], although efforts are being made internationally to categorize variants in a systematic way. Issues related to misled interpretation of findings, false-positive findings, and the harms they may create, would have to be considered more thoroughly [171]. Initiatives such as the BRCA Exchange provide researchers with "curated expert interpretations and some supporting evidence for genetic variants identified in BRCA1 and BRCA2", the genes associated with increased risk of breast and ovarian cancer [172]. However, these initiatives are for the most part in their starting phase and currently target only a few genes.

Should guidelines focus only on variants of documented pathology, or should they also indicate how to handle variants of uncertain significance (VUS) [173]? Currently, most variants unveiled in research are VUS that are difficult to categorize, although it may be found in the future, as new knowledge accumulates, that they are clinically important [173, 174]. Studies have documented that research participants have an interest in learning about VUS; this could indicate that a restrictive view on which variants to report may not always be appropriate [175, 176]. However, reporting VUS may also be ethically dubious if it cannot provide guidance regarding a potential course of medical action. Clinical geneticists regularly

experience that the borderline between clinically significant variants that are worth reporting, and less important variants, remains blurry [177]. These questions illustrate that establishing a pre-determined list of genetic variants to report could be challenging.

Should the guidelines describe how to organize the feedback process in research settings? In general, some flexibility in the timing and the way results are provided is expected to be appropriate as the preferences of research participants regarding the feedback process are often context-dependent, and the resources of researchers vary [178]. For instance, some researchers may be able to establish collaborations with treating clinicians and genetic counsellors to provide results to research participants, as suggested by the PM researchers we consulted, while others may have to use alternative methods of communication such as telephone for efficiency and budgetary reasons [179]. Some researchers may also encounter problems if, as emphasized in paper I, the research participants are not aware of the possibility to receive results, and have not consented to feedback. In such situations, procedures have to established to inform participants about the potential for such feedback [180]. When designing feedback procedures, it may also be important to be aware that creating "quasi-clinical settings for return of clinically relevant results" to research participants [181] could prejudice the research participants if it leads them to overestimate the benefits of research participation [182]. Developing harmonized European guidelines for the feedback of genetic research results to research participants may require making decisions regarding the level of granularity of the guidelines, the different aspects of the feedback process to be covered in the guidelines, and the extent to which the guidelines may offer some flexibility to enable researchers to adapt to local circumstances.

Implementation of dynamic consent platforms in research projects

As explained earlier, our research results show that stakeholders enthusiastically support the development of dynamic consent tools in research projects. To date, dynamic consent has been rolled out in a few research projects and recent reports show that research participants appreciate its use [183-185]. However, a main challenge encountered with dynamic consent is the still limited amount of empirical data to demonstrate its effectiveness and capacity to reach out to all. For instance, although research participants show interest in using dynamic consent platforms, it is unclear whether such interest can be maintained over time, in particular if the use of the platform puts many demands on participants, or whether "consent fatigue" may arise [118]. This may be a particular salient issue if individuals participating in several research projects have to use different dynamic consent platforms; a problem that could potentially be addressed by developing national platforms for dynamic consent [114]. One may also question whether the use of dynamic consent may jeopardize the quality of the research if many research participants have the possibility to withdraw their consent by simply clicking on a button, thus compromising the reliability and reproducibility of the data [186].

It is also unclear whether all groups of research participants will use dynamic consent. For instance, participants originating from socio-economically disadvantaged groups of populations, who have less experience with or access to technology, may have difficulties in using dynamic consent [187], as illustrated by a recent study which shows that these groups have a limited use of web-based tools for research despite high reported interest [188]. In such cases, it may be useful to combine the use of online tools with other solutions such as personal contact to increase the likelihood to reach out to all [188]. Another recently published study shows that participants recruited in biobank research through an electronic consent platform are often less diverse in terms of ethnicity and education than those enrolled

during in-person interactions with research staff [117]. One can also reasonably suspect that the elderly, who often have limited technology literacy, are less likely to use an online platform than younger generations. The same applies to severely ill patients who have been through series of interventions and are physically and cognitively weakened but choose to participate in clinical research: to which extent can they be expected to use an online platform? It could be argued that dynamic consent is not meant to replace all other forms of communication between researchers and research participants but can be combined with other approaches (e.g. personal contact) depending on the context of the research and the research population. Generally, it may be wise in some projects to implement dynamic consent progressively and in parallel with traditional communication methods in order to enable participants to familiarize with the platform.

Although our research results document interest in dynamic consent, we should acknowledge that these results might have been influenced by our choice of method. We collected our data for paper IV during a workshop gathering experts working to develop dynamic consent platforms in their projects. These experts presented their work and the types of dynamic consent platforms they had developed in their projects. One could argue that researchers who contribute to the development of dynamic consent solutions cannot objectively assess the usefulness of such solutions. However, they are also the ones who have concrete experience of the use of dynamic consent and can give some feedback regarding what works and what does not work in "real-life" for their projects. Such insight cannot be obtained from researchers who do not have an experience of the use of dynamic consent but only have a conceptual understanding of it. As the complexity of the research increases and researchers are confronted with new situations that require having a dialogue with research participants, it seems inevitable that tools such as dynamic consent will be needed in research projects. Thus, implementing dynamic consent tools may be ethically desirable as it reinforces the principle

of respect for the autonomy of research participants [115]. It also aligns with the principles outlined in the Responsible Research Innovation (RRI) framework of the European Union, which encourages greater transparency of research, and engagement of stakeholders, including research participants [85]. More empirical data will, however, have to be collected to evaluate the impact of the use of dynamic consent in research projects, and to confirm or refute our findings. Importantly, it will be important to establish minimum standards regarding which components of an online platform are necessary to qualify as a dynamic consent platform. Such standards are necessary to ensure a common understanding regarding what constitutes dynamic consent and what its main features should be [personal reference: Teare H and al. Standards for dynamic consent - Investigating the ethical, legal and regulatory requirements. Paper in preparation, 2017].

Engagement of patient and interest organizations (PIOs) in PM

Finally, our research results suggest that PIOs are clearly willing to contribute to the PM agenda [125]. PIOs have unique expertise and resources that should be used to a greater extent than currently practiced. However, some challenges are expected to arise when inviting PIOs to engage in PM. For instance, thousands of PIOs of varying organizational form and mandate are active and it can be difficult to identify the ones that best represents the interests of large groups of patients [189]. Inviting some PIOs to engage in PM may also not be feasible as their ability to engage depends on their resources and priorities. As explained by one PIO representative, some PIOs do not have resources to do more than conducting daily activities such as providing guidance to patients, and supporting families in their encounter with health care services [125]. These PIOs may need time and help to build the necessary professional capacity to participate in the PM agenda.

Another challenge is how to prioritize and use inputs from diverse PIOs when these differ on specific issues [190]. Some PIOs are more experienced and have better resources to advocate for their patients than others; reconciling different views and priorities in a fair way could therefore be demanding. As an illustration, powerful PIOs could be tempted to steer health technology assessment processes in the direction that best suits their patient group to the detriment of other patient groups. One may also question whether some PIOs can be invited to be involved in research projects if they are not financially dependent or have an affiliation to industry. It may be necessary to require that PIOs declare "all sources and amounts of funding and specify the role of funders and sponsors in [their] activities" [191]. In the absence of a simple "recipe" for engaging stakeholders such as PIOs in PM, it will be necessary to conduct more research to determine the most efficient methods of engagement, the areas in which contributions from PIOs are most needed, and how their input can best be incorporated into PM policy [189].

6.3. Potential ways forward

Our consultations among key groups of stakeholders gave us useful insights into what they perceived as important challenges of relevance for the integration of PM in health care systems, and what they proposed as potential strategies to address those challenges. While some of these strategies are well known and are gradually being developed, others are rather new and may have to be fine-tuned and explored further. Several steps can be taken to follow-up on the strategies discussed in the papers:

- **Discuss in more details the content and design of harmonized European guidelines for the feedback of genetic research results to research participants**. PM researchers have specifically expressed a need for concrete guidelines. If such

guidelines are to be developed, it will require that more discussions take place regarding their content, and which specific components of the feedback process can actually be harmonized across European countries. Importantly, one will have to discuss which group or organization will be responsible (and will have sufficient authority and oversight) to develop the guidelines. As emphasized in paper I, one potential way to move forward is to rely upon existing European clinical guidelines for genetic testing to develop guidelines for use in research settings, including "additional criteria and assessment methods to certify the quality and accuracy of genetic results produced through research" [126]. In principle, it is possible to establish a task force with funding from the European Union or under the umbrella of the European Society of Human Genetics [192] (which has developed guidelines for feedback of results in clinical contexts). This task force could gather the necessary expertise from clinical and research milieus to start working on harmonized guidelines for research in a collaborative way. Enabling clinical and research milieus to work together on this task may be particularly useful if, as we suggest in paper I, genome sequencing equipment is to be more commonly used both for research and clinical purposes. If technological differences, for instance regarding the depth of sequencing, are reduced between clinical and research milieus, this may open for the development of joint guidelines between milieus [126]. Another option is to develop procedural guidance, i.e. guidelines that provide an overview of the steps to take in order to enable a feedback process, and the different strategies and methods that researchers can use to realize each step. Such a document would not provide concrete guidance regarding the types of genetic variants to feedback but would describe how to integrate the feedback process, using which methods, in all stages of research, from the design of the research protocol, to the provision of research results to research participants. Irrespective of

which strategy is chosen to develop guidelines, it will be particularly important to take into consideration the views and perspectives of patients and patient groups.

- **Discuss mechanisms for the sustainable funding of PM.** Our research confirms that the funding of activities of relevance for PM (e.g. the feedback of genetic research results to research participants), and of PM in general, is an important concern of stakeholders. Practical steps can be taken to address this concern, and some of these steps have been discussed in our research (e.g. allocate funding in research applications for the feedback process, develop drug-pricing limitations [121]). However, the feedback we received from stakeholders suggests that a debate on the sustainable funding of PM is needed in Europe, and that an overall strategy, perhaps at European level, has to be developed to ensure that PM develops in alignment with core European values of access to good quality care, equity, and solidarity. One potential way to move forward is to encourage the tenure of deliberative processes, following the principles of the RRI framework, to gather key stakeholders in discussions surrounding issues of priority-setting and sustainability of PM [193]. Doing so may help reach consensus regarding the types of priorities that are acceptable to society, and facilitate "social learning about limits" [193]. These deliberations should be conducted in a way that is inclusive, respectful of all parties, informed by the best medical knowledge available, and in a spirit of transparency and open-mindedness [194]. The RRI framework of the European Union provides some guidance regarding how such deliberations may be organized among stakeholders [17]. Special attention should be given to take into consideration the interests of marginalised, socio-economic disadvantaged groups usually underserved by health care systems. Encouraging discussions regarding the sustainable and equitable funding

of PM should be done with a clear purpose to achieve concrete outcomes, for instance, in the form of a roadmap for the long-term funding of PM that is respectful of expected budgetary constraints and reflects health care priorities. It may also be necessary to investigate further the use of inclusive programs, such as low-cost programs, to reach out to those populations who most likely will have limited access to PM.

- **Encourage the development of dynamic consent platforms.** More work will be needed to design dynamic consent platforms that address the needs of researchers and research participants, and to document the benefits, and potential drawbacks, of using dynamic consent in research projects. However, some concrete steps can be taken to encourage the use of dynamic consent in research. For instance, research ethics committees could require that solutions for dynamic consent are described and included in the protocol of new research projects seeking ethics approval. In Norway, the Norwegian National Research Ethics Committees [195] have recommended the development of dynamic consent in research that uses large amounts of data from biobanks and registers [196], preferably by integrating a dynamic consent platform into the national health care portal currently under development [197]. Such an approach would be cost-efficient and would secure the adoption of uniform standards for dynamic consent. Research funders could also use as an evaluation criterion the presence or absence of solutions for dynamic consent in research applications.

- **Invite PIOs to the table.** Incentives are needed to encourage researchers to come into dialogue and develop partnerships with PIOs. The Research Council of Norway [21], which funded the NCGC, has recently included in its latest health research programs

new requirements for researchers to have stakeholder representation in their research projects [198]. In research funding applications, researchers are now required to describe who their "users" or stakeholders are and how these are involved in the planning of the research and the implementation and utilization of research results [198]. Researchers are expected to create connections with patients and invite some of their representatives to join, for instance, reference groups or scientific boards. It will, however, be necessary to train researchers in stakeholder engagement as this is something rather new to them, and provide them with best practices regarding potential ways to work in partnership with PIOs [191]. Inviting PIOs to join research projects should also be done based on a genuine willingness to collaborate with patient groups and not be seen as an obligation to satisfy the requirements of funders. More research will be needed to explore which approaches may best contribute to foster a culture of collaboration between research projects and PIOs, and how such collaborations can in practice help move the PM agenda forward.

- **Work collaboratively at international level.** A general observation we made while collecting data for the papers is that challenges appear to be very similar across countries. For instance, it was clear that finding the necessary resources and practical tools to feedback individual genetic research results to research participants was difficult in many European countries. The same applied to finding appropriate ways to deal with informed consent in research projects. Similarly, the PIO representatives we consulted seemed to share the same concerns irrespective of their geographical location or the specific disease they represented. This highlights opportunities for international collaboration to address key challenges; something that is needed to a much greater extent than currently practiced. Experts representing national genomics

projects worldwide made a similar observation. They emphasized that opportunities for working collaboratively at an international level to address challenges to the realization of PM are underexplored and should be developed [199]. This is important knowing that the promoters of PM have primarily focused on developing solutions and tools for the realization of PM at a national rather than international level. However, developing joint international strategies is useful to avoid duplication of efforts and spread knowledge and competences across research milieus more rapidly. Issues surrounding data sharing are illustrative in this context. During the last two decades, significant efforts have been made to foster international data sharing through international collaborations and research consortia [9, 200]. Such a culture of international collaboration has contributed to the production of hundreds of scientific publications that provide critical new insights into disease mechanisms. A similar culture of international collaboration is needed within other areas that are relevant for PM, for instance for the development of European harmonized guidelines for the feedback of genetic research results to research participants or the design of dynamic consent platforms. This would be in line with recent suggestions from the British Academy of Medical Sciences to develop global 'Good Genomic Practice' guidelines and tools [45].

- **Continue the discussions in the spirit of the RRI framework.** Our experience from consulting stakeholders is that it is a "learn-as-we-talk" process. Ideas develop in partnership, and even if some of these ideas are neither new nor ground-breaking, they are a reflection of what those who are central to PM think, see as main issues, and envision as solutions for the future. I discussed earlier in this thesis that empirical work, although it has the advantage that it provides a "real-life" view of the situation

at a certain moment in time, has limited normative impact. However, the RRI framework calls for some degree of "institutionalized responsiveness" to demands from stakeholders [85]. This means that if stakeholders express some concerns, needs and aspirations, policymakers and funders should not ignore them but rather consider them, even if the evidence needed to document such concerns and needs is not fully in place. For instance, when our research suggests that PM researchers call for the development of dynamic consent platforms, this should serve as an indication for policymakers, research institutions and research funders that current models for informed consent are not sufficient and that new solutions are needed, even if the exact needs are not fully documented. When our research indicates that a central concern of stakeholders relates to the funding of PM and its sustainability, this suggests that work should be done to ensure that PM is developed in compliance with European values of sustainable and equitable health care, and in a way that is respectful of the interests of patients. An interesting aspect of the RRI framework is that it emphasizes the importance of "thinking together". Responsible innovation evokes a duty to "(…) rethink what we want from innovation and how we can make its pathways responsive in the face of uncertainty" [85]. It is through such collaborative thinking that we can draw the contours of "(…) the kind of future we want innovation to bring into the world" [85]. PM is a central innovation currently being brought to the medical world. It is therefore critical to ensure that its many aspects are discussed broadly and in a democratic, transparent and inclusive way.

6.4. Study limitations

The work conducted in this thesis provides new insight into what key stakeholders of PM see as important challenges that may affect the provision of PM to patients and citizens, and

potential strategies to address these challenges. It is, however, important to consider some important limitations of our work.

Methodology

Two international workshops were conducted to collect data for paper I and paper IV. Using such method was congruent with the principles of the RRI framework and the requirements of the COST Action. However, it did not enable us to discuss issues in-depth or to check whether the workshop participants might have underreported certain things or might have misinterpreted the current situation in their country. Organizing workshops in English is advantageous for those participants whose mother tongue is English. They could have influenced the direction that the discussions took in the workshop while other participants, due to language barriers, remained silent. To overcome this challenge, we focused on consistently analyzing the information collected using the same neutral method of content analysis across studies. We also invited the workshop participants to comment on early versions of the papers (I, III, and IV) to check whether our interpretation of the data was adequate.

When conducting the work to investigate the impact of using dynamic consent solutions in research projects, we followed the recommendations of the COST Action and organized a workshop with researchers who are implementing dynamic consent solutions in their research. Although this approach enabled us to explore how to develop dynamic consent in research projects, organizing a workshop with researchers heavily involved in the development of dynamic consent may be problematic if they are unable to assess objectively the platforms they develop. This may potentially have affected our results in paper IV. However, to understand how dynamic consent may help conduct PM research, it is necessary to establish a

dialogue with those who have a hands-on experience from the development of dynamic consent. As more projects endorse the use of dynamic consent, it will be useful to conduct a systematic evaluation of these projects to evaluate their impact on the conduct of research.

Representativeness

To collect data for paper I and paper IV, we run consultations among a limited sample of PIOs within the network of the NCGC and the European Patients' Forum. One underlying objective was to achieve broad geographical representation by interviewing representatives from all parts of Europe. However, it proved difficult to achieve such goal as most of the representatives we recruited were from Western Europe. With one exception, we did not manage to reach out to representatives from Eastern Europe. This could be due to language barriers, or because the representatives in these countries believed that the questions we raised were not relevant. Unbalanced geographical representation between different European countries is problematic as it is difficult to know whether the challenges discussed with the PIO representatives exist only in Western Europe or are also encountered in other parts of Europe. In the future, it would be interesting to investigate potential differences between the different regions of Europe regarding the issues discussed, and how these differences impact views regarding which steps to take to enable PM.

The four studies included in this thesis were conducted among a limited number of stakeholder groups. We primarily used the networks of the NCGC and the COST Action. The research results presented in this thesis cannot be considered to be representative of what the larger community of PM stakeholders think. However, the findings presented herein are largely congruent with those from previous studies. This suggests that the number of stakeholders we consulted do not significantly impact the utility of the information we present

to inform the PM agenda. Next steps may be to conduct more consultations among other groups of stakeholders to build a stronger overall evidence base for these findings. The numerically largest group of stakeholders (i.e. prospective patients) was not consulted in this thesis, although we discussed PM with representatives from PIOs. The PIOs work at protecting the rights and interests of patients; it is therefore reasonable to expect that they have good insight into what patients think and how they might behave. However, consulting patients directly is necessary to gain a more in-depth understanding of their concerns and wishes. We realized this when conducting the interviews with the sarcoma patients in the NCGC in conjunction with the NoSarC ELSA study (results to be reported in another PhD thesis). Although the patients did not make statements that significantly contradicted what the PIO representatives had told us, it was clear that they have varying expectations, concerns, and wishes depending on their personal situation and life experience. How to take into consideration this variety of views and perspectives into policy of practical application remains to be explored.

7.0. CONCLUSIONS

The science of PM is progressing rapidly and new targeted treatment are increasingly brought to patients in Europe. Policymakers have extensively discussed PM and provided stakeholders with recommendations for its advancement. Importantly, this has occurred as a "top-down" approach. In contrast, this thesis took a "bottom-up" approach and explored the views of key groups of stakeholders regarding specific themes of relevance for PM, with the objective to inform policymakers regarding potential strategies to adopt. The "bottom-up" approach aims to give stakeholders a voice, and help elucidate real-life issues that may be crucial to address for the successful transition to PM in the health care sector. Our findings reveal that considerable attention should be placed on developing PM in a way that is congruent with European values of health care. Issues of sustainability and practical feasibility of PM exist that need to be addressed. Implementing the strategies discussed in this thesis may help address some of these challenges. However, more research will be needed to develop the strategies proposed. The integration of PM into health care within Europe will require stakeholders to join forces and work collaboratively, nationally and internationally, to ensure that PM is developed "for society, with society" [85].

8.0. FURTHER RESEARCH

This work indicates a need for further research on the following topics:

- Research on how to develop harmonized European guidelines for the feedback of genetic research results to research participants that are based on empirical evidence and open for contextual flexibility.
- Research on how to involve PIOs in PM and take greater advantage of their competency, expertise and experience. For instance, which new collaboration models should be established between PIOs, researchers, and policymakers? What should be done to promote the engagement of smaller PIOs with limited economic resources?
- Research on the impact of using a consent and engagement platform such as dynamic consent. For instance, which models of dynamic consent are most effective to engage research participants over time, and what are the limitations of using such models? Research on which minimum standards to include in an online platform for it to qualify as a dynamic consent platform.
- Research on the impact of implementing inclusive mechanisms such as free or low-cost genetic testing targeting socio-economically disadvantaged groups. Do these mechanisms work and what are their limitations?
- Research on the impact of targeted educational strategies for patients vs. large-scale information campaigns targeting the general public
- Finally, research on the global ethical challenges pertaining to promoting PM research and development. Where, on the list of research for health priorities, does PM belong?

REFERENCES

1. European Science Foundation. **ESF Forward Look: Personalised Medicine for the European Citizen.** http://archives.esf.org/fileadmin/Public_documents/Publications/Personalised_Medicine.pdf. Accessed 25 Nov 2016.

2. Collins FS, Green ED, Guttmacher AE, Guyer MS, U. S. National Human Genome Research Institute: **A vision for the future of genomics research**. *Nature* 2003, **422**(6934):835-847.

3. Spear BB, Heath-Chiozzi M, Huff J: **Clinical application of pharmacogenetics**. *Trends Mol Med* 2001, **7**(5):201-204.

4. **Preventable Adverse Drug Reactions: A Focus on Drug Interactions** https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm. Accessed 30 Oct 2017.

5. Sultana J, Cutroneo P, Trifiro G: **Clinical and economic burden of adverse drug reactions**. *J Pharmacol Pharmacother* 2013, **4**(Suppl 1):S73-77.

6. Committee on a Framework for Development a New Taxonomy of Disease; National Research Council: **Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease**: The National Academies Press; 2011.

7. Working Group Report to the Advisory Committee to the Director, National Institues of Health: **The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine - Precision Medicine Initiative (PMI).** https://www.nih.gov/precision-medicine-initiative-cohort-program/pmi-working-group. Accessed 30 Oct 2017.

8. **ELIXIR and GA4GH Beacon Team Up to Advance Genomic Data Sharing** https://www.elixir-europe.org/news/elixir-and-ga4gh-beacon-team-advance-genomic-data-sharing. Accessed 30 Oct 2017.

9. Harris JR, Burton P, Knoppers BM, Lindpaintner K, Bledsoe M, Brookes AJ, *et al*: **Toward a roadmap in global biobanking for health**. *Eur J Hum Genet* 2012.

10. Global Alliance for Genomics and Health & Public Population Project in Genomics and Society: International Policy interoperability and data Access Clearinghouse: **Consent tools.** http://www.p3g.org/sites/default/files/site/default/files/GA4GH-Consent%20Tools-FINAL%20%281%29.pdf. Accessed 30 Oct 2017.

11. Knoppers BM: **Framework for responsible sharing of genomic and health-related data**. *HUGO J* 2014, **8**(1):3.

12. Borry P, Bentzen HB, Budin-Ljosne I, Cornel MC, Howard HC, Feeney O, *et al*: **The challenges of the expanded availability of genomic information: an agenda-setting paper**. *Journal of community genetics* 2017.

13. Official Journal of the European Union. **Council Conclusions on Common values and principles in European Union Health Systems (2006/C 146/01).** http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2006:146:0001:0003:EN:PDF. Accessed 30 Oct 2017.

14. **Personal responsibility**. *Nature* 2015, **525**(7567):5.

15. Aitken M, de St Jorre J, Pagliari C, Jepson R, Cunningham-Burley S: **Public responses to the sharing and linkage of health data for research purposes: a systematic review and thematic synthesis of qualitative studies**. *BMC medical ethics* 2016, **17**(1):73.

16. Fernandez CV, Kodish E, Weijer C: **Informing study participants of research results: an ethical imperative**. *IRB* 2003, **25**(3):12-19.

17. **RRI Toolkit.** www.rri-tools.eu. Accessed 30 Oct 2017.

18. **Norwegian Cancer Genomics Consortium**. http://kreftgenomikk.no/en/. Accessed 30 Oct 2017.

19. COST Action CHIP ME IS1303. **Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives**. http://chipme.eu/eng/home.aspx. Accessed 30 Oct 2017.

20. Horizon 2020. The EU Framework Programme for Research and Innovation **Responsible research & innovation.** https://ec.europa.eu/programmes/horizon2020/en/h2020-section/responsible-research-innovation. Accessed 30 Oct 2017.

21. **Research Council of Norway.** http://www.forskningsradet.no/. Accessed 30 Oct 2017.

22. Research Council of Norway **. Publicly-initiated Clinical Cancer Studies (KREFT)** https://www.forskningsradet.no/prognett-kreft/Home_page/1253968049623. Accessed 30 Oct 2017.

23. Research Council of Norway. **Biotechnology for innovation (BIOTEK2021)** http://www.forskningsradet.no/prognett-biotek2021/Home_page/1253970728140. Accessed 30 Oct 2017.

24. **Cancer Registry of Norway.** https://www.kreftregisteret.no/en/. Accessed 30 Oct 2017.

25. **The Biotechnology Advisory Board.** http://www.bioteknologiradet.no/english/. Accessed 30 Oct 2017.

26. **Oslo Cancer Cluster.** http://oslocancercluster.no/. Accessed 30 Oct 2017.

27. **COST - European Cooperation in Science and Technology.** http://www.cost.eu/. Accessed 30 Oct 2017.

28. COST Action IS1303. **Memorandum of Understanding (MoU).** http://www.cost.eu/COST_Actions/isch/IS1303. Accessed 30 Oct 2017.

29. COST Action IS1303. **Working Group 1 (Research ethics)** http://chipme.eu/eng/working-groups/research-ethics.aspx. Accessed 30 Oct 2017.

30. Kolata, G: **Cancer Drug Proves to Be Effective Against Multiple Tumors.** The New York Times. https://www.nytimes.com/2017/06/08/health/cancer-drug-keytruda-tumors.html. Accessed 30 Oct 2017.

31. U.S. Department of Health and Human Services. U.S. Food and Drug Administration. **Paving the Way for Personalized Medicine** http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf. Accessed 30 Oct 2017.

32. Vogenberg FR, Isaacson Barash C, Pursel M: **Personalized medicine: part 1: evolution and development into theranostics**. *P T* 2010, **35**(10):560-576.

33. European Science Foundation. **ESF Forward Look: Personalised Medicine for the European Citizen.** http://archives.esf.org/coordinating-research/forward-looks/biomedical-sciences-med/current-forward-looks-in-biomedical-sciences/personalised-medicine-for-the-european-citizen.html. Accessed 30 Oct 2017.

34. Personalized Medicine Coalition. **The case for personalized medicine.** http://personalizedmedicinecoalition.org/Resources/The_Case_for_Personalized_Medicine. Accessed 30 Oct 2017.

35. Collins F: **The Language of Life. DNA and The Revolution in Personalized Medicine**. In. New York: HarperCollins; 2009: p. 674-p. 675.

36. Abettan C: **Between hype and hope: What is really at stake with personalized medicine?** *Med Health Care Philos* 2016, **19**(3):423-430.

37. European Commission Health Research Directorate. **Personalised Medicine: Opportunities and challenges for European healthcare** https://ec.europa.eu/research/health/pdf/13th-european-health-forum-workshop-report_en.pdf. Accessed 30 Oct 2017.

38. National Cancer Institute. **Targeted Cancer Therapies.** http://www.cancer.gov/about-cancer/treatment/types/targeted-therapies/targeted-therapies-fact-sheet#q1. Accessed 30 Oct 2017.

39. Leyens L, Horgan D, Lal JA, Steinhausen K, Satyamoorthy K, Brand A: **Working towards personalization in medicine: main obstacles to reaching this vision from today's perspective**. *Personalized medicine* 2014, **11**(7):641-649.

40. Reitz C: **Toward precision medicine in Alzheimer's disease**. *Ann Transl Med* 2016, **4**(6):107.

41. Lund University. Faculty of Medicine. **100 million SEK for personalized medicine in diabetes.** http://www.ludc.med.lu.se/news-archive/100-million-sek-for-personalized-medicine-in-diabetes/. Accessed 30 Oct 2017.

42. U.S. Food and Drug Administration. **Targeted Drug Development: Why Are Many Diseases Lagging Behind?** July 2015. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM454996.pdf. Accessed 30 Oct 2017.

43. National Institutes of Health. **The future of health begins with all of us.** https://www.nih.gov/precision-medicine-initiative-cohort-program. Accessed 30 Oct 2017.

44. Katsnelson A: **Momentum grows to make 'personalized' medicine more 'precise'**. *Nat Med* 2013, **19**(3):249-249.

45. The Academy of Medical Sciences. **Realising the Potential of Stratified Medicine.** https://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf. Accessed 30 Oct 2017.

46. Hood L: **Systems biology and p4 medicine: past, present, and future**. *Rambam Maimonides Med J* 2013, **4**(2):e0012.

47. Schleidgen S, Klingler C, Bertram T, Rogowski WH, Marckmann G: **What is personalized medicine: sharpening a vague term based on a systematic literature review**. *BMC medical ethics* 2013, **14**:55.

48. Rose N: **Personalized Medicine: Promises, Problems and Perils of a New Paradigm for Healthcare**. *Procedia - Social and Behavioral Sciences* 2013, **77**:341-352.

49. Dorschner MO, Amendola LM, Turner EH, Robertson PD, Shirts BH, Gallego CJ, *et al*: **Actionable, pathogenic incidental findings in 1,000 participants' exomes**. *American journal of human genetics* 2013, **93**(4):631-640.

50. Amendola LM, Dorschner MO, Robertson PD, Salama JS, Hart R, Shirts BH, *et al*: **Actionable exomic incidental findings in 6503 participants: challenges of variant classification**. *Genome Res* 2015, **25**(3):305-315.

51. American Pharmacists Association. **FDA panel endorses gene therapy for a form of childhood blindness.** http://www.pharmacist.com/article/fda-panel-endorses-gene-therapy-form-childhood-blindness. Accessed 30 Oct 2017.

52. Evans JP, Meslin EM, Marteau TM, Caulfield T: **Genomics. Deflating the genomic bubble**. *Science* 2011, **331**(6019):861-862.

53. Vogt H, Hofmann B, Getz L: **The new holism: P4 systems medicine and the medicalization of health and life itself**. *Medicine, Health Care and Philosophy* 2016:1-17.

54. Hollands GJ, French DP, Griffin SJ, Prevost AT, Sutton S, King S, Marteau TM: **The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis**. *BMJ* 2016, **352**:i1102.

55. Gefenas E, Cekanauskaite A, Tuzaite E, Dranseika V, Characiejus D: **Does the "new philosophy" in predictive, preventive and personalised medicine require new ethics?** *EPMA J* 2011, **2**(2):141-147.

56. Nuffield Council on Bioethics. **Medical Profiling and Online Medicine: the Ethics of 'Personalised Healthcare' in a Consumer Age.** http://nuffieldbioethics.org/wp-content/uploads/2014/07/Medical-profiling-and-online-medicine-the-ethics-of-personalised-healthcare-in-a-consumer-age-Web-version-reduced.pdf. Accessed 30 Oct 2017.

57. Chadwick R: **Personal Identity: Genetics and Determinism**. In: *eLS.* John Wiley & Sons, Ltd; 2001.

58. Alyass A, Turcotte M, Meyre D: **From big data analysis to personalized medicine for all: challenges and opportunities**. *BMC Med Genomics* 2015, **8**:33.

59. Joly Y, Saulnier KM, Osien G, Knoppers BM: **The ethical framing of personalized medicine**. *Curr Opin Allergy Clin Immunol* 2014, **14**(5):404-408.

60. Kaye J: **The Tension Between Data Sharing and the Protection of Privacy in Genomics Research**. *AnnuRev Genomics Hum Genet* 2012.

61. Gymrek M, McGuire AL, Golan D, Halperin E, Erlich Y: **Identifying personal genomes by surname inference**. *Science* 2013, **339**(6117):321-324.

62. Homer N, Szelinger S, Redman M, Duggan D, Tembe W, Muehling J, Pearson JV, *et al:* **Resolving individuals contributing trace amounts of DNA to highly complex mixtures using high-density SNP genotyping microarrays**. *PLoS Genet* 2008, **4**(8):e1000167.

63. Tutton R, Jamie K: **Personalized medicine in context: social science perspectives**. *Drug Discovery Today: Therapeutic Strategies* 2013, **10**(4):e183-e187.

64. Green RC, Lautenbach D, McGuire AL: **GINA, genetic discrimination, and genomic medicine**. *N Engl J Med* 2015, **372**(5):397-399.

65. Vayena E, Gasser U: **Between Openness and Privacy in Genomics**. *PLoS Med* 2016, **13**(1):e1001937.

66. HUGO Ethics Committee: **Statement on Benefit Sharing.** 2000. http://www.hugo-international.org/Resources/Documents/CELS_Statement-BenefitSharing_2000.pdf. Accessed 30 Oct 2017.

67. Horgan D, Jansen M, Leyens L, Lal JA, Sudbrak R, Hackenitz E, *et al*: **An index of barriers for the implementation of personalised medicine and pharmacogenomics in Europe**. *Public Health Genomics* 2014, **17**(5-6):287-298.

68. Delaney SK, Hultner ML, Jacob HJ, Ledbetter DH, McCarthy JJ, Ball M, *et al*: **Toward clinical genomics in everyday medicine: perspectives and recommendations**. *Expert Rev Mol Diagn* 2016, **16**(5):521-532.

69. Godman B, Finlayson AE, Cheema PK, Zebedin-Brandl E, Gutierrez-Ibarluzea I, Jones J, *et al*: **Personalizing health care: feasibility and future implications**. *BMC Med* 2013, **11**:179.

70. Eurohealth International. **CSA PerMed: Europe's Commitment to Personalised Medicine.** www.permed2020.eu/_media/EuroHealth_PerMed(1).pdf. Accessed 30 Oct 2017.

71. PHG Foundation. **Public health in an era of genome-based and personalised medicine.** http://www.phgfoundation.org/reports/6617/. Accessed 30 Oct 2017.

72. BioSHaRE. **Catalogue of Tools and Services for Data Sharing** http://www.bioshare.eu/content/catalogue-tools-and-services-data-sharing. Accessed 30 Oct 2017.

73. BBMRI-ERIC. **Biobanking and Biomolecular Resources Research Infrastructure - European Research Infrastructure Consortium.** http://www.bbmri.eu/. Accessed 30 Oct 2017.

74. Kaye J, Briceno Moraia L, Mitchell C, Bell J, Bovenberg JA, Tasse AM, Knoppers BM: **Access Governance for Biobanks: The Case of the BioSHaRE-EU Cohorts**. *Biopreservation and biobanking* 2016, **14**(3):201-206.

75. PHG Foundation. **Next steps in the sequence. The implications of whole genome sequencing for health in the UK.** http://www.phgfoundation.org/report/next-steps-in-the-sequence. Accessed 30 Oct 2017.

76. Presidential Commission for the Study of Bioethical Issues. **Privacy and Progress in Whole Genome Sequencing.** https://bioethicsarchive.georgetown.edu/pcsbi/node/764.html. Accessed 30 Oct 2017.

77. European Medicines Agency. **Adaptive pathways.** ttp://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp. Accessed 30 Oct 2017.

78. **European Medicines Agency.** http://www.ema.europa.eu/ema/. Accessed 30 Oct 2017.

79. Hall PS, McCabe C: **What evidence is there for the reimbursement of personalised medicine?** *Pharmacoeconomics* 2013, **31**(3):181-183.

80. **INVOLVE.** http://www.invo.org.uk/. Accessed 30 Oct 2017.

81. European Alliance for Personalised Medicine. **Innovation and Patient Access to Personalised Medicine.** https://www.euapm.eu/pdf/EAPM_REPORT_on_Innovation_and_Patient_Access_to_Personalised_Medicine.pdf. Accessed 30 Oct 2017.

82. President's Council of Advisors on Science and Technology (PCAST). **Priorities for Personalized Medicine.** 2008.

83. Lipworth W, Axler R: **Towards a bioethics of innovation**. *J Med Ethics* 2016, **42**(7):445-449.

84. 2014 Italian Presidency of the Council of the European Union. **Rome Declaration on Responsible Research and Innovation in Europe.** https://ec.europa.eu/research/swafs/pdf/rome_declaration_RRI_final_21_November.pdf. Accessed 30 Oct 2017.

85. Owen R, Macnaghten P, Stilgoe J: **Responsible research and innovation: From science in society to science for society, with society**. *Sci Publ Policy* 2012, **39**(6):751-760.

86. Horizon 2020. **The EU Framework Programme for Research and Innovation** http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020. Accessed 30 Oct 2017.

87. The Council of the European Union. **Council conclusions on personalised medicine for patients (2015/C 421/03).** http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52015XG1217(01). Accessed 30 Oct 2017.

88. Kantarjian H, Steensma D, Rius Sanjuan J, Elshaug A, Light D: **High cancer drug prices in the United States: reasons and proposed solutions**. *J Oncol Pract* 2014, **10**(4):e208-211.

89. Pollack, A. **Drug Prices Soar, Prompting Calls for Justification.** The New York Times. 2015. http://www.nytimes.com/2015/07/23/business/drug-companies-pushed-from-far-and-wide-to-explain-high-prices.html?_r=0 . Accessed 30 Oct 2017.

90. Research Council of Norway. **A framework for Responsible Innovation - under BIOTEK2021, IKTPLUSS, NANO2021 and SAMANSVAR.**

91. Gardner J, Williams C: **Responsible research and innovation: A manifesto for empirical ethics?** *Clin Ethics* 2015, **10**(1-2):5-12.

92. Ives J, Draper H: **Appropriate methodologies for empirical bioethics: it's all relative**. *Bioethics* 2009, **23**(4):249-258.

93. Bombard Y, Abelson J, Simeonov D, Gauvin FP: **Citizens' perspectives on personalized medicine: a qualitative public deliberation study**. *European journal of human genetics : EJHG* 2013, **21**(11):1197-1201.

94. Nicholls SG, Wilson BJ, Craigie SM, Etchegary H, Castle D, Carroll JC, *et al*: **Public attitudes towards genomic risk profiling as a component of routine population screening**. *Genome* 2013, **56**(10):626-633.

95. Diaz VA, Mainous AG, 3rd, Gavin JK, Wilson D: **Racial differences in attitudes toward personalized medicine**. *Public Health Genomics* 2014, **17**(1):1-6.

96. Dye T, Li D, Demment M, Groth S, Fernandez D, Dozier A, Chang J: **Sociocultural Variation in Attitudes Toward use of Genetic Information and Participation in Genetic Research by Race in the United States: Implications for Precision Medicine**. *J Am Med Inform Assoc* 2016.

97. Halverson CM, Clift KE, McCormick JB: **Was it worth it? Patients' perspectives on the perceived value of genomic-based individualized medicine**. *Journal of community genetics* 2016, **7**(2):145-152.

98. McGowan ML, Glinka A, Highland J, Asaad G, Sharp RR: **Genetics patients' perspectives on clinical genomic testing**. *Personalized medicine* 2013, **10**(4):339-347.

99. Gray SW, Hicks-Courant K, Lathan CS, Garraway L, Park ER, Weeks JC: **Attitudes of patients with cancer about personalized medicine and somatic genetic testing**. *J Oncol Pract* 2012, **8**(6):329-335, 322 p following 335.

100. Lupo PJ, Robinson JO, Diamond PM, Jamal L, Danysh HE, Blumenthal-Barby J, Lehmann LS, Vassy JL, Christensen KD, Green RC *et al*: **Patients' perceived utility of whole-genome sequencing for their healthcare: findings from the MedSeq project**. *Personalized medicine* 2016, **13**(1):13-20.

101. Haga SB, Burke W, Ginsburg GS, Mills R, Agans R: **Primary care physicians' knowledge of and experience with pharmacogenetic testing**. *Clinical genetics* 2012, **82**(4):388-394.

102. Vassy JL, Christensen KD, Slashinski MJ, Lautenbach DM, Raghavan S, Robinson JO, *et al*: **'Someday it will be the norm': physician perspectives on the utility of genome sequencing for patient care in the MedSeq Project**. *Personalized medicine* 2015, **12**(1):23-32.

103. Hamilton AB, Oishi S, Yano EM, Gammage CE, Marshall NJ, Scheuner MT: **Factors influencing organizational adoption and implementation of clinical genetic services**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2014, **16**(3):238-245.

104. McGowan ML, Settersten RA, Jr., Juengst ET, Fishman JR: **Integrating genomics into clinical oncology: ethical and social challenges from proponents of personalized medicine**. *Urol Oncol* 2014, **32**(2):187-192.

105. Mahlmann L, Rocke C, Brand A, Hafen E, Vayena E: **Attitudes towards personal genomics among older Swiss adults: An exploratory study**. *Appl Transl Genom* 2016, **8**:9-15.

106. Middleton A: **Your DNA, Your Say**. *New Bioeth* 2017, **23**(1):74-80.

107. Barazzetti G, Cavalli S, Benaroyo L, Kaufmann A: **"Still Rather Hazy at Present": Citizens' and Physicians' Views on Returning Results from Biobank Research Using Broad Consent**. *Genet Test Mol Biomarkers* 2017, **21**(3):159-165.

108. Chokoshvili D, Belmans C, Poncelet R, Sanders S, Vaes D, Vears D, Janssens S, Huys I, Borry P: **Public Views on Genetics and Genetic Testing: A Survey of the General Public in Belgium**. *Genet Test Mol Biomarkers* 2017, **21**(3):195-201.

109. European Commission. **Responsible Research and Innovation - Europe's ability to respond to societal challenges.** 2012. https://ec.europa.eu/research/swafs/pdf/pub_public_engagement/responsible-research-and-innovation-leaflet_en.pdf. Accessed 30 Oct 2017.

110. Oslo University Hospital. **NoSarc - A national study on gene mutations in sarcoma.** http://www.ous-research.no/home/myklebost/NoSarc. Accessed 30 Oct 2017.

111. **Norwegian Cancer Society.** https://kreftforeningen.no/. Accessed 30 Oct 2017.

112. **Sarkomer.** http://www.sarkomer.no/english/. Accessed 30 Oct 2017.

113. Schleidgen S, Marckmann G: **Re-focusing the ethical discourse on personalized medicine: a qualitative interview study with stakeholders in the German healthcare system**. *BMC medical ethics* 2013, **14**:20.

114. Budin-Ljøsne I, Bentzen HB, Solbakk JH, Myklebost O: **Genome sequencing in research requires a new approach to consent**. *Tidsskr Nor Laegeforen* 2015, **135**(22):2031-2032.

115. Kaye J, Whitley EA, Lund D, Morrison M, Teare H, Melham K: **Dynamic consent: a patient interface for twenty-first century research networks**. *European journal of human genetics : EJHG* 2015, **23**(2):141-146.

116. Thiel DB, Platt J, Platt T, King SB, Fisher N, Shelton R, Kardia SL: **Testing an online, dynamic consent portal for large population biobank research**. *Public Health Genomics* 2015, **18**(1):26-39.

117. Boutin NT, Mathieu K, Hoffnagle AG, Allen NL, Castro VM, Morash M, *et al*: **Implementation of Electronic Consent at a Biobank: An Opportunity for Precision Medicine Research**. *J Pers Med* 2016, **6**(2).

118. Steinsbekk KS, Kare MB, Solberg B: **Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem?** *EurJHumGenet* 2013.

119. Strong KA, Lipworth W, Kerridge I: **The strengths and limitations of empirical bioethics**. *J Law Med* 2010, **18**(2):316-319.

120. Elo S, Kyngas H: **The qualitative content analysis process**. *Journal of advanced nursing* 2008, **62**(1):107-115.

121. Budin-Ljøsne I, Harris JR: **Ask not what personalized medicine can do for you - ask what you can do for personalized medicine**. *Public Health Genomics* 2015, **18**(3):131-138.

122. **European Patients' Forum.** http://www.eu-patient.eu/. Accessed 30 Oct 2017.

123. Nuffield Department of Population Health. Medical Sciences Division. **Centre for Health, Law and Emerging Technologies (HeLEX), University of Oxford, UK** http://www.ndph.ox.ac.uk/research/centre-for-health-law-and-emerging-technologies-helex. Accessed 30 Oct 2017.

124. Gale NK, Heath G, Cameron E, Rashid S, Redwood S: **Using the framework method for the analysis of qualitative data in multi-disciplinary health research**. *BMC Med Res Methodol* 2013, **13**:117.

125. Budin-Ljøsne I, Harris JR: **Patient and interest organizations' views on personalized medicine: a qualitative study**. *BMC medical ethics* 2016, **17**(1):28.

126. Budin-Ljøsne I, Mascalzoni D, Soini S, Machado H, Kaye J, Bentzen HB, *et al*: **Feedback of Individual Genetic Results to Research Participants: Is It Feasible in Europe?** *Biopreservation and biobanking* 2016, **14**(3):241-248.

127. Budin-Ljøsne I, Teare HJA, Kaye J, Beck S, Bentzen HB, Caenazzo L, *et al*: **Dynamic Consent: a potential solution to some of the challenges of modern biomedical research**. *BMC medical ethics* 2017, **18**(1):4.

128. Christensen KD, Roberts JS, Shalowitz DI, Everett JN, Kim SY, Raskin L, Gruber SB: **Disclosing individual CDKN2A research results to melanoma survivors: interest, impact, and demands on researchers**. *Cancer Epidemiol Biomarkers Prev* 2011, **20**(3):522-529.

129. Keogh LA, Fisher D, Sheinfeld Gorin S, Schully SD, Lowery JT, Ahnen DJ, *et al*: **How do researchers manage genetic results in practice? The experience of the multinational Colon Cancer Family Registry**. *Journal of community genetics* 2014, **5**(2):99-108.

130. Siddiqui M, Rajkumar SV: **The high cost of cancer drugs and what we can do about it**. *Mayo Clin Proc* 2012, **87**(10):935-943.

131. Bach, PB; Saltz, LB; Wittesoct, RE: **In Cancer Care, Cost Matters.** The New York Times. 2012. http://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html?_r=0. Accessed 30 Oct 2017.

132. Ferkol T, Quinton P: **Precision Medicine: At What Price?** *Am J Respir Crit Care Med* 2015, **192**(6):658-659.

133. Lawrence L, Sincan M, Markello T, Adams DR, Gill F, Godfrey R, *et al*: **The implications of familial incidental findings from exome sequencing: the NIH Undiagnosed Diseases Program experience**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2014, **16**(10):741-750.

134. Ramoni RB, McGuire AL, Robinson JO, Morley DS, Plon SE, Joffe S: **Experiences and attitudes of genome investigators regarding return of individual genetic test results**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2013, **15**(11):882-887.

135. BBMRI-ERIC. **Genetics Clinic of the Future survey.** http://www.bbmri-eric.eu/news-events/genetics-clinic-of-the-future-survey/. Accessed 30 Oct 2017.

136. Sorensen K, Pelikan JM, Rothlin F, Ganahl K, Slonska Z, Doyle G, *et al*: **Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU)**. *Eur J Public Health* 2015, **25**(6):1053-1058.

137. Seror V, Marino P, Bertucci F, Mancini J, Extra JM, Ferrero JM, *et al*: **Breast cancer patients' views on the use of genomic testing to guide decisions about their postoperative chemotherapy**. *Public Health Genomics* 2013, **16**(3):110-117.

138. European Commission. **Europeans and Biotechnology in 2010 Winds of change?** https://ec.europa.eu/research/swafs/pdf/pub_archive/europeans-biotechnology-in-2010_en.pdf. Accessed 30 Oct 2017.

139. European Medicines Agency. **Adaptive pathways to patients: report on the initial experience of the pilot project.** 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2014/12/WC500179560.pdf. Accessed 30 Oct 2017.

140. The European Personalised Medicine Association. White Paper. **Personalised Medicine in Europe - Enhancing Patient Access to Pharmaceutical Drug-Diagnostic Companion Products**. 2014. http://www.epemed.org/online/www/content2/104/107/910/pagecontent2/4339/791/ENG/EpemedWhitePaperNOV14.pdf. Accessed 30 Oct 2017.

141. Koehring, M. **Value-based healthcare in the UK: A system of trial and error.** The Economist. 2016. http://www.eiuperspectives.economist.com/healthcare/value-based-healthcare-uk-system-trial-and-error**.** Accessed 30 Oct 2017.

142. Javaid MK, Forestier-Zhang L, Watts L, Turner A, Ponte C, Teare H, *et al*: **The RUDY study platform - a novel approach to patient driven research in rare musculoskeletal diseases**. *Orphanet J Rare Dis* 2016, **11**(1):150.

143. Hansson MG, Dillner J, Bartram CR, Carlson JA, Helgesson G: **Should donors be allowed to give broad consent to future biobank research?** *The Lancet Oncology* 2006, **7**(3):266-269.

144. D'Abramo F: **Biobank research, informed consent and society. Towards a new alliance?** *J Epidemiol Community Health* 2015, **69**(11):1125-1128.

145. Patient-Centered Outcomes Research Institute. **PCORI Engagement Rubric.** http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf. Accessed 30 Oct 2017.

146. **The 100,000 Genomes Project.** https://www.genomicsengland.co.uk/the-100000-genomes-project/. Accessed 30 Oct 2017.

147. Genomics England. **Research in the 100,000 Genomes Project.** https://www.genomicsengland.co.uk/about-gecip/. Accessed 30 Oct 2017.

148. Lyon GJ, Segal JP: **Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape**. *Applied & Translational Genomics* 2013, **2**:34-40.

149. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL: **The research-treatment distinction: a problematic approach for determining which activities should have ethical oversight**. *The Hastings Center report* 2013, **Spec No**:S4-S15.

150. PHG Foundation. **Genomics and the boundary between research and clinical care and treatment.** http://www.phgfoundation.org/briefing_notes/303/. Accessed 30 Oct 2017.

151. Mehrian-Shai R, Reichardt JK: **Genomics is changing personal healthcare and medicine: the dawn of iPH (individualized preventive healthcare)**. *Hum Genomics* 2015, **9**:29.

152. Vogt H, Ulvestad E, Eriksen TE, Getz L: **Getting personal: can systems medicine integrate scientific and humanistic conceptions of the patient?** *J Eval Clin Pract* 2014, **20**(6):942-952.

153. Wolf SM, Crock BN, Van NB, Lawrenz F, Kahn JP, Beskow LM, *et al*: **Managing incidental findings and research results in genomic research involving biobanks and archived data sets**. *GenetMed* 2012, **14**(4):361-384.

154. Fabsitz RR, McGuire A, Sharp RR, Puggal M, Beskow LM, Biesecker LG *et al*: **Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute working group**. *CircCardiovascGenet* 2010, **3**(6):574-580.

155. Jarvik GP, Amendola LM, Berg JS, Brothers K, Clayton EW, Chung W, *et al*: **Return of genomic results to research participants: the floor, the ceiling, and the choices in between**. *American journal of human genetics* 2014, **94**(6):818-826.

156. van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV, *et al*: **Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics**. *European journal of human genetics : EJHG* 2013, **21 Suppl 1**:S1-5.

157. Claustres M, Kozich V, Dequeker E, Fowler B, Hehir-Kwa JY, Miller K, *et al*: **Recommendations for reporting results of diagnostic genetic testing (biochemical, cytogenetic and molecular genetic)**. *European journal of human genetics : EJHG* 2014, **22**(2):160-170.

158. Hehir-Kwa JY, Claustres M, Hastings RJ, van Ravenswaaij-Arts C, Christenhusz G, Genuardi M, *et al*: **Towards a European consensus for reporting incidental findings during clinical NGS testing**. *European journal of human genetics : EJHG* 2015.

159. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, *et al*: **ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2013, **15**(7):565-574.

160. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, *et al*: **Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2016.

161. Burke W, Antommaria AH, Bennett R, Botkin J, Clayton EW, Henderson GE, *et al*: **Recommendations for returning genomic incidental findings? We need to talk!** *Genetics in medicine : official journal of the American College of Medical Genetics* 2013, **15**(11):854-859.

162. Gourna EG, Armstrong N, Wallace SE: **Compare and contrast: a cross-national study across UK, USA and Greek experts regarding return of incidental findings from clinical sequencing**. *European journal of human genetics : EJHG* 2016, **24**(3):344-349.

163. Trinidad SB, Ludman EJ, Hopkins S, James RD, Hoeft TJ, Kinegak A, *et al*: **Community dissemination and genetic research: moving beyond results reporting**. *American journal of medical genetics Part A* 2015, **167**(7):1542-1550.

164. Joseph G, Guerra C: **To worry or not to worry: breast cancer genetic counseling communication with low-income Latina immigrants**. *Journal of community genetics* 2015, **6**(1):63-76.

165. Bloss CS, Madlensky L, Schork NJ, Topol EJ: **Genomic information as a behavioral health intervention: can it work?** *Personalized medicine* 2011, **8**(6):659-667.

166. Fox, D. **Genetic Testing Needs a Nudge.** Huffpost. http://www.huffingtonpost.com/dov-fox/genetic-testing-needs-a-n_b_4836298.html. Accessed 30 Oct 2017.

167. Fleck LM: **Just caring: assessing the ethical and economic costs of personalized medicine**. *Urol Oncol* 2014, **32**(2):202-206.

168. Budin-Ljøsne I, Isaeva J, Maria KB, Marie TA, Shen HY, McCarthy MI, Harris JR: **Data sharing in large research consortia: experiences and recommendations from ENGAGE**. *EurJHumGenet* 2013.

169. Chalmers D, Nicol D, Kaye J, Bell J, Campbell AV, Ho CW, *et al*: **Has the biobank bubble burst? Withstanding the challenges for sustainable biobanking in the digital era**. *BMC medical ethics* 2016, **17**(1):39.

170. Abadi-Korek I, Glazer J, Granados A, Luxenburg O, Trusheim MR, Hakak N, Shemer J: **Personalized medicine and health economics: is small the new big? A white paper**. *Isr Med Assoc J* 2013, **15**(10):602-607.

171. Holm IA, Yu TW, Joffe S: **From Sequence Data to Returnable Results: Ethical Issues in Variant Calling and Interpretation**. *Genet Test Mol Biomarkers* 2017, **21**(3):178-183.

172. University of California Santa Cruz. **BRCA Exchange aggregates publicly accessible data on breast cancer genes.** http://news.ucsc.edu/2016/04/brca-exchange.html. Accessed 30 Oct 2017.

173. Berg JS, Amendola LM, Eng C, Van Allen E, Gray SW, Wagle N, *et al*: **Processes and preliminary outputs for identification of actionable genes as incidental**

findings in genomic sequence data in the Clinical Sequencing Exploratory Research Consortium. *Genetics in medicine : official journal of the American College of Medical Genetics* 2013, **15**(11):860-867.

174. Green RC, Berg JS, Berry GT, Biesecker LG, Dimmock DP, Evans JP, *et al*: **Exploring concordance and discordance for return of incidental findings from clinical sequencing**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2012, **14**(4):405-410.

175. Bollinger JM, Scott J, Dvoskin R, Kaufman D: **Public preferences regarding the return of individual genetic research results: findings from a qualitative focus group study**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2012, **14**(4):451-457.

176. Lakes KD, Vaughan E, Lemke A, Jones M, Wigal T, Baker D, Swanson JM, Burke W: **Maternal perspectives on the return of genetic results: Context matters**. *Am J Med GenetA* 2013, **161**(1):38-47.

177. Kolata, G. **When Gene Tests for Breast Cancer Reveal Grim Data but No Guidance.** The New York Times. 2016. https://www.nytimes.com/2016/03/12/health/breast-cancer-brca-genetic-testing.html?_r=0. Accessed 30 Oct 2017.

178. McBride KA, Hallowell N, Tattersall MH, Kirk J, Ballinger ML, Thomas DM, *et al*: **Timing and context: important considerations in the return of genetic results to research participants**. *Journal of community genetics* 2016, **7**(1):11-20.

179. Patrick-Miller L, Egleston BL, Daly M, Stevens E, Fetzer D, Forman A, *et al*: **Implementation and outcomes of telephone disclosure of clinical BRCA1/2 test results**. *Patient education and counseling* 2013, **93**(3):413-419.

180. Leitsalu L, Alavere H, Jacquemont S, Kolk A, Maillard AM, Reigo A, *et al*: **Reporting incidental findings of genomic disorder-associated copy number variants to unselected biobank participants**. *Personalized medicine* 2016, **13**(4):303-314.

181. Burke W, Evans BJ, Jarvik GP: **Return of results: ethical and legal distinctions between research and clinical care**. *Am J Med Genet C Semin Med Genet* 2014, **166C**(1):105-111.

182. Appelbaum PSL, C.W.: **The therapeutic misconception**. In: *The Oxford Textbook of Clinical Research Ethics.* Edited by Emanuel EJG, C.; Crouch, R.A.; Lie, R.K; Miller, F.G.; Wendler, D.: Oxford University Press; 2008.

183. **The Rudy Study.** https://research.ndorms.ox.ac.uk/rudy/. Accessed 30 Oct 2017.

184. Teare HJ, Morrison M, Whitley EA, Kaye J: **Towards 'Engagement 2.0': Insights from a study of dynamic consent with biobank participants**. *Digital Health* 2015, **1**.

185. EURAC Research. **CHRIS (Cooperative Health Research In South Tyrol).** http://www.eurac.edu/en/research/health/biomed/projects/Pages/default.aspx. Accessed 30 Oct 2017.

186. Vayena E, Blasimme A: **Biomedical Big Data: New Models of Control Over Access, Use and Governance**. *J Bioeth Inq* 2017.

187. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB: **Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials**. *BMC medical ethics* 2013, **14**:28.

188. Hartz SM, Quan T, Ibiebele A, Fisher SL, Olfson E, Salyer P, Bierut LJ: **The significant impact of education, poverty, and race on Internet-based research participant engagement**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2016.

189. Lemke AA, Harris-Wai JN: **Stakeholder engagement in policy development: challenges and opportunities for human genomics**. *Genetics in medicine : official journal of the American College of Medical Genetics* 2015, **17**(12):949-957.

190. Burton H, Adams M, Bunton R, Schroder-Back P: **Developing stakeholder involvement for introducing public health genomics into public policy**. *Public Health Genomics* 2009, **12**(1):11-19.

191. European Science Foundation. **Implementation of Medical Research in Clinical Practice.** http://archives.esf.org/fileadmin/Public_documents/Publications/Implem_MedReseach_ClinPractice.pdf. Accessed 30 Oct 2017.

192. **The European Society of Human Genetics.** https://www.eshg.org/home.0.html. Accessed 30 Oct 2017.

193. Daniels N: **Accountability for reasonableness**. *BMJ* 2000, **321**(7272):1300-1301.

194. Fleck LM: **"Just caring": can we afford the ethical and economic costs of circumventing cancer drug resistance?** *J Pers Med* 2013, **3**(3):124-143.

195. **The Norwegian National Research Ethics Committees.** https://www.etikkom.no/en/. Accessed 30 Oct 2017.

196. Severinsen, J. **- Etikk og personvern er forutsetninger for forskning på persondata.** 2016. https://www.etikkom.no/Aktuelt/Nyheter/2016/--etikk-og-personvern-er-forutsetninger-for-forskning-pa-persondata/. Accessed 30 Oct 2017.

197. **Helsenorge.no.** https://helsenorge.no/. Accessed 30 Oct 2017.

198. The Research Council of Norway. **Brukermedvirkning i helseforskningsprogrammene.** https://www.forskningsradet.no/prognett-bedrehelse/Brukermedvirkning_i_helseforskningsprogrammene/1254019677460. Accessed 30 Oct 2017.

199. Manolio TA, Abramowicz M, Al-Mulla F, Anderson W, Balling R, Berger AC, Bleyl S, Chakravarti A, Chantratita W, Chisholm RL *et al*: **Global implementation of genomic medicine: We are not alone**. *Sci Transl Med* 2015, **7**(290):290ps213.

200. Burke W, Burton H, Hall AE, Karmali M, Khoury MJ, Knoppers B, Meslin EM, Stanley F, Wright CF, Zimmern RL *et al*: **Extending the reach of public health genomics: what should be the agenda for public health in an era of genome-based and "personalized" medicine?** *Genetics in medicine : official journal of the American College of Medical Genetics* 2010, **12**(12):785-791.

PAPERS I - IV

APPENDICES

Appendix A. COST Action CHIP ME e-mail survey, July-August 2014

Appendix B. Case study for COST Action CHIP ME workshop, University of Coimbra, October 2014

Appendix C. Request for participation in a research study

Appendix D. Study approval from the Norwegian Social Science Data Services (NSD)

Appendix E. Study extension approval (NSD)

I

BIOPRESERVATION AND BIOBANKING
Volume 14, Number 3, 2016
Mary Ann Liebert, Inc.
DOI: 10.1089/bio.2015.0115

Feedback of Individual Genetic Results to Research Participants: Is It Feasible in Europe?

Isabelle Budin-Ljøsne,[1,2] Deborah Mascalzoni,[3,4] Sirpa Soini,[5] Helena Machado,[6] Jane Kaye,[7] Heidi Beate Bentzen,[1,2,8] Emmanuelle Rial-Sebbag,[9] Flavio D'Abramo,[10] Michał Witt,[11] Geneviève Schamps,[12] Višnja Katić,[13] Dusanca Krajnovic,[14] Working Group 1,[15] and Jennifer R. Harris[16]

Background: There is growing consensus that individual genetic research results that are scientifically robust, analytically valid, and clinically actionable should be offered to research participants. However, the general practice in European research projects is that results are usually not provided to research participants for many reasons. This article reports on the views of European experts and scholars who are members of the European COST Action CHIP ME IS1303 (Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives) regarding challenges to the feedback of individual genetic results to research participants in Europe and potential strategies to address these challenges.
Materials and Methods: A consultation of the COST Action members was conducted through an email survey and a workshop. The results from the consultation were analyzed following a conventional content analysis approach.
Results: Legal frameworks, professional guidelines, and financial, organizational, and human resources to support the feedback of results are largely missing in Europe. Necessary steps to facilitate the feedback process include clarifying legal requirements to the feedback of results, developing harmonized European best practices, promoting interdisciplinary and cross-institutional collaboration, designing educational programs and cost-efficient IT-based platforms, involving research ethics committees, and documenting the health benefits and risks of the feedback process.
Conclusions: Coordinated efforts at pan-European level are needed to enable equitable, scientifically sound, and socially robust feedback of results to research participants.

Introduction

The question of whether to provide feedback on individual genetic research results from genome sequencing to research participants has been discussed for almost two decades.[1] Although the debate is still intense, there is growing consensus among bioethicists, researchers, and policy makers that research participants should be provided with at least some genetic results.[2] Research groups and research funders have recently developed guidelines and recommendations[3,4]

[1]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, Oslo, Norway.
[2]Norwegian Cancer Genomics Consortium, Kreftgenomikk.no, Oslo, Norway.
[3]Center for Research Ethics and Bioethics, Uppsala University, Uppsala, Sweden.
[4]Center for Biomedicine, EURAC, Bolzano, Italy.
[5]Helsinki Biobank, Helsinki University Hospital, Helsinki, Finland.
[6]Centre for Social Studies, University of Coimbra, Coimbra, Portugal.
[7]Nuffield Department of Population Health, Centre for Health, Law and Emerging Technologies (HeLEX), University of Oxford, Oxford, United Kingdom.
[8]Norwegian Research Center for Computers and Law, Faculty of Law, University of Oslo, Oslo, Norway.
[9]UMR 1027, Inserm, Université de Toulouse, Toulouse, France.
[10]Charité–Universitätsmedizin Berlin, Berlin, Germany.
[11]Institute of Human Genetics, Polish Academy of Sciences, Poznań, Poland.
[12]Centre for Medical and Biomedical Law, Université Catholique de Louvain, Leuven, Belgium.
[13]School of Medicine, University of Rijeka, Rijeka, Croatia.
[14]Faculty of Pharmacy, Belgrade University, Belgrade, Serbia.
[15]COST Action CHIP ME IS1303 ''Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives,'' European Commission, Brussels, Belgium.
[16]Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, Norway.

that encourage researchers to provide participants with genetic research results, including secondary findings, which are analytically valid, clinically significant, and clinically actionable, that is, offer reliable information about health conditions that can be medically prevented or treated.[3] However, these guidelines are not completely congruent with policies recently developed in Europe for the feedback of genetic results in clinical settings.[5,6] This lack of harmonization reflects, in part, differences between the genome sequencing analyses conducted for clinical care versus those used in research. Clinical applications are generally limited to the analysis of specific sets of genes to establish a diagnosis or determine the best treatment alternatives. In contrast, research is often discovery oriented and involves conducting analyses encompassing a broader spectrum of variants or genome-wide inquiry. Consequently, there is a greater likelihood that research will generate incidental or other findings that cannot be readily interpreted, but, which still require ethical guidelines regarding how these findings are handled.

With a few recent exceptions,[7,8] the current practice in most European research projects is that individual genetic research results are not provided to research participants.[9] Such practice is, however, expected to be challenged as an increasing number of large-scale research projects are planned or have been launched across Europe, which utilize next-generation sequencing technologies, and most likely will produce individual research results of potential health utility for research participants.[10,11] Another force impacting the practice surrounding return-of-results stems from the research participants themselves, who are increasingly interested in accessing their genetic research results[12,13] and interacting with researchers.[14]

The development of ethically and socially robust feedback mechanisms for providing genetic research results to research participants relies on the identification of potential challenges that may hinder such feedback in Europe, exploration of intercountry similarities concerning these challenges, and determination of whether these challenges can be addressed in a harmonized way. This is particularly relevant given the types of challenges encountered by several projects located outside of Europe that have started to provide results to their participants.[15–21] For instance, data from some projects showed that it was difficult to know whether results could be provided to research participants when the original informed consent did not address this possibility.[16]

Another problem relates to the burden associated with allotting the necessary time and resources needed to implement a meaningful feedback process when the services of genetic counselors and clinicians are not available.[17,18] Moreover, projects often did not have the necessary resources to use the services of laboratories that are accredited to verify the accuracy of the results, and struggled to evaluate the clinical utility of the results in the absence of reference nomenclatures establishing the pathogenicity of variants.[19,20] Finally, some projects reported that it was difficult to know which specific results could be legally provided to participants[21] and often found that research ethics committees were reluctant to support the feedback process.[20]

BioSHaRE-EU (Biobank Standardisation and Harmonisation for Research Excellence in the European Union),[22] a collaborative research project funded by the European Commission Seventh Collaboration Framework (2010–2015), developed frameworks and tools for the harmonization and standardization of biobank activities.[23] Through its ''Ethics'' and ''Strategic Integration, Coordination, and Dissemination'' work packages, it interfaced and worked closely with the COST Action CHIP ME IS1303 (Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives),[24] a European Union framework, which brings together 95 professionals from 25 European countries with expertise in genetics, medicine, bioethics, law, psychology, social sciences and humanities, and informatics. This article reports on results from a consultation with the COST Action members regarding challenges to the feedback of individual genetic results to research participants in Europe and potential ways to address these challenges.

Materials and Methods

Between July and August 2014, the chairs of WG1 (Budin-Ljøsne and Mascalzoni) conducted an email survey among the COST Action members consisting of an open-ended questionnaire to inquire about challenges and practical issues that may impede the feedback of clinically actionable genetic results to research participants in their country and to identify potential steps that could be taken to facilitate such feedback. The COST Action members were asked, whenever possible, to coordinate responses within their country. To follow up on the information provided through the email survey, WG1 convened a 1-day workshop at the University of Coimbra, Portugal, in October 2014, which included 43 members of the COST Action from 21 European countries. The workshop was organized as an open space technology (OST) day,[25] an approach to organizing meetings that enables participants to openly discuss a specific theme without having to follow a predefined detailed agenda. The workshop was moderated by a COST Action member with expertise in leading OST events.

Notes were taken by appointed participants during the workshop and gathered by the WG1 chairs at the end of the day. The data from the email survey and the workshop notes were collated, summarized, and analyzed using a content analysis approach in an inductive way.[26] Three categories emerged from the data: legal, financial, and organizational/societal issues. Coding was conducted independently by Budin-Ljøsne and Mascalzoni and disagreements in abstractions were discussed with Soini and Machado and resolved by consensus. Interrater reliability and reflection were maximized through comparing coding between all the authors.

Results

Nineteen questionnaires were collected, providing information from 14 of the 25 COST Action countries (Bosnia and Herzegovina, Croatia, Czech Republic, Estonia, Finland, Germany, Greece, Italy, Norway, Poland, Portugal, Serbia, Slovenia, and United Kingdom). In addition, representatives from eight countries (Belgium, Denmark, France, Iceland, Ireland, Malta, The Netherlands, and Sweden) contributed to the workshop discussions. The COST Action members identified challenges to the feedback of individual research results to research participants in Europe, which fall into three broad categories spanning legal, financial, and organizational/societal issues as described below and summarized in Table 1.

Challenges to the feedback of individual genetic results to research participants

Legal challenges. The current legal landscape in Europe provides a framework for returning results under the Convention on Human Rights and Biomedicine,[27] the accompanying

Table 1. Challenges to the Feedback of Individual Genetic Results to Research Participants in Europe and Potential Strategies to Address Challenges

Challenges
Legal challenges
Unclear how current provisions in European conventions should be interpreted
European conventions often neither ratified by countries nor implemented in national legislation
When national legislation exists, unclear how it applies in practice
Financial challenges
No specific funding to support the feedback process
Unclear whether healthcare systems are willing to finance the feedback process
Organizational/societal challenges
Lack of professional guidelines and best practices to govern the feedback of results
Lack of qualified staff (e.g., genetic counselors) to feedback results to research participants
Insufficient collaboration between professions to support the feedback process
Lack of awareness among research participants regarding the possibility of feedback
Potential strategies to address challenges
Develop harmonized European guidelines for the feedback of results
Allocate specific funding to the feedback process
Document the health benefits of providing genetic results to research participants
Involve research ethics committees early in the design of the feedback process
Promote interdisciplinary and cross-institutional collaboration, for example, through expert networks
Develop educational programs for healthcare professionals
Explore cost-efficient and IT-based tools (e.g., dynamic consent, web-based feedback)
Discuss the modalities of the feedback process with research participants and the general public

Additional Protocol on Biomedical Research,[28] and through the Council of Ministers Recommendation on biological materials of human origin.[29] These legal instruments state that research participants have a right to know any information collected on their health. The Additional protocol also outlines a researcher's "duty of care," stating that, "If research gives rise to information of relevance to the current or future health or quality of life of research participants, this information must be offered to them. That shall be done within a framework of healthcare or counseling. In communication of such information, due care must be taken to protect confidentiality and to respect any wish of a participant not to receive such information."[28] However, there is still uncertainty about which kind of information equals relevant health information and what a researcher's duty of care entails. Furthermore, while many European countries have ratified the Convention and implemented it into national legal frameworks, there are still notable exceptions such as the United Kingdom, Belgium, Sweden, and Germany, and the number of countries that have ratified the Additional Protocol on Biomedical Research remains small.

Only a few countries such as Estonia,[30] France,[31] Finland,[32] Italy,[33] and Norway[34] are known to have national regulations offering research participants the possibility to access (usually upon request) their genetic and other results. However, the modalities of such access remain largely unclear. For instance, it is uncertain whether access to raw sequences should be granted to research participants. Furthermore, national legislations often require that research data and clinical patient data are processed separately, thus potentially hindering the use of research data for clinical purposes.

Financial challenges. Currently, there is no specific financing dedicated to support the feedback process. However, such a process may require additional funding, for instance to verify the analytical validity of the findings, cover the cost of genetic counseling, or to pay for the necessary administrative support to recontact participants. Funding schemes for research normally do not encompass the cost of feedback. Similarly, it is unclear whether healthcare systems are willing to finance the feedback of genetic results that are not produced in a clinical setting and do not comply with clinical standards.

Organizational/societal challenges. Lack of professional guidelines and best practices. Professional guidelines and best practices for the feedback of results to research participants are largely missing in Europe, with the exception of a few countries such as the United Kingdom and Norway.[7,35–37] Where guidelines do exist, they are often general and do not offer guidance regarding the specific genetic variants for which feedback of results should be provided to participants. In the absence of clear guidelines, the research participants' access to their genetic results may be handled on a case-by-case basis. This may lead to inequitable treatment, for instance if some projects provide results to their participants, while other similar projects do not provide results or decide to apply different criteria for doing so. This may be a particularly salient issue in multicenter European studies where individuals participating in the same study, but living in different countries, may have differential access to their results.

Lack of qualified staff. Providing genetic results to research participants within a qualified professional framework may be difficult as there are few genetic counselors and clinical geneticists in Europe, in particular in rural regions. Furthermore, the qualifications of genetic counselors often vary due to the lack of standard training requirements. General practitioners and family doctors, who could potentially contribute in the feedback process, may not have the necessary education in genetics or the capacity to perform additional tasks, in particular in countries where there are too few medical doctors per inhabitant. Prioritization of national healthcare provisions also plays a major role here; the workload of professionals is primarily allocated based on clinical needs.

Insufficient interdisciplinary and cross-institutional collaboration. The feedback process normally requires that professions work together. For instance, researchers and

healthcare professionals may collaborate to validate research results to a clinical standard or to include results communication in a healthcare setting procedure. However, such collaboration is often not well established. While clinicians leading research projects may be able to use their established networks to organize such activities, researchers operating outside of clinical settings, for instance in biobanks projects, may struggle to develop the necessary alliances.

Lack of awareness regarding the possibility of receiving research results. In most established research projects, the participants are not aware that genetic results may be provided to them, as this possibility was not mentioned in the original informed consent. Collecting the renewed consent of participants to allow for the feedback process may be burdensome, expensive, or even impossible for research projects with limited resources. However, future informed consents are expected to inform participants about the possibility of feedback, thus potentially eliminating the need for renewed consent.

Proposed strategies to address challenges

The strategies proposed by the COST Action members to address the challenges described above are listed below and summarized in Table 1.

Clarify legal requirements for the feedback of results. The current legal situation is ambiguous for both researchers and participants. However, any pursuit of legally binding access rights to research results ought to also pay attention to practical and economical obstacles. Researchers should be encouraged to have clear policies regarding whether or not they report back the results, and in the former case, what would be the process for validation of results, counseling, and care. Further international legal harmonization in this area should be sought.

Elaborate harmonized European best practices. European researchers, research funders, research and healthcare institutions, medical societies, and community representatives should collaborate at a European level to develop harmonized European best practices for the feedback of genetic research results to research participants. These discussions should take into consideration the specific needs, contexts, laws, and cultural norms of European research. Recent recommendations for the management of genetic results in research settings (listed in Table 2)[7,35–47] and clinical settings[5,6] may be used to guide such work.

Allocate specific funding to the feedback process. Funding schemes should include specific funding that can be granted to researchers and healthcare services that establish collaboration to provide results to participants. The expected cost

Table 2. Main Recommendations and Guidelines for the Feedback of Genetic Research Results to Research Participants

Origin	*Recommendations/guidelines*
Canada (LDP)	An implementation framework for the feedback of individual research results and incidental findings in research[38]
Canada (P^3G)	Return of research results and incidental findings policy statement[41]
Canada (RMGA)	Statement of principles on the return of research results and incidental findings[40]
Norway (NBAB)	Proposal for a guideline for the use of genome sequencing and genome data in clinical and research settings[35]
The Netherlands	Feedback of individual genetic results to research participants: in favor of a qualified disclosure policy[43]
United Kingdom (MRC and Wellcome Trust)	Framework on the feedback of health-related findings in research[37]
United Kingdom (UK10K)	Managing clinically significant findings in research: the UK10K example[7]
United Kingdom (PHG Foundation)	Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project[36]
USA	Managing incidental findings and research results in genomic research involving biobanks and archived data sets[42]
USA (CSER and eMERGE)	Return of genomic results to research participants: the floor, the ceiling, and the choices in between[39]
USA (NHLBI)	Ethical and practical guidelines for reporting genetic research results to study participants: updated guidelines from a National Heart, Lung, and Blood Institute[44]
USA (Presidential Commission for the Study of Bioethical Issues)	Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research, and Direct-to-Consumer contexts[47]
Origin	*Recommendations/guidelines for pediatric research*
Canada (P^3G)	Return of whole-genome sequencing results in pediatric research: a statement of the P3G international pediatrics platform[45]
Canada (ICOB)	Guidelines for return of research results from pediatric genomic studies: deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board[46]

CSER, Clinical Sequencing Exploratory Research; eMERGE, Electronic Medical Records and Genomics Network; ICOB, Informed Cohort Oversight Board; LDP, Liver Disease Project; MRC, Medical Research Council; NBAB, Norwegian Biotechnology Advisory Board; NHLBI, National Heart, Lung, and Blood Institute; PHG Foundation, Foundation for Genomics and Population Health; P^3G, Public Population Project in Genomics and Society; RMGA, Network of Applied Genetic Medicine.

of the feedback process should be determined as early as possible in research projects and specified in research applications.[2]

Document the health benefits of genetic research results. Providing genetic research results to research participants may enable clinicians to establish more precise diagnoses and prevent serious conditions. It may also help research participants inform their own health decisions. Documenting the health benefits of genetic research results may convince funders, policy makers, and decision makers to take the necessary legal, financial, and organizational steps to support the feedback process.

Involve research ethics committees in the feedback process. Research ethics committees should carefully consider the feedback process before research is commenced and evaluate to what extent and how results may be provided to research participants. These committees may also develop an ethical framework for determining the researchers' responsibilities for feedback of results and reviewing the appropriateness of researchers' plans for communicating results.

Enhance the feedback process through interdisciplinary and cross-institutional collaboration. Expert networks of clinicians, molecular biologists, bioinformaticians, and geneticists should be established in research projects to facilitate the feedback process. If necessary, alliances may be developed with commercial actors for the supply of specific services (e.g., laboratory services), which are not available to research teams, but are needed to provide results.

Increase counseling expertise. Educational programs should be developed to enhance genetic knowledge among healthcare professionals such as medical doctors, clinicians, clinical ethicists, psychologists, nutritionists, nurses, biologists, and laboratory geneticists who are strategically placed in the community and may potentially contribute to the feedback process. Such programs could for instance build upon the common set of core competences in genetics recently proposed by the European Society of Human Genetics.[48]

Explore cost-efficient solutions and tools. Participants' preferences regarding the use of interactive and cost-efficient IT-based tools such as dynamic consent[49] and web-based[50] and telephone-based platforms[51] for access to genetic results should be explored. Cognitive computing for the translation of genetic results into information of clinical utility[52] may also be considered. This includes research to investigate ethical and legal requirements pertaining to the use of such platforms.

Increase research participants' and the general public's awareness regarding the feedback of results. Promoting citizens' participation in science is central to the European scientific reform.[53] Researchers should develop mechanisms to discuss with citizens and research participants the modalities of the feedback of results, for instance through public consultations, debates, and social networks. While it may often not be feasible to provide individual level results, the overall results of the study could be meaningful for people and provided as an acknowledgement that their participation and contribution are important.

Discussion

The perspective of European researchers and scholars who are members of the COST Action CHIP ME is that providing genetic research results to research participants in Europe is, at present, hardly feasible due to numerous legal, financial, organizational, and societal challenges. Our study results corroborate observations made by respondents to a recent European public consultation who emphasized that providing genetic results to research participants may be difficult in the absence of agreement on best practices, clarity regarding which results to provide, standards for validation of research results, and allocated funding.[54] Similar observations have been made in clinical genetics settings where the feedback process is often reported to be practically unfeasible due to legal, psychological, and organizational issues.[55] Logistical issues may also be encountered when results are available, but the research participants who should receive the results cannot be found, such as when personal identifiers are removed to protect the participants' privacy, which is a common practice in biobank research.[38]

To help overcome these challenges, the COST Action members believe that the proposed recommendations would help develop a unified strategy to support a pan-European approach to the feedback of results. These recommendations are founded on important intercountry commonalities that emerged in our research. First, challenges to the feedback process are strikingly similar across European countries; addressing these challenges collaboratively may therefore reduce duplication of efforts and reinforce cross-border research collaboration. Second, European countries are committed to provide, to the extent of their available resources and capacities, equitable access to healthcare of appropriate quality.[27] If, as most COST Action members believe, research participants' access to genetic research results that are clinically significant and actionable can contribute to better prevention and healthcare, such access should be made equal and fair across research projects and across countries. However, this is only possible if legal provisions, best practices, and organizational structures for the feedback of results are harmonized throughout Europe. Third, European research is increasingly collaborative, cross-national, and multicentered. Researchers rely steadily more on European financial instruments such as the Horizon 2020 of the EU Research and Innovation programme[56]for funding. In a context of strained resources and limited time, it therefore makes sense to give priority to developing European harmonized strategies for the feedback of results that can be applicable in all research projects independent of their geographical location, rather than national strategies that may differ dramatically between countries or even require contradictory action. It should, however, be noted that developing European harmonized strategies for the feedback of genetic research results to research participants does not mean that a single approach to the feedback process must be adopted throughout Europe. The specificities and varying contexts of research projects and countries should be taken into consideration and strategies for the feedback of results adapted accordingly.

The recommendations proposed by the COST members aim to address a wide range of considerations spanning legal, financial, organizational, and societal issues. Realization of the ideas comprising these recommendations will require a stepwise process with some endeavors more readily implementable than others. For instance, involving research committees in the design of the feedback process and developing interdisciplinary and cross-institutional collaboration to support such feedback does not pose critical barriers; established channels already exist for engaging the relevant actors and entities. In contrast, increasing counseling expertise among healthcare professionals,

documenting the health benefits of genetic research results, and allocating additional funding to the feedback process require more extensive efforts, are time-consuming, and may be difficult to achieve in countries where the financial resources of healthcare systems are scarce. To help move this agenda forward, it is important to work together as a community to build consensus and momentum through projects and initiatives that bring relevant stakeholders together such as this COST action.

Furthermore, we can start to prioritize efforts on those recommendations that can be implemented rapidly and at a reasonable cost. As an illustration, work has already been completed in exploring how the feedback process may be supported through the use of online tools.[57] Some of these tools are open source and are readily available to research groups.[57] By incorporating information in the informed consent process about the possibility that genetic results may be provided in the future and offering research participants the opportunity to reflect upon such possibility, research groups may be able to gradually start providing the results that are most urgent. Researchers could take a number of actions such as discussing with their research ethics committee and cooperating with clinical laboratories and clinicians in their network to identify the results that should be given priority. Importantly, researchers urgently need clarification regarding legal requirements for the feedback of results and access to practical guidelines outlining which type of results should be fed back and how. As noted above, such guidelines may be developed on the basis of already existing policies.

A critical consideration going forward is how to best harmonize such policies between clinical and research milieus. The current situation in which clinical recommendations[5,6] may only be partly transferable to research settings due to differences in methodologies and quality requirements may change rapidly as the methodologies and sequencing coverage used in each setting become more similar. Currently, clinicians often use high levels of sequencing coverage and focus on specific sets of genes to produce precise results that can be used for diagnostic purposes. In contrast, researchers usually produce, in a single test, data for up to billions of individual analytes.[58] Assessing the analytical performance of genetic tests, including their specificity, sensitivity, and level of precision, is challenging when such large amounts of data are produced.[58] Similarly, determining which genetic variants have clinical utility is difficult as the significance of most variants detected by researchers is currently unknown, and our current knowledge of polygenic risk assessment is in nascent stages, as is our understanding of population differences associated with the risk of specific variants. Research guidelines will need to include additional criteria and assessment methods to certify the quality and accuracy of genetic results produced through research and provide references to well-annotated genetic reference databases establishing the pathogenicity of variants.

With the rapid changes in technologies and the increased integration of personal genomes and sequencing in healthcare, the divide between research and clinical care may diminish considerably (or completely disappear) with regard to the technical differences underlying genomic information that is generated about a participant versus a patient. This will add new nuance regarding the differences in the requirements between clinical care and research to provide results to the individual.

Providing individual research results to participants is expected to benefit research participants as it enables more proactive behavior, whereby individuals may be able to seek qualified medical help and receive appropriate advice or treatment. However, it is important to consider the risks, as well as the benefits, of providing results. Research participants may react differently when learning about their genetic status: some with anxiety and others with eagerness to act, for instance by starting treatment or undergoing surgery. Knowledge about genetic disease or predisposition may also impact the life of biological relatives and could have significance for future family planning.[19] It is therefore important that results are provided in a qualified and transparent manner, and in accordance with the participants' wishes, and that researchers specify the extent to which the results are accurate and reliable to guide people's choices and avoid unnecessary harm and distress.

Implications for European decision makers

Providing individual genetic research results that are clinically useful and actionable is increasingly seen as an ethical and legal obligation, and a healthcare necessity.[3] Informing research participants about their results makes sense in today's world where patients and research participants are increasingly willing to share their personal health information,[59] including clinical and lifestyle data, with researchers and healthcare providers and also take initiatives to share their data through web-based portals[60] and devices.[61] However, relying solely on the good will and initiative of researchers to provide results to research participants is not sufficient. European policy makers, funders, and research and healthcare institutions have a joint responsibility to ensure that the necessary prerequisites are in place to enable research participants to access their genetic research results of health relevance in an equitable, scientifically sound, and ethically and socially robust way across Europe. The COST Action members will continue their efforts to coordinate activities at the European level to help advance this agenda. We hope that our research results will contribute to increased awareness regarding the need to develop mechanisms that enable biobanks and research groups to fulfill their ethical obligations toward research participants.

Acknowledgments

The authors would like to thank Professor Heather Skirton, Plymouth University, for skillfully leading the OST workshop in Coimbra; the COST Action CHIP ME chairs of WG2 and WG3 for helping at collecting questionnaires; the COST Action CHIP ME members for their useful contributions; Professor Michael Hummel, Charité–Universitätsmedizin Berlin, Professor Jan Helge Solbakk, University of Oslo, and Professor Jean-Marc Hausman, Université catholique de Louvain, for their comments. This article is based upon work from COST Action IS1303 ''Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives,'' and is supported by COST (European Cooperation in Science and Technology) (www.cost.eu); the Biobank Standardisation and Harmonisation for Research Excellence in the European Union (BioSHaRE-EU) program, which received funding from the European Union Seventh Framework Programme (FP7/2007–2013) under Grant Agreement No.

261433; the National Research and Innovation Platform for Personalized Cancer Medicine funded by the Norwegian Research Council (NFR BIOTEK2021/ES495029); the European Union Seventh Framework Programme (FP7/2007–2013) under Grant Agreement No. 305444 (RD-Connect); the Innovative Medicines Initiative project BTCure (Grant Agreement No. 115142-1); the BioBanking and Molecular Resource Infrastructure of Sweden project financed by the Swedish Research Council (BBMRI)LPC (313010); LegRegPCM (Legal Regulation of Information Processing relating to Personalized Cancer Medicine) funded by the Norwegian Research Council (NFR BIOTEK2021/238999/O30); the European Research Council, under Grant Agreement No. 648608; and Biobank Norway, funded by the Norwegian Research Council (NFR 197443/F50). JK is funded under Wellcome Trust Award 096599/2/11/Z and the EU F7 project BIOSHARE.

Author Disclosure Statement

No conflicting financial interests exist.

References

1. Bredenoord AL, Kroes HY, Cuppen E, et al. Disclosure of individual genetic data to research participants: The debate reconsidered. Trends Genet 2011;27:41–47.
2. Wolf SM. Return of individual research results and incidental findings: Facing the challenges of translational science. Annu Rev Genomics Hum Genet 2013;14:557–577.
3. Knoppers BM, Zawati MH, Senecal K. Return of genetic testing results in the era of whole-genome sequencing. Nat Rev Genet 2015;16:553–559.
4. Shkedi-Rafid S, Dheensa S, Crawford G, et al. Defining and managing incidental findings in genetic and genomic practice. J Med Genet 2014;51:715–723.
5. van El CG, Cornel MC, Borry P, et al. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. Eur J Hum Genet 2013; 21(Suppl 1):S1–S5.
6. Claustres M, Kozich V, Dequeker E, et al. Recommendations for reporting results of diagnostic genetic testing (biochemical, cytogenetic and molecular genetic). Eur J Hum Genet 2014;22:160–170.
7. Kaye J, Hurles M, Griffin H, et al. Managing clinically significant findings in research: The UK10K example. Eur J Hum Genet 2014; 22:1100–1104.
8. Haukkala A, Kujala E, Alha P, et al. The return of unexpected research results in a biobank study and referral to health care for heritable long QT syndrome. Public Health Genomics 2013;16:241–250.
9. Chakradhar S. Many returns: Call-ins and breakfasts hand back results to study volunteers. Nat Med 2015;21:304–306.
10. Genomics England. The 100,000 Genomes Project. Available at: www.genomicsengland.co.uk/the-100000-genomes-project/ Accessed August 31, 2015.
11. Estonian Genome Center, University of Tartu. Available at: www.geenivaramu.ee/en Accessed August 31, 2015.
12. Facio FM, Eidem H, Fisher T, et al. Intentions to receive individual results from whole-genome sequencing among participants in the ClinSeq study. Eur J Hum Genet 2013; 21:261–265.
13. Middleton A, Morley KI, Bragin E, et al. Attitudes of nearly 7000 health professionals, genomic researchers and publics toward the return of incidental results from sequencing research. Eur J Hum Genet 2016;24:21–29.
14. Kaye J, Curren L, Anderson N, et al. From patients to partners: Participant-centric initiatives in biomedical research. Nat Rev Genet 2012;13:371–376.
15. Kullo IJ, Haddad R, Prows CA, et al. Return of results in the genomic medicine projects of the eMERGE network. Front Genet 2014;5:50.
16. Fullerton SM, Wolf WA, Brothers KB, et al. Return of individual research results from genome-wide association studies: Experience of the Electronic Medical Records and Genomics (eMERGE) Network. Genet Med 2012;14:424–431.
17. Johns AL, Miller DK, Simpson SH, et al. Returning individual research results for genome sequences of pancreatic cancer. Genome Med 2014;6:42.
18. Christensen KD, Roberts JS, Shalowitz DI, et al. Disclosing individual CDKN2A research results to melanoma survivors: Interest, impact, and demands on researchers. Cancer Epidemiol Biomarkers Prev 2011;20:522–529.
19. Lawrence L, Sincan M, Markello T, et al. The implications of familial incidental findings from exome sequencing: The NIH Undiagnosed Diseases Program experience. Genet Med 2014;16:741–750.
20. Keogh LA, Fisher D, Sheinfeld Gorin S, et al. How do researchers manage genetic results in practice? The experience of the multinational Colon Cancer Family Registry. J Community Genet 2014;5:99–108.
21. Klitzman R, Buquez B, Appelbaum PS, et al. Processes and factors involved in decisions regarding return of incidental genomic findings in research. Genet Med 2014;16:311–317.
22. BioSHaRE-EU (Biobank Standardisation and Harmonisation for Research Excellence in the European Union). Available at: www.bioshare.eu Accessed December 18, 2015.
23. BioSHaRE-EU. Catalogue of tools and services for data sharing. Available at: www.bioshare.eu/sites/default/files/BioSHaRE%20Catalogue%20of%20tools%20and%20services%20for%20data%20sharing.pdf Accessed December 18, 2015.
24. COST. COST Action CHIP ME IS1303. Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives. Available at: www.cost.eu/COST_Actions/isch/Actions/IS1303 Accessed August 31, 2015.
25. Open Space Technology. Available at: http://en.wikipedia.org/wiki/Open_Space_Technology Accessed March 31, 2015.
26. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs 2008;62:107–115.
27. Council of Europe. Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Available at: http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm Accessed March 31, 2015.
28. Council of Europe. Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research. Available at: http://conventions.coe.int/Treaty/en/Treaties/Html/195.htm Accessed March 31, 2015.
29. Council of Europe. Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin. Available at: https://wcd.coe.int/ViewDoc.jsp?id=977859 Accessed March 31, 2015.
30. Riigi Teataja. Estonian Human Genes Research Act. Available at: www.riigiteataja.ee/en/eli/531102013003/consolide Accessed March 31, 2015.

31. LOI n° 2012-300 du 5 mars 2012 relative aux recherches impliquant la personne humaine. Available at: www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000025441587&dateTexte=&categorieLien=id Accessed March 31, 2015.
32. Ministry of Social Affairs and Health, Finland. Finnish Biobank Act 688/2012. Available at: www.finlex.fi/en/laki/kaannokset/2012/en20120688.pdf Accessed March 31, 2015.
33. The Garante per la protezione dei dati personali. General Authorisation No. 8/2012 for the Processing of Genetic Data—13 December 2012. Available at: www.garanteprivacy.it/web/guest/home/docweb/-/docweb-display/docweb/2474250 Accessed March 31, 2015.
34. LOV 2008-06-20 nr 44. Lov om medisinsk og helsefaglig forskning (helseforskningsloven). Available at: www.lovdata.no/all/hl-20080620-044.html#28 Accessed March 31, 2015.
35. Norwegian Biotechnology Advisory Board. Forslag til veileder og retningslinjer for bruk av genomsekvensering og genomdata i klinikk og forskning. Available at: www.bioteknologiradet.no/filarkiv/2012/11/Veileder_genomsekvensering_091112_til_nett.pdf Accessed March 31, 2015.
36. Phg Foundation. Managing incidental and pertinent findings from WGS in the 100,000 Genomes Project. Available at: www.phgfoundation.org/file/13772/ Accessed August 31, 2015.
37. Medical Research Council and Wellcome Trust. Framework on the feedback of health-related findings in research. Available at: www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtp056059.pdf Accessed August 31, 2015.
38. Thorogood A, Joly Y, Knoppers BM, et al. An implementation framework for the feedback of individual research results and incidental findings in research. BMC Med Ethics 2014; 15:88.
39. Jarvik GP, Amendola LM, Berg JS, et al. Return of genomic results to research participants: The floor, the ceiling, and the choices in between. Am J Hum Genet 2014;94:818–826.
40. Centre of Genomics and Policy, McGill University. Statement of principles for the return of research results and incidental findings. Available at: www.rmga.qc.ca/en/documents/RMGAStatement_Principles_English_May272013_000.pdf Accessed August 31, 2015.
41. Knoppers BM, Deschenes M, Zawati MH, et al. Population studies: Return of research results and incidental findings Policy Statement. Eur J Hum Genet 2013;21:245–247.
42. Wolf SM, Crock BN, Van NB, et al. Managing incidental findings and research results in genomic research involving biobanks and archived data sets. Genet Med 2012;14:361–384.
43. Bredenoord AL, Onland-Moret NC, Van Delden JJ. Feedback of individual genetic results to research participants: In favor of a qualified disclosure policy. Hum Mutat 2011;32:861–867.
44. Fabsitz RR, McGuire A, Sharp RR, et al. Ethical and practical guidelines for reporting genetic research results to study participants: Updated guidelines from a National Heart, Lung, and Blood Institute working group. Circ Cardiovasc Genet 2010;3:574–580.
45. Knoppers BM, Avard D, Senecal K, et al. Return of whole-genome sequencing results in paediatric research: A statement of the P3G international paediatrics platform. Eur J Hum Genet 2014;22:3–5.
46. Holm IA, Savage SK, Green RC, et al. Guidelines for return of research results from pediatric genomic studies: Deliberations of the Boston Children's Hospital Gene Partnership Informed Cohort Oversight Board. Genet Med 2014;16:547–552.
47. Presidential Commission for the Study of Bioethical Issues. Anticipate and communicate: Ethical management of incidental and secondary findings in the clinical, research, and direct-to-consumer contexts. Available at: http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf Accessed August 31, 2015.
48. Skirton H, Lewis C, Kent A, et al. Genetic education and the challenge of genomic medicine: Development of core competences to support preparation of health professionals in Europe. Eur J Hum Genet 2010;18:972–977.
49. Williams H, Spencer K, Sanders C, et al. Dynamic consent: A possible solution to improve patient confidence and trust in how electronic patient records are used in medical research. JMIR Med Inform 2015;3:e3.
50. Coriell Personalized Medicine Collaborative. Available at: https://cpmc.coriell.org/ Accessed August 31, 2015.
51. Graves KD, Sinicrope PS, Esplen MJ, et al. Communication of genetic test results to family and health-care providers following disclosure of research results. Genet Med 2014;16:294–301.
52. IBM Watson. Available at: www.ibm.com/smarterplanet/us/en/ibmwatson/index.html Accessed August 31, 2015.
53. European Commission. Public Consultation "Science 2.0". Science in transition. Available at: http://ec.europa.eu/research/consultations/science-2.0/background.pdf Accessed August 31, 2015.
54. Council of Europe Committee on Bioethics. Compilation of replies to the public consultation concerning the Working document on research on biological materials of human origin. Available at: www.coe.int/t/dg3/healthbioethic/Activities/10_Biobanks/INF(2014)13%20compilation%20biobanks%20e.pdf Accessed August 31, 2015.
55. Otten E, Plantinga M, Birnie E, et al. Is there a duty to recontact in light of new genetic technologies? A systematic review of the literature. Genet Med 2015;17:668–678.
56. European Commission. Horizon 2020. The EU Framework Programme for Research and Innovation. Available at: http://ec.europa.eu/programmes/horizon2020/en/what-horizon-2020 Accessed August 31, 2015.
57. The Rudy Study. Available at: https://research.ndorms.ox.ac.uk/rudy/ Accessed December 18, 2015.
58. Food and Drug Administration. Developing analytical standards for NGS testing. Available at: www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf Accessed 17, February 2016.
59. Truven Health Analytics NPR. Health Poll. Data Privacy. Available at: http://truvenhealth.com/Portals/0/NPR-Truven-Health-Poll/NPRPulseDataPrivacy_Nov2014.pdf Accessed August 31, 2015.
60. Free the data. Available at: www.free-the-data.org/ Accessed August 31, 2015.
61. Apple. ResearchKit. Available at: www.apple.com/researchkit/ Accessed August 31, 2015.

Address correspondence to:
Isabelle Budin-Ljøsne, MA
Centre for Medical Ethics
Institute of Health and Society
University of Oslo
P.O. Box 1130 Blindern
Oslo NO-0318
Norway

E-mail: i.b.ljosne@medisin.uio.no

II

Original Paper

Public Health Genomics

Public Health Genomics 2015;18:131–138
DOI: 10.1159/000373919

Received: September 23, 2014
Accepted after revision: January 8, 2015
Published online: March 6, 2015

Ask Not What Personalized Medicine Can Do for You – Ask What You Can Do for Personalized Medicine

Isabelle Budin-Ljøsne[a, b] Jennifer R. Harris[c]

[a]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, [b]Norwegian Cancer Genomics Consortium, and [c]Division of Epidemiology, Department of Genes and Environment, Norwegian Institute of Public Health, Oslo, Norway

Key Words
Personalized medicine · Ethics and society · Citizen behavior · Genetics

Abstract
Background: Personalized medicine (PM) aims to offer tailored health care to individuals on the basis of their genetic profile. This paper explores the types of behaviors and practices that citizens are expected to adopt under PM, examines whether such expectations are realistic, and proposes strategies that could support citizens in the adoption of these behaviors. ***Methods:*** Recent reports from national and international medical organizations and funders of PM are reviewed to investigate the types of behaviors and practices that citizens are expected to adopt under PM. These behaviors are examined in light of the current knowledge regarding citizen involvement in health care. ***Results:*** Under PM, citizens are expected to be much more educated, proactive, and engaged in their health care than under conventional medical models. Actualizing such behaviors and practices may, however, be difficult or even unattainable for some groups of citizens. ***Conclusions:*** Educating citizens in PM, as proposed in the reports, is important but may not suffice for the adoption of new behaviors and practices by a majority of citizens. Approaches taking into consideration the heterogeneity of backgrounds, abilities, and resources among citizens are needed and include modifying reimbursement and pricing mechanisms, diversifying research, and developing low-cost PM programs.

Introduction

Since the mapping of the human genome in 2003, enormous progress has been made in understanding molecular and genetic pathways underpinning human health and disease. The acquisition of new knowledge coupled with rapid developments within genetic sequencing and testing as well as plummeting costs of new technologies continually improve our potential to provide better health care. Genetic and genomic information can be used to unveil disease predisposition and onset in individuals much earlier and more accurately than previously possible, and an increasing number of therapies will target disease-specific molecules and biological pathways, rather than simply treating the symptoms of diseases [1]. The traditional one-size-fits-all approach to disease prevention, diagnosis, and treatment, which has proved to be inefficient, expensive, and sometimes even hazardous, is expected to be progressively replaced by a more individu-

KARGER 125

E-Mail karger@karger.com
www.karger.com/phg

1662–4246/15/0183–0131$39.50/0

Isabelle Budin-Ljøsne
Centre for Medical Ethics
PO Box 1130 Blindern
NO–0318 Oslo (Norway)
E-Mail i.b.ljosne@medisin.uio.no

alized and tailor-made approach. This 'personalization' of health care has captured worldwide attention, with various strategies under development to facilitate its realization. For instance, precision medicine aims to create a new taxonomy of diseases based on molecular biology with the objective to improve disease classification and inform health-care treatment and decisions [2]. Stratified medicine aims to group patients based on their genetic risk of disease or response to therapy with the objective to offer treatment that specifically targets those groups [3]. Personalized medicine (PM) aims to use information about an individual's genotype to guide decisions regarding the prevention, diagnosis, and treatment of diseases [4]. These strategies work towards the common objective to provide 'the right patient with the right drug at the right dose at the right time' [5].

The production, integration, and use of genetic and genomic information in health care requires significant changes in the way such care is organized and provided to individuals. Recent reports discussing precision medicine [2], stratified medicine [3], and PM [6–9] have highlighted the roles and actions that relevant stakeholders of PM should undertake to enable a smooth integration of genetic and genomic information into health care and, thus, facilitate the transition to a tailor-made approach to medicine, which we hereafter refer to as personalized medicine (PM). These reports (published by national and international medical organizations and funders) provide practical recommendations to researchers, health-care professionals, policy makers, health authorities, and pharmaceutical companies. For instance, researchers are encouraged to develop data management infrastructures to handle the growing amount of data produced from genetic sequencing, health-care suppliers are advised to reorganize their clinical services to enable the integration of genetic and molecular information in the electronic health records of patients, and pharmaceutical companies are encouraged to identify and qualify a range of new biomarkers that predict clinical response [9]. However, the successful integration of genetic and genomic information into health care also depends upon the actions of another central group of stakeholders, namely citizens. While many of the reports emphasize the importance of citizen engagement in PM and propose strategies to educate and engage citizens regarding new medical developments, they do not systematically provide recommendations for what citizens could do to enhance the realization of PM but rather describe the behaviors and actions that are important for individuals to adopt. In this paper, we scrutinize the content of these reports to identify the specific behaviors and practices that are targeted, examine obstacles that could prohibit many citizens to adopt these behaviors, and propose strategies that may facilitate such adoption.

Methods

In October 2013, we conducted an internet search using Google and the following search terms: ['personalized medicine'] and/or [personalised medicine] and/or ['stratified medicine'] and/or ['precision medicine'] combined with [report] and [pdf] to identify publicly available reports discussing the realization of PM. Reports from national and international medical organizations and funders published between January 2008 and October 2013, written in English and providing recommendations for the adoption of PM, were selected.

The reports were reviewed using a qualitative content analysis method [10] according to the following steps. First, the content in the reports that describes behaviors and/or practices of citizens and/or patients was identified, extracted, and compiled into a list of verbatim texts. Next, the substantive content of these texts was examined in order to code and categorize it according to the type of behavior and/or practice it describes. Then, the categories were further examined to identify overarching themes into which the specific types of behaviors and practices could be grouped. Each category of behavior and/or practice was then analyzed in light of current knowledge regarding citizen and/or patient involvement in health care to determine the extent to which citizens and/or patients may realistically adopt, wholly or partly, such behaviors and practices. Hurdles that may impede such adoption were identified and discussed, and potential strategies to overcome these challenges were proposed.

Results

Eighteen publicly available reports were identified (table 1) [2, 3, 5–9, 11–21]. Importantly, these reports do not make a clear distinction regarding when expectations apply to citizens in general or to patients in particular. All the reports use the term 'patient' at least once to refer to the end users of PM. Eight reports either use the term 'citizen' or a combination of 'citizen' and 'patient'. For instance, some reports emphasize the importance of patients sharing their data for research purposes [2, 6, 14], while others refer to citizens when describing this type of activity [7, 21]. Similarly, some reports mention that patients will be involved in the decision-making processes regarding treatment [2, 6, 9, 21], while other reports state that patients and citizens will be involved [7, 21]. This may reflect that PM, due to its proactive nature, will progressively blur the patient/non-patient dichotomy that has characterized traditional health-care models. For the

Table 1. PM reports

Report title [Ref]	Publisher	Year of publication
Priorities for Personalized Medicine [20]	The President's Council of Advisors on Science and Technology	2008
Public Health in an Era of Genome-Based and Personalised Medicine [12]	PHG Foundation	2010
Medical Profiling and Online Medicine: The Ethics of 'Personalised Health Care' in a Consumer Age [13]	Nuffield Council on Bioethics	2010
Personalised Medicine: Opportunities and Challenges for European Health Care [19]	European Commission Health Research Directorate	2010
Toward Precision Medicine: Building a Knowledge Network of Biomedical Research and a New Taxonomy of Disease [2]	National Research Council of the National Academies	2011
The Case for Personalised Medicine [6]	Personalized Medicine Coalition	2011
Signature Event Report: Mapping a Way Through the Double Helix [8]	Cancer Quality Council of Ontario	2011
Next Steps in the Sequence [14]	PHG Foundation	2011
Advancing Access to Personalized Medicine: A Comparative Assessment of European Reimbursement Systems [15]	Personalized Medicine Coalition	2011
Addressing Race and Genetics. Health Disparities in the Age of Personalized Medicine [17]	Science Progress	2011
European Perspectives in Personalised Medicine. Conference report [18]	European Commission	2011
Personalised Medicine: Status Quo and Challenges [9]	The European Association for Bioindustries	2012
Privacy and Progress in Whole Genome Sequencing [16]	Presidential Commission for the Study of Bioethical Issues	2012
ESF Forward Look: Personalised Medicine for the European Citizen [7]	European Science Foundation	2012
Realising the Potential of Stratified Medicine [3]	The Academy of Medical Sciences	2013
Paving the Way for Personalized Medicine [5]	U.S. Food and Drug Administration	2013
Use of '-omics' Technologies in the Development of Personalised Medicine [11]	European Commission	2013
Innovation and Patient Access to Personalised Medicine [21]	European Alliance for Personalised Medicine	2013

purpose of our analysis, we use the term 'citizen' when referring to citizens and patients; many of the behaviors and practices described in the reports do not require that the end users of PM are patients when they endorse the expected behaviors and practices.

Our review of the reports reveals that citizens are expected to adopt a range of new behaviors and practices in relation to their health care. These are grouped into three overarching themes as described below and summarized in table 2.

(1) Citizens Are Expected to Actively Engage in Their Health Care

Citizens are expected to increasingly participate in the decision-making process regarding prevention, diagnosis, and treatment [2, 6, 7, 9, 13, 14, 21]. For instance, they may discuss information about their individual genetic risk predisposition with their health-care provider and contribute to the design of tailor-made prevention strategies to reduce their risk of becoming ill [7, 13, 14, 21]. One report mentions that they may also discuss the choice of genetic tests and therapeutic options [9]. To ensure that prevention strategies are efficient, citizens may regularly enrich and update their personal health information, including genetic risk predisposition information, through the use of technologies such as web-based interfaces, self-tracking systems, personal health records, smart phone applications, and biofeedback systems [6, 7, 9, 13, 14, 21]. They may decide to voluntarily share information about their genetic predisposition with their relatives in order to increase the possibility that their relatives also take necessary measures to prevent disease onset [7, 16]. Some reports foresee that groups of citizens will purchase services from direct-to-consumer genetic testing companies and seek help from their public health-care services to interpret the results of genetic tests [13–14]. Finally, one report assumes that citizens will endorse targeted treatment strategies and understand that access to conventional treatment may be restricted when no positive effect for the individual's specific genetic profile is documented [18].

(2) Citizens Are Expected to Actively Contribute to the Research Endeavor

Citizens are expected to contribute many different types of data about themselves such as '-omics' data and imaging, clinical, environmental, behavioral, and socioeconomic data [2, 6, 7, 16, 17, 21]. To do so, citizens may

Table 2. Behaviors and practices expected of citizens as described in the reports

Citizens engage in their own health care
✓ Participate in the decision-making process regarding prevention, diagnosis, and treatment [2, 5–7, 9, 13, 14, 21]
✓ Use new technology to manage their health information (including genetic risk predisposition information) [6, 7, 9, 13, 14, 21]
✓ Share their genetic risk predisposition information with family members [7, 16]
✓ Purchase genetic services and health-care products online [13, 14]
✓ Endorse targeted treatment strategies based on their genetic profile [18]
Citizens contribute to the research endeavor
✓ Consent to research uses of their biological samples and health-related data [2, 6, 7, 16, 17, 21]
✓ Participate in research projects [2, 6, 7, 16, 17, 21]
✓ Join citizen-led and health social networks data-sharing initiatives [2, 5, 7]
✓ Contribute to the establishment of patient registries [2, 13, 16, 22–24]
✓ Report health data to public health authorities [7, 12]
✓ Communicate with researchers about patient values [11, 18]
Citizens engage in the design of PM
✓ Participate in public consultations and debates on PM [3, 7, 13, 14, 16, 18, 19]
✓ Collaborate with health professionals and drug manufacturers through involvement in patient advocacy groups, advisory boards and health technology assessment bodies [5, 7, 8, 13, 16, 18–21]

consent to participation in research projects, for instance population health surveys or biobank projects, or agree that their biological samples and data collected through clinical and research settings be used for future research [2, 6, 7, 16, 17, 21]. Some reports mention that citizens may also take the initiative to share their personal health data through citizen-led initiatives and health social networks [2, 5, 7], as already practiced within some communities of patients and health-care users [22–24], and may contribute to the establishment of patient registries that are made available to the research community [2, 13, 16, 22–24]. One report emphasizes that contributions from citizens with rare genotypes and phenotypes are particularly useful [2]. Additionally, as stated in two reports, citizens may take the initiative to report health data to public health authorities in case of potential infection or contamination in the community [7, 13]. Finally, two reports mention that citizens may communicate with researchers about patient values, informing them of their expectations regarding the translation of research discoveries into clinical practice [11, 18].

(3) Citizens Are Expected to Actively Engage in the Design of PM

Citizens are expected to participate in the design of PM by discussing its development and contributing to setting up priorities. This may be achieved through participation in public debates and deliberations, for instance to discuss the use of new technologies in health care or policies for reimbursement of targeted treatments [3, 7, 13, 14, 16, 18, 19]. Some reports also describe expectations that citizens may participate in corporations and advisory bodies and work in close cooperation with public health authorities and drug manufacturers [5, 7, 8, 18, 21], for instance to advocate for the development of targeted drugs [5, 13] or participate in the choice and validation of new diagnostics and therapeutics [5]. Citizens may also be involved in the design and development of educational tools to inform diverse publics about genetics and PM [8]. Examples of educational projects in which citizens play an active role are provided in some reports, such as the National Institute for Health and Care Excellence (NICE) project in the UK [3]. Patient advocacy groups may be central drivers of citizen engagement [2, 21], and two reports mention that strong public engagement from ethnic groups and minorities, which traditionally have been underrepresented, is particularly important [7, 21].

Discussion

The data we reviewed reveal that citizens are expected to adopt a whole range of behaviors and practices considered to be critical for the realization of PM. Citizens are seen as proactive, engaged, educated, responsible, and contributing partners of PM. These knowledgeable, rational, and resourceful citizens not only engage in healthful behaviors by following early prevention strategies, participating in the decision-making process regarding their medical follow-up, and sharing their genetic information

with relatives and public health authorities, they also actively contribute to the development of PM by, for instance, providing access to their health data, taking the initiative to produce more data to feed both their own health records and research databases, and participating in public debates to discuss the design and development of PM. Additionally, they actively seek to access more comprehensive information about their health by using the services of direct-to-consumer genetic testing companies and buying technological devices and applications to manage personal health information in real time.

These new behaviors and practices represent a radical change in the role of citizens compared with the way citizens traditionally have been involved in their health care. This change echoes recent developments which encourage a move away from the rather paternalistic model, under which citizens are primarily passive recipients of health care, to a participatory model of health care under which citizens are responsible drivers of their health, contributors to the health-care system, and partners sharing decisions with health-care providers [25].

Although PM offers the opportunity for citizens to be more proactive and engaged in their own health care, there are several challenges towards the realization of such citizen engagement as described below.

Challenges towards the Realization of Citizen Engagement in PM

Health Literacy

Citizens must have sufficient health literacy to be able to actively engage in their health care. However, such literacy is not widespread in the population. As an illustration, a recent comparative study on health literacy in 8 European Union member states reports that nearly every second respondent has limited health literacy and that a majority of respondents find it easier to follow instructions from their health-care provider than to make their own decisions or judgments [26]. Empirical data show that individuals who receive information about their personal genetic risk predisposition often fail to interpret it, either overestimating or minimizing it [27], and may prefer more intuitive, experience-based types of evidence [28]. The same individuals often do not change their lifestyle [29], either because they do not understand the information provided, do not want to change their life style, cannot afford to change it, or because genetic counseling protocols fail to raise some groups' awareness of risk predisposition [30]. Educational interventions developed to improve risk perception do not seem to influence the way people understand their genetic risk [31]. The lack of health literacy is worrisome knowing that citizens are not always accompanied by professionals to interpret their genetic information. For instance, citizens who decide to order genetic tests through commercial companies may not be able to assess the validity and clinical utility of these tests and may make misguided health-related decisions. The recent US Food and Drug Administration's [32] ban on 23andme personal genetic tests demonstrates that information produced through commercial genetic tests may not be reliable.

Technology Literacy

Citizens must also have sufficient technology literacy to be able to fully benefit from PM. However, groups of citizens, for instance the elderly, who are the heaviest users of health-care services, often do not have the necessary skills and abilities to use new technologies such as web-based health platforms or self-tracking devices, or are reluctant to use them [13]. Other groups, although more interested in technology, may not have access to it if the e-infrastructures are missing or if the technology is too expensive.

Lack of Economic Resources

Interfacing regularly with health-care provider, purchasing genetic tests, and endorsing the prescription of targeted therapies require economic resources that some groups may not have. This may be particularly true in countries where health care is funded through a variety of private insurers that can decide to restrict access to genetic tests and targeted therapies if considered too expensive or 'investigational' [21, 33]. Even in countries where health care is publicly funded, public payers may decide not to cover additional costs of targeted drugs and require that the patients cover such costs themselves. To illustrate our point, we refer to ongoing plans in the UK to modify pricing systems with the objective to increase prices for targeted drugs [34] and allow drug producers to achieve sufficient return on investment [35]. For the time being, it is still unclear who will cover potential additional costs related to the use of targeted drugs.

Other Barriers to Contribution

Citizen contribution to the research endeavor, for instance through participation in research trials, may be impeded by traditional research practices. For instance, ethnic groups and minorities are often excluded from research and deprived of the opportunity to contribute and benefit from medical progress [17]. As an illustration, 9 out of 10 genome-wide association studies are reported to

be conducted on populations of European descent, unveiled gene-disease correlations therefore primarily applying to Caucasians [17]. Paradoxically, groups of population who are given the opportunity to contribute to the scientific endeavor may not be willing to do so. For instance, 44% of Europeans are not willing to provide personal information to a biobank, and 67% prefer being asked to consent to every new piece of research instead of consenting only once to a broad range of research uses [36].

Finally, broad citizen engagement in the public debate may be difficult to realize in practice. Current initiatives to engage a variety of citizen groups – other than the white and educated – in the design of research and health care often fail to reach groups which are usually underrepresented. As an illustration, a recent review of citizens' juries – a frequently used tool for engaging citizens in health policy decision-making – demonstrates that even when the organizers intend to recruit juries that are representative of the community, such juries primarily gather the most privileged groups of populations and fail to engage less advantaged groups [37].

Numerous initiatives are currently being developed which may make it possible for groups of citizens to adopt the new behaviors and practices that are needed for the realization of PM. For instance, patient-activated social networks such as the 'quantified self' [38] network offer individuals the opportunity to use simple technological devices to take their own health measurements [39], disease-oriented social networks such as 'Patients like me' [23] offer patients the opportunity to share experiences and even launch research projects [39], and participant-centric initiatives in biomedical research enable research participants to actively engage in the research process [40]. More and more citizens are taking the initiative to collect and gather medical information through the use of web-based technologies and participation in e-patient networks [22–24]. However, a general concern is that the early adopters of PM may primarily be citizens who are resourceful, highly educated, and socioeconomically advantaged. Adopting new behaviors and practices may be much more challenging for those who have lower levels of education and fewer socioeconomic resources. Some of the reports we have reviewed acknowledge this challenge but propose few solutions to address it. Instead, the focus is put on the importance of educating citizens in PM [2, 3, 7, 8, 13, 14, 16, 20, 21]. Citizen education, for instance, encompasses introducing genetics and genomics in the educational program of students, developing websites and television channels to inform citizens about genetics and the use of genetic tests, and organizing public forums and debates. These strategies are of great importance but may not suffice to address the socioeconomic, cultural, and generational challenges we have described.

In recognition of these challenges, we review below recently proposed strategies which may enable larger groups of citizens to participate in PM. At first glance, some of these strategies may seem too expensive and resource-demanding to implement. However, the current resources of health-care systems are allocated inefficiently [41–43]. If such resources can be used in a more efficient and coherent manner, implementing the strategies we describe may not be unrealistic or insurmountable.

Reach Out to Larger Groups of Population

Alliances may be developed with local media, community representatives, and advocacy groups [44] to reach out to groups that usually are underrepresented in research and health care, such as low-income groups, ethnic minorities, and groups living in rural areas [17]. These groups could be involved in the design of educational tools and interventions that they know will be useful to them [30]. Similarly, research programs may be developed in close cooperation with local communities to include a wider variety of populations. For instance, clinical trials which focus on genetic variation instead of 'race' or 'ethnicity' could be designed [17]. Community-based participatory research programs under which communities and researchers work together in all phases of research may be particularly fruitful [45].

Rethink Financial Schemes

Approval and reimbursement processes may be modified to provide quicker access to genetic tests and targeted treatments [15]. For instance, patient outcome and risk-sharing models [46] could be more systematically used to document the efficiency of biomarkers and companion diagnostics rather than stringent clinical data [47]. Limitations may also be put on the pricing of targeted drugs [35]. Such limitations, albeit controversial, can be more acceptable for pharmaceutical companies if financial incentives are offered, for instance through internationally financed funds [48], for the development of targeted drugs that benefit large numbers of people, such as drugs used for the treatment of infectious diseases and cancer [49].

Develop Low-Cost Programs and Tools

Free or low-cost programs offering access to genetic tests and targeted therapies may be proposed to groups

that are susceptible of not being able to afford those or may not want to use them [50]. Such programs may, for instance, consist of publicly funded annual health check including mapping of genetic risk predisposition and lifestyle intervention provided free of charge [51]. In general, low-cost solutions should be preferred to expensive solutions. For instance, health-care providers may prioritize investment in wireless medicine, which is cheaper than traditional technology and offers the possibility to perform medical tests remotely and at reduced cost while simultaneously limiting the number of medical consultations [13].

Develop Alternative Solutions

Extensive health and technology literacy among large groups of citizens may be difficult to achieve. Alternative solutions could be proposed to citizens who do not have the ability to assess their own health or use modern technology but may benefit from personalized strategies. For instance, personal accompaniment and counselling could be proposed to senior citizens.

Finally, systematically mapping disparities in the access and use of genetic tests and targeted therapies and making the results publicly available may motivate changes in policy in areas where disparities are the most striking [50].

One may question whether these strategies can guarantee that citizens will make the necessary efforts to adopt new behaviors and practices. Although no guarantee can ever be provided that people will behave in certain ways, investing in programs which target specific groups of populations may be the helping hand that is needed to motivate the adoption of new behaviors among specific groups. For instance, publicly funded programs which offer genetic risk mapping and lifestyle intervention free of charge have proved to increase the participation rate of high-risk patients in prevention programs while simultaneously potentially reducing future treatment costs [51].

Conclusion

The reports we have reviewed envision citizens as educated, engaged, resourceful, and responsible partners rather than passive recipients of health care. This new role of citizens offers exciting opportunities but requires levels of health and technology literacy as well as socioeconomic resources that some groups of citizens may not have. Although some of the reports acknowledge that educational, technological, and socioeconomic hurdles may be encountered, they primarily focus on the importance of educating citizens in PM and propose few other solutions to address such challenges. Education in PM is critical. However, we suggest that the promoters of PM take into greater consideration the heterogeneity of citizens and develop policies and programs which specifically address the needs of the less educated and resourceful citizens. In Europe, discussions are currently taking place to reduce inequalities in access to PM [21]. Such discussions should particularly be encouraged in countries where health is financed by a variety of private actors and individual access to PM may be depending on the socioeconomic resources of each individual. Citizens will be more receptive to adopting new behaviors and practices and contribute to the realization of PM only if educational, socioeconomic, cultural, and generational hurdles are properly addressed.

Acknowledgments

The authors would like to thank Prof. Jan Helge Solbakk, University of Oslo, for his comments. This work was supported through funds from the Norwegian Cancer Genomics Consortium funded by the Norwegian Research Council (NFR BIOTEK2021/ES495029), BioSHaRE-EU, grant agreement HEALTH-F4-2010-261433, and Biobank Norway funded by the Norwegian Research Council (NFR 197443/F50).

References

1 Ginsburg GS, McCarthy JJ: Personalized medicine: revolutionizing drug discovery and patient care. Trends Biotechnol 2001;19:491–496.
2 Committee on a Framework for Development of a New Taxonomy of Disease; National Research Council of the National Academies: Toward Precision Medicine: Building a Knowledge Network of Biomedical Research and a New Taxonomy of Disease. Washington, The National Academies Press, 2011. http://www.ucsf.edu/sites/default/files/legacy_files/documents/new-taxonomy.pdf.
3 The Academy of Medical Sciences: Realising the Potential of Stratified Medicine. 2013. http://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf.
4 National Human Genome Research Institute: Talking Glossary of Genetic Terms. http://www.genome.gov/glossary/index.cfm?id=150.
5 U.S. Food and Drug Administration: Paving the Way for Personalized Medicine. 2013. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf.

6 Personalized Medicine Coalition (PMC): The Case for Personalized Medicine, ed 3. 2011. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/the_case_for_pm1.pdf.
7 European Science Foundation: ESF Forward Look: Personalised Medicine for the European Citizen. Towards more precise medicine for the diagnosis, treatment and prevention of diseases (iPM). 2012. http://www.esf.org/uploads/media/Personalised_Medicine.pdf.
8 Cancer Quality Council of Ontario: Signature Event Report: Mapping a Way Through the Double Helix. 2011. http://www.cqco.ca/common/pages/UserFile.aspx?fileId=98415.
9 The European Association for Bioindustries (EuropaBio): Personalised Medicine: Status Quo and Challenges. http://www.europabio.org/personalised-medicine-status-quo-and-challenges.
10 Elo S, Kyngäs H: The qualitative content analysis process. J Adv Nurs 2008;62:107–115.
11 European Commission: Commission Staff Working Document: Use of '-omics' Technologies in the Development of Personalised Medicine. 2013. http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf.
12 PHG Foundation: Public Health in an Era of Genome-Based and Personalised Medicine. 2010. http://www.phgfoundation.org/reports/6617/.
13 Nuffield Council on Bioethics: Medical Profiling and Online Medicine: The Ethics of 'Personalised Health Care' in a Consumer Age. 2010. http://nuffieldbioethics.org/wp-content/uploads/2014/07/Medical-profiling-and-online-medicine-the-ethics-of-personalised-healthcare-in-a-consumer-age-Web-version-reduced.pdf.
14 PHG Foundation: Next Steps in the Sequence. 2011. http://www.phgfoundation.org/reports/10364/.
15 Personalized Medicine Coalition (PMC): Advancing Access to Personalized Medicine: A Comparative Assessment of European Reimbursement Systems. 2011. http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_bridgehead_issue_brief_european_reimbursement.pdf.
16 Presidential Commission for the Study of Bioethical Issues: Privacy and Progress in Whole Genome Sequencing. 2012. http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf.
17 Science Progress: Addressing Race and Genetics. Health Disparities in the Age of Personalized Medicine. 2011. https://cdn.americanprogress.org/wp-content/uploads/issues/2011/06/pdf/race_genetics.pdf.
18 European Commission: European Perspectives in Personalised Medicine. Conference report. 2011. http://ec.europa.eu/research/health/pdf/personalised-medicine-conference-report_en.pdf.
19 European Commission Health Research Directorate: Personalised Medicine: Opportunities and Challenges for European Health Care. Workshop 5 report. 13th European Health Forum Gastein. 2010. http://ec.europa.eu/research/health/pdf/13th-european-health-forum-workshop-report_en.pdf.
20 The President's Council of Advisors on Science and Technology: Priorities for Personalized Medicine. 2008. http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf.
21 European Alliance for Personalised Medicine: Report from Irish Presidency Conference: Innovation and Patient Access to Personalised Medicine. 2013. http://euapm.eu/wp-content/uploads/2012/07/EAPM-REPORT-on-Innovation-and-Patient-Access-to-Personalised-Medicine.pdf.
22 Free the data. www.free-the-data.org.
23 Patients like me. www.patientslikeme.com.
24 Patients know best. http://www.patientsknowbest.com/.
25 Society for Participatory Medicine. http://participatorymedicine.org/.
26 HLS-EU Consortium: Comparative Report of Health Literacy in Eight EU Member States. The European Health Literacy Survey HLS-EU, Online Publication. 2012. https://www.health-literacy.eu.
27 Aspinwall LG, Taber JM, Kohlmann W, Leaf SL, Leachman SA: Perceived risk following melanoma genetic testing: a 2-year prospective study distinguishing subjective estimates from recall. J Genet Couns 2014;23:421–437.
28 Han PK, Hootsmans N, Neilson M, Roy B, Kungel T, Gutheil C, Diefenbach M, Hansen M: The value of personalised risk information: a qualitative study of the perceptions of patients with prostate cancer. BMJ Open 2013;3:e003226.
29 Marteau TM, French DP, Griffin SJ, Prevost AT, Sutton S, Watkinson C, Attwood S, Hollands GJ: Effects of communicating DNA-based disease risk estimates on risk-reducing behaviours. Cochrane Database Syst Rev 2010:CD007275.
30 Kulchak Rahm A: Gaining Perspective: Issues and Potential Barriers from Other Populations. Presentation at the 9thAnnual Texas Conference on Health Disparities, May 29–30, 2014. http://web.unthsc.edu/info/200610/texas_center_for_health_disparities/2714/conference_2014.
31 Dieng M, Watts CG, Kasparian NA, Morton RL, Mann GJ, Cust AE: Improving subjective perception of personal cancer risk: systematic review and meta-analysis of educational interventions for people with cancer or at high risk of cancer. Psychooncology. 2014;23:613–625.
32 BBC News Technology: FDA bans 23andme personal genetic tests. http://www.bbc.com/news/technology-25100878.
33 Vogenberg FR, Barash CI, Pursel M: Personalized medicine. Part 2. Ethical, legal, and regulatory issues. PT 2010;35:624–642.
34 Chinthapalli K: Higher drug prices will boost development of personalised medicine, says new report. BMJ 2013;347:f4549.
35 Finlayson AE, Godman B, Paterson K, et al: Personalizing healthcare: from genetics through payment to improving care? J R Soc Med 2013;106:41–44.
36 European Commission: Europeans and Biotechnology in 2010: Winds of Change? 2010. http://ec.europa.eu/public_opinion/archives/ebs/ebs_341_winds_en.pdf.
37 Street J, Duszynski K, Krawczyk S, Braunack-Mayer A: The use of citizens' juries in health policy decision-making: a systematic review. Soc Sci Med 2014;109:1–9.
38 Quantified Self. http://quantifiedself.com/.
39 Hood L, Auffray C: Participatory medicine: a driving force for revolutionizing healthcare. Genome Med 2013;5:110.
40 Kaye J, Curren L, Anderson N, et al: From patients to partners: participant-centric initiatives in biomedical research. Nat Rev Genet 2012;13:371–376.
41 Garber AM, Skinner J: Is American health care uniquely inefficient? J Econ Perspect 2008;22:27–50.
42 Godman B, Malmström RE, Diogene E, et al: Are new models needed to optimize the utilization of new medicines to sustain healthcare systems? Expert Rev Clin Pharmacol 2015;8:77–94.
43 Schmid EF, Ashkenazy R, Merson J, Smith DA: Will biomedical innovation change the future of healthcare? Drug Discov Today 2009;14:1037–1044.
44 Claeys A, Vialatte : Les progrès de la génétique, vers une médecine de précision ? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée. Office parlementaire d'évaluation des choix scientifiques et technologiques. http://www.assemblee-nationale.fr/14/pdf/rap-off/i1724.pdf.
45 Rangi SK, Terry SF: Genetic testing and native peoples: the call for community-based participatory research. Genet Test Mol Biomarkers 2014;18:531–532.
46 Jakka S, Rossbach M: An economic perspective on personalized medicine. The HUGO J 2013;7:1–6.
47 Hall PS, McCabe C: What evidence is there for the reimbursement of personalised medicine? Pharmacoeconomics 2013;31:181–183.
48 Banerjee A, Hollis A, Pogge T: The Health Impact Fund: incentives for improving access to medicines. Lancet 2010;375:166–169.
49 Plasència A: Global health challenges and personalised medicine. Contributions to Science 2012;8:175–180.
50 Ward MM: Personalized therapeutics: a potential threat to health equity. J Gen Intern Med 2012;27:868–870.
51 Passey ME, Laws RA, Jayasinghe UW, Fanaian M, McKenzie S, Powell-Davies G, Lyle D, Harris MF: Predictors of primary care referrals to a vascular disease prevention lifestyle program among participants in a cluster randomised trial. BMC Health Serv Res 2012;12:234.

III

Budin-Ljøsne and Harris *BMC Medical Ethics* (2016) 17:28
DOI 10.1186/s12910-016-0111-7

BMC Medical Ethics

RESEARCH ARTICLE Open Access

Patient and interest organizations' views on personalized medicine: a qualitative study

Isabelle Budin-Ljøsne[1,2*] and Jennifer R. Harris[3]

Abstract

Background: Personalized medicine (PM) aims to tailor disease prevention, diagnosis, and treatment to individuals on the basis of their genes, lifestyle and environments. Patient and interest organizations (PIOs) may potentially play an important role in the realization of PM. This paper investigates the views and perspectives on PM of a variety of PIOs.

Methods: Semi-structured telephone interviews were conducted among leading representatives of 13 PIOs located in Europe and North-America. The data collected were analysed using a conventional content analysis approach.

Results: The PIO representatives supported the realization of PM but feared that many financial, structural and organizational challenges may delay its realization. They encouraged strategies to modernize drug licencing mechanisms, develop research and data sharing infrastructures, and educate patients and health care professionals in PM. Notably, they emphasized the importance of developing PM in an equitable way and taking into consideration the patients' needs, values and personal situation. Despite varying levels of awareness regarding PM, the PIO representatives expressed willingness to engage in the PM agenda and recommended that PIOs work closely with policy-makers to design PM in a way that truly addresses the needs and concerns of patients.

Conclusions: PIOs have the potential to become central drivers of the PM agenda. Collaborations should be further developed between PIOs, researchers, drug developers and health care authorities.

Keywords: Personalized medicine, Patient organizations, Genetics, Ethics, Precision medicine

Background

Recent advances in biomedical research and biotechnology offer new possibilities to tailor prevention, diagnostic and treatment to the specific needs of patients. By utilizing information about the patients' genetic and molecular profile combined with their family history and clinical and environmental data, it is hoped that health care providers will be able to start interventions earlier and select therapies that are more precise, efficient and provide less side-effects – strategies broadly known as personalized medicine (PM) [1]. Large investments are being made worldwide to support such strategies. In the United States, the $215 million Precision Medicine Initiative [2] was recently launched with the objective to accelerate biomedical discoveries and improve the effectiveness of treatment. In Europe, the European Commission has since 2007 committed over €1 billion of health research funding to the development of '-omics' technologies and targeted therapies, and more funds are expected to be released in the coming years [3]. PM has been extensively described in recent reports from national and international medical organizations and funders [4–6]. These reports emphasise the importance of engaging a variety of stakeholders such as health care providers, biomedical researchers, regulators, drug developers, patients and patient organizations in driving PM forward. Among these stakeholders, patient organizations are particularly valuable players regarding their role in patient education [7], assessing new biomedical developments [8], and supporting research projects [4]. However, with the exception of recent surveys in which patient organizations identified potential barriers in PM implementation [9] and key priority areas within cancer [10], little empirical data are available to

* Correspondence: i.b.ljosne@medisin.uio.no
[1]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, P.O Box 1130, Blindern NO-0318 Oslo, Norway
[2]Norwegian Cancer Genomics Consortium, kreftgenomikk.no, Oslo, Norway
Full list of author information is available at the end of the article

document the views and perspectives of patient organizations on PM.

Investigating how patient organizations perceive PM and which role they are willing to play in its realization is important for several reasons. First, patient organizations have close contact with the communities of patients they represent. They are therefore well-placed to provide qualified opinions regarding how to implement PM in a way that addresses the needs and concerns of these communities. For instance, PM may require that patients learn about their genetic risk profile, engage more actively in the medical decision-making process and share their health data with researchers and clinicians more broadly than conventionally practised [11]. Patient organizations are well-qualified to familiarize patients and communities with such developments. Second, patient organizations may provide useful guidance in addressing potential ethical and societal challenges that may arise when new medical approaches are implemented. For instance, PM may imply that patients are offered differential access to treatment depending on their genetic profile [12]. Patient organizations may be well placed to explore how dialogue with patients and communities should take place when access to conventional treatment may be restricted. Third, patient organizations have comprehensive expertise within the areas of patient and health care professional capacity building [13, 14], the development of online patient communities [15], the design of regulatory frameworks and patenting policies [16], the financing and management of clinical trials and biobanks [15, 17–19], and more recently, in developing databases and web-based platforms for patient-driven data sharing [13, 20]. Making use of these skills and experiences may accelerate the realization of PM.

Although patient organizations are often referred to as one homogenous group, they are rather a constellation of entities that vary considerably in size, organizational structure, denomination and mandate [13]. For instance, patient organizations may be publicly or privately-funded, small entities which represent only a limited network of families suffering from a particular condition, or they may be large-scale, international organizations bringing together national organizations which focus on one specific disease or specialize in improving the living conditions of all patients. We conducted a qualitative interview study among leading representatives of non-profit patient organizations which are concerned with one specific disease or disease area and define themselves as patient advocacy organizations, umbrella organizations for patient advocacy organizations or interest organizations, hereafter referred to as patient and interest organizations (PIOs). The objective of our study was to collect information about three main issues: 1) the PIOs' views and perspectives on PM, 2) recommendations for facilitating the realization of PM, and 3) the role they foresee that they may play in the realization of PM.

Methods

Recruitment of study sample

To collect information about the views of a variety of PIOs, we proceeded in two steps. First, in July 2014, we sent an e-mail invitation to the leaders of a small number of PIOs that co-operate with the research network of the Norwegian Cancer Genomics Consortium (NCGC) [21], a national research platform aiming to establish personalized clinical strategies for cancer treatment in Norway. The email invitation provided an outline of the study objectives and a description of what participation in the study entailed. In the invitation, PM was described as "an emerging practice of medicine that uses an individual's genetic profile to guide decisions made with regard to the prevention, diagnosis, and treatment of disease" as defined in the Talking Glossary of Genetic Terms of the National Human Genome Research Institute [22]. The email invitation included a request for written informed consent. The study was approved by the Norwegian Social Science Data Services.

The first PIO leaders who accepted our invitation helped us identify other PIO representatives that might want to participate in the study. Through such snowball sampling, we were able to recruit representatives from 8 PIOs concerned with one specific disease or disease area (6 PIOs in Norway, 1 in the United Kingdom and 1 in the USA) between July 2014 and January 2015. In parallel and in order to extend our sampling, we sent email invitations to 20 leaders of disease-specific PIOs members of the European Patients' Forum (EPF) [23], an umbrella organisation of pan-European patient advocacy organizations. The PIO representatives were recruited in the study until a point of saturation was attained, i.e. when no significant new information was collected. Five PIO representatives agreed to join the study, six responded that they did not have time to participate or did not want to participate, and nine did not respond to our invitation. In total, thirteen PIOs working within the areas of cancer (4), hereditary and genetic disorders (3), mental health (1), diabetes (1), psoriasis (1), AIDS (1), lupus (1), and primary immunodeficiencies (1) participated in the study (Table 1). The representatives interviewed were organizational leaders (10) (e.g. CEO, secretary general, director) and senior managers (3) employed by the PIOs. As leading representatives of their PIOs, they were able to speak on behalf of their organization although many specified that their organization did not have an official position on PM. The size of the PIOs varied from small PIOS gathering

Table 1 PIOs participating in the study

PIO name	Membership	Country
DEBRA Hrvatska (Dystrophic Epidermolysis Bullosa Research Association)	Approx. 50 families	Croatia
Genetic Alliance UK	>100 organizational members	UK
Genetic Alliance USA	>1,000 organizational members	USA
LUPUS Europe	Approx. 22 country memberships	Denmark
Sarcoma	Approx. 350 individual members	Norway
The European AIDS Treatment Group	Approx. 110 individual members	Belgium
The European Umbrella Organisation for Psoriasis Movements (EUROPSO)	Approx. 20 country memberships	Norway
The International Patient Organisation for Primary Immunodeficiencies (IPOPI)	Approx. 55 country memberships	UK
The Norwegian Breast Cancer Society	Approx. 14,500 individual members	Norway
The Norwegian Cancer Society	Approx. 113,000 individual members	Norway
The Norwegian Childhood Cancer Organization	>3,000 individual members	Norway
The Norwegian Council for Mental Health	Approx. 29 organizational members	Norway
The Norwegian Diabetes association	Approx. 40,000 individual members	Norway

families suffering from a rare genetic disorder to large PIOs gathering more than a thousand organizational members.

Data collection and analysis

Semi-structured telephone interviews were conducted with the thirteen PIO representatives, lasting forty minutes on average. An interview guide was used to lead the conversation, which included open-ended questions about the PIOs' perspectives regarding PM, PM-related activities, perceived challenges with regard to the realization of PM, recommendations for the adoption of PM, and the potential roles the PIOs may play in the realization of PM. The interviews were conducted in English or Norwegian by the first author trained in qualitative methods and fluent in both languages. The interviews were audio recorded and transcribed verbatim in English and Norwegian. The transcripts were analysed manually by the first author using a qualitative content analysis approach in an inductive way [24]. First, a thematic analysis of the interview texts was conducted to identify overarching themes that emerged from the responses to each open-ended question formulated in the interview guide. Next, the substantive content of the text was extracted, coded and categorized according to the overarching themes. If new codes were identified, the coding frame was updated accordingly. Then, the text pertaining to each of these themes was condensed to reflect the main points raised by the PIO representatives. In August 2015, a two-page report summarizing the main findings was sent by email to the PIOs representatives for validation. Their comments and corrections to the report were integrated in the results.

Results

The PIO representatives described their interest in PM and potential challenges that may impede or delay the realization of PM. Particular emphasis was put on possible side effects of focusing on PM strategies. Then, the representatives made a number of recommendations for the realization of PM and discussed how their organizations may contribute to the PM endeavour.

PIOs interest in PM

Overall, the PIO representatives expressed interest in PM. They explained that the current medical needs of their patient groups are largely unmet and medical strategies which address issues of side effects, overtreatment and undertreatment are strongly needed. As outlined by this representative:

> (1) If you create a medicine that directly targets the individual, you will then be able to avoid all these unsuccessful attempts to find the right treatment without getting better, having to deal with the side effects, the downturns, the disappointments (…) when you use a medicine that has side effects for a long period, you are sick for months and then it turns out that [the medicine] does not help anyway. Developing medicines that will perhaps work at once and not after the fifth attempt, (…) we see this as perhaps the most important thing to achieve.

However, several representatives confessed that PM was a topic that had not been thoroughly discussed in their organization. Most PIOs did not use the terms PM and did not specifically mention PM in their strategic documents with the exception of some cancer PIOs.

Several representatives also explained that the concept of PM and its possible practical implications were still unclear. As an illustration, one representative believed that PM meant that health care professionals allocate more face-to-face time with each patient.

PM challenges

High cost of PM

Most representatives feared that PM may be too expensive for many health care systems which are currently dealing with significant financial constraints. They experienced that patient access to conventional treatment is increasingly restrained due to cost issues, and observed that new targeted drugs that are launched on the market are so highly-priced that patients can hardly afford them unless their cost is fully covered by payers. As expressed by this representative:

> (2) If we end up with the same level of cost to get an authorization for a targeted drug that would effectively treat 10% of a population of people with a given disease, rather than being used to treat a 100% of the population with a given disease, then the cost for (…) personalized medicine per patient treated will have to be higher.

Although the representatives acknowledged PM's potential to save costs as treatment becomes more targeted and waste is avoided, they expected PM to require significant up-front capital investments in equipment and infrastructures that most countries cannot afford. They also suspected that PM may lead to increased medical follow-up as genetic tests are more frequently used in clinical settings to confirm a diagnostic. Another concern was that patients who purchase genetic testing kits from direct-to-consumer genetic testing companies may seek medical advice from their physician to interpret the results, thus creating additional burdens on health care services.

Lack of health literacy

Several PIO representatives expressed scepticism regarding the patients' ability to understand and endorse PM strategies. They noted that patients often struggle to understand basic medical information:

> (3) People do not understand information well enough, this is where we see a big job for the patient organizations and patient groups in each of the countries in Europe, (…) educate, bring awareness of how important (…) the different kinds of medications are, when they are supposed to be used and for what, (…) there is a reason why it has been prescribed (…). There is a huge communication aspect that we have just picked up.

Another representative suspected that many patients are not ready to learn about their genetic profile, in particular if unexpected findings are discovered:

> (4) Genetic testing for rare genetic conditions and other disorders can now be performed in hospitals, you can get some answers that are incidental and that no one asked for and for which a decision must be made. We think that this is a challenge (…), the patients are not aware of this. They can get a lot of information that is hard to digest.

These views were however nuanced by the perspectives of other representatives who emphasized that patients who have been waiting for a diagnostic for many years are often eager to learn about their genetic profile. Several PIO representatives also explained that general practitioners often do not understand the specificities of disease, and suspected that many are insufficiently trained in genetics to use PM strategies in their medical practice. Similarly, several representatives explained that policy-makers often do not understand why patients need specific types of treatment rather than a "one-size-fits-all" treatment.

Lack of mechanisms and infrastructures to support PM

Several PIO representatives explained that current drug licensing mechanisms unnecessarily delay the launching of personalized treatments. Receiving drug approval from regulatory authorities often takes years and is particularly cumbersome if such approval is needed across borders. Although the representatives largely believed that data protection regulations are needed to protect the rights and interests of patients, some representatives suspected that such regulations may be too stringent and hinder the conduct of biomedical research. As expressed by this representative:

> (5) When it comes to access to this information in relation to biobanks, there are so many rules already dealing with this, I know that many are concerned about this (…), but what is it we are scared about? There are rules for how [information] can be managed and used, I do not see any danger that [information] will be misused.

Unwanted consequences of PM

In general, the PIO representatives worried that PM, because of its high costs, may reinforce already existing health care disparities among social groups unless specific measures are taken by policymakers to enable equitable access to PM. Some representatives also expressed concerns that patient groups may be forgotten if they represent a genetic subset that is not considered

lucrative by pharmaceutical companies. As expressed by one representative:

> (6) If it is really individualized, if it's really about genetics, there will be populations that will be marketwise less interesting, maybe population-wise they are, meaning that you should not only look at the benefit for the rich white community but also for the populations that are maybe research-wise less interesting to include but might really benefit from more research.

Some representatives feared that the increased use of technology in health care may lead professionals to reduce patients to their genetic profile. As described by this representative:

> (7) I think it is essential that the patient remains at the center and that he doesn't become a data or an entity; it's really a patient and a face and the [health care professionals] need to treat that patient, that's the main goal.

Genetic discrimination was a shared concern of some representatives. An example was provided of patients being denied health insurance because of their medical history even if the law prohibits such practice. As expressed by one representative:

> (8) If we, sometime in the future, find genes that you would like to have and genes you would prefer not having, it is clear that it may contribute to creating A-people and B-people. From the moment our genes become a question of value, it may create differences between people. Some people may be worth more than others and then we are back to the 30's, so from a historical point of view, this is important.

Finally, one representative worried that priority may be given to genetic research, not because it may lead to the most useful results, but because it is technologically exciting and may benefit the commercial interests of pharmaceutical companies. This representative emphasized the importance of also conducting other types of research such as social and behavioural research.

Main recommendations for the realization of PM

The PIO representatives made recommendations for the realization of PM that can be assigned to five main categories as described below and summarized in Table 2.

Policy-making

Overall, the representatives emphasized the importance of providing equitable access to PM. They explained that access to genome sequencing technologies and targeted drugs should not be limited by financial constraints but offered according to specific priority criteria that are jointly established by policymakers, health care professionals and patient representatives. They believed that modernizing drug licensing mechanisms is necessary to enable quicker access to targeted drugs. Adaptive pathways mechanisms were mentioned as a potential approach to improve timely access for patients to new medicines [25]. The representatives also recommended allocating specific funding to the implementation of PM, for instance to develop necessary biobanks and data sharing infrastructures. Some representatives suggested

Table 2 PIOs' recommendations for the realization of PM

Recommendations
Policy-making
• Establish principles and criteria for equitable patient access to PM
• Modernize drug licensing mechanisms, e.g. through adaptive pathways
• Allocate specific funding to the implementation of PM
• Implement PM gradually, e.g. through pilot projects including the most needy patients
Patient-centered health care
• Provide simple, actionable genetic information to patients; ally with genetic counselors
• Take into consideration the patients' values, personal situation and health literacy level
• Protect the patient's right not to know
• Educate patients and health care professionals in PM strategies
Increased, inclusive research
• Conduct more basic/epidemiological research
• Invite patients and PIOs early in the planning and design of clinical trials
• Broaden eligibility criteria to recruit more patients in research
Data sharing and protecting privacy
• Develop privacy-solid biobanks and data sharing infrastructures
• Ask for permission before using personal health data
• Develop flexible and interactive consent mechanisms
PIOs' active participation in agenda setting
• Engage as early as possible in the development of PM
• Contribute to educate stakeholders in PM
• Contribute to design the PM agenda, e.g. by identifying priority areas
• Support the development of collaborative research projects
• Respond to national hearings of relevance for PM
• Join research ethics committees and drug approval boards
• Develop partnerships with medical professions, e.g. through medical expert panels
• Develop partnerships between PIOs nationally and internationally
• Develop partnerships between PIOs and researchers, medical professions, and policy makers

implementing PM gradually, starting with the patients groups that are most in need such as those for whom no established treatment currently exists.

Patient-centered health care

Most representatives emphasized the importance of an open dialogue between health care professionals and patients. They believed that patients should be provided with information that is simple, understandable, actionable and adapted to the patient's needs, values, level of health literacy and way of dealing with disease. They explained that the value of an intervention should not only be measured in medical, biological or scientific terms but also in terms of how it impacts the patients' quality of life and ability to function in society, and recommended that these aspects are taken into consideration when assessing patient needs. They strongly recommended providing genetic counselling to patients when genetic information is available. In general, the representatives believed that the medical literacy of patients should be improved. However, they explained that patients differ in their willingness to learn about their disease and engage in their health care, and that their personal preferences, for instance regarding access to their genetic information, should be respected. In addition, the representatives considered it important to educate health care professionals in PM strategies. In contrast, educating the general public about PM was seen as useful but not an absolute priority. The representatives believed that public awareness about PM may gradually develop as targeted treatments are becoming more broadly available in health care.

Increased, inclusive research

In general, the representatives believed that more research should be conducted to understand the causes underlying disease, investigate the mechanisms of side effects, explore the consequences of living a long time with a specific treatment and develop strategies to improve the quality of life of patients. They explained that patients are willing to participate in medical research but are often denied such opportunity because of strict eligibility criteria. They recommended engaging patients and patient representatives as early as possible in the planning and design of clinical trials and broadening eligibility criteria to include more varied populations across socio-economic groups.

Data sharing and protecting privacy

The representatives supported the development of biobanks and data sharing infrastructures that are governed by solid and transparent privacy protection frameworks as these are essential to maintain the trust of patients and protect their interests. Privacy protection was seen as particularly important when the health data that are shared originate from patients suffering from socially stigmatizing diseases. The representatives explained that more work is needed to make people comfortable with sharing their personal health data.

PIOs' active participation in agenda setting

The representatives believed that PIOs should be involved as early as possible in the planning and design of the PM agenda. They explained that the main role of PIOs in PM includes helping to: a) increase literacy in PM among patients and health care professionals, b) identify the areas in which PM is most needed, and c) support the development of research projects that are attractive to patients. The representatives envisioned increased collaboration between PIOs and research groups, medical bodies, drug developers and policy-makers, nationally and internationally to encourage the development of PM. They also believed that patients and lay representatives should be more frequently invited to join research ethics committees and drug approval boards. The representatives recommended the development of inter-PIOs collaborations to enable the organizations which are more knowledgeable about PM to help others join the PM endeavour. Finally, they called for initiatives to educate PIOs in PM as finding the right information about PM may be challenging and many PIOs do not have a clear understanding of how they can contribute to the successful realization of PM.

Discussion

Our findings show that PIO representatives had a positive although cautious attitude toward PM. They believed that PM is needed but suspected that many financial, structural and organizational challenges may delay its realization. Although the recommendations forwarded by the representatives to support the realization of PM are largely congruent with those made by the promoters of PM [4–6], they also shed light on specific ethical and societal challenges that may arise in the process of adopting PM. Importantly, attention to these considerations has not been emphasized in the public debate but they should be addressed to enable the successful realization of PM in a way that truly addresses the needs and concerns of patients.

Developing PM in an equitable way, and involving discussions with decision-makers about how such equity may be achieved, was seen as the main priority. The PIO representatives based their rationale on the types of problems that their patients encounter daily in health care systems. For instance, the prices of new targeted drugs have steadily increased during the last decade [26] and health care systems frequently deny patients access to such drugs because of financial constraints unless the patients can pay out-of-pocket [27, 28]. The PIO

representatives expressed concern that issues of social injustice may arise if individuals who are more socio-economically advantaged benefit most from new treatments because they have the financial ability to pay for them. The fundamental principle of equitable access to health care may be threatened when "niche buster drugs" designed for smaller groups of patients are more expensive and therefore less accessible than blockbuster drugs [28]. This issue has already been raised by coalitions of patient organizations which have called for an equitable and universal patient access to PM independent of the patient's socio-economic status and geographical location [9, 29, 30].

Although the PIO representatives emphasized that equitable access to PM was critical, they did not articulate in detail what such equity should entail. Equity is a broadly acknowledged ethical concept that is concerned with the fair and impartial "distribution of benefits and costs to distinct individuals or groups" [31]. Although most health care systems strive to achieve equity, it has shown to be difficult to operationalize. For instance, it is usually considered as equitable to allocate health care resources on the basis of consideration of the actual needs of patients [32]. However, how to determine which needs are most important, and how they should be prioritized is often challenging. As an illustration, should the needs of terminally ill patients be addressed in priority, or those of patients who may yield significant gains in life expectancy if treatment is provided [33]? Two PIO representatives mentioned that patients for whom no standard treatment exists, for instance some groups of cancer patients, should be prioritized to receive access to genome sequencing in the hope that a potential treatment may be found. However, neither the importance nor the implications of providing genome sequencing to cancer patients if little is known about the genes involved in their cancer types are well understood. Other criteria may also have to be taken into consideration for resource allocation such as the efficacy and effectiveness of the intervention (its ability to lead to a positive outcome for the patient) and its cost-effectiveness (ability to provide value for money) [34]. Even if it is seen as morally justifiable to give priority to the patients who are in greatest need, it may not be wise from a cost-effectiveness perspective if the intervention is not expected to benefit the patient. Decision-makers are faced with having to balance between these different considerations (equity, efficacy, cost-effectiveness) and make decisions that do not unjustifiably discriminate some groups of patients. In the absence of a clear normative framework providing guidance on how to distribute resources fairly [35], it may be useful to investigate processes that are deliberative, transparent, and "appeal to rationales that all can accept as relevant to meeting health needs fairly" [36]. This is where PIOs may play an important role by collaborating with decision-makers in order to find pragmatic solutions for an equitable and reasonable resource allocation. As an illustration, the Scottish Medicines Consortium convenes clinicians, health economists and patient representatives to identify and prioritize those medicines and interventions which represent good value for money to patients and should be launched on the market [37]. Such collaboration may be good example of how a fair process may take place.

Taking into consideration patients' interests and values to a greater extent than traditionally practised was also seen as critically important by the PIO representatives. PM is often described as a holistic approach to medicine that utilizes information about the patient's clinical and family history, genetic susceptibility to disease, response to certain drugs, and lifestyle to assess the patient's health [4–6]. The PIO representatives interpreted the meaning of "personalized" medicine slightly differently from the promoters of PM. Although the PIO representatives largely agreed that focusing on the biological and environmental factors that may affect the health of the patient is important, they also believed that "personalizing" health care means that greater attention should also include taking the time to listen to the patient, learn about her values, assess her mental and spiritual well-being, understand her personal circumstances, and improve her quality of life and ability to function in society with a condition. The views expressed by the PIO representatives are in concordance with recent calls for a more "humanistic" medicine that approaches the patient as a whole person with a personal history, emotions, beliefs and sufferings [38]. A humanistic doctor takes the time to listen to the patient's story, shows compassion and empathy, makes sure that the patient feels valued and respected, and takes into consideration the patient's personality and experience in the process of medical care. As the PIO representatives repeatedly emphasized during our interviews, no technological advancement or biological instrument can substitute the importance of the doctor-patient relationship.

PM aims to strengthen dialogue and collaboration between doctor and patient through increased patient engagement [8]. In accounts of PM, patients are encouraged to discuss various treatment options with their healthcare provider, communicate about their preferences, values and lifestyle, and provide feedback on health care processes and outcomes [8]. At such, patient engagement may be a critical strategy to enable the provision of health care that is responsive to the patient's specific needs and situation as envisioned by the PIO representatives. Patient engagement enables a better power balance between patients and doctors, thus making it easier for patients to express their concerns and

preferences, and bring perspectives on their own care [8]. However, while patient engagement strategies may work for those patients who are eager to take responsibility for their health care, seek knowledge and understand the details of their clinical situation, they may not be suitable for those who prefer to delegate the majority of the responsibility for their health care to their health care professional [8]. Similarly, some patients may not have the ability to engage in their health, for instance because they lack the necessary health literacy to understand what is at stake [39]. In this context, the PIOs that have available resources and are willing to engage in PM may have an important role to play in enhancing the health literacy of patients and familiarizing them with engagement strategies. Other patients may be so physically and mentally ill that they do not have the capability to engage. For these patients, providing health care with compassion and empathy may be particularly important; time should be allocated in the PM agenda to enable health care professionals to interact in a "humanistic" manner with their patients.

Finally, our study results indicate that levels of awareness regarding PM vary considerably between PIO representatives. In general, the representatives from the larger PIOs were more familiar with the concept of PM and worked more mindfully toward PM than representatives from smaller PIOs. Similarly, cancer PIOs were more likely to integrate the concept or aspects of PM in their strategy independent of their organizational size. Larger PIOs may have more resources to investigate new medical strategies than smaller PIOs which struggle with basic issues such as guiding their patients through the health care bureaucracy or educating health care professionals. Engaging in PM may be more challenging when the organizations' resources are limited. Similarly, the general attention given to cancer in the PM discourse and the fact that most targeted drugs that have been marketed are cancer drugs [40] may explain why cancer PIOs were generally more aware of PM than non-cancer PIOs. As an illustration, several representatives from non-cancer PIOs believed PM to be primarily focusing on cancer to the disservice of other disease areas; a belief previously observed among health care professionals [41] and patient representatives [9]. It is therefore important that decision-makers work to increase levels of awareness regarding PM among PIOs, and provide support to those PIOs that have limited resources and competency but are willing to contribute to the PM agenda.

Conclusions

The development and realization of PM requires the involvement of PIOs. Historically, PIOs have shown an impressive ability to engender important changes on a large scale that benefit patients. If the PIOs become sufficiently convinced that PM is the future of medicine and will benefit their patients, then they have the potential to play a significant role in driving the PM agenda forward. It is therefore important that researchers, health care funders, drug developers and policy makers invite PIOs to the table, not only the biggest and most influential PIOs but also the smaller ones should be engaged so that PM is developed in ways that address the "health care needs of patients. It is also important that PIOs work together to become effective advocates of PM. The European Patients' Academy (EUPATI), a pan-European platform for patients and PIO engagement, may be a potential springboard for intra-PIO collaborations [42]. The European Alliance for Personalised Medicine (EAPM) [43], a coalition bringing together European healthcare experts and patient advocates, may also be one of the central arenas where PIOs could discuss with key stakeholders issues related to priority setting and resource allocation. Such models of collaboration and engagement are needed to give PIOs an increased opportunity to contribute to the decision making process regarding the design of PM.

Study limitations

The results from our study provide insights into how PIOs working within a range of diseases perceive PM and reflect upon the PM agenda. Deciding on which PIOs to include in our study was challenging: there are thousands of active PIOs and they vary widely in organizational structure, areas of activity and funding. It was difficult to learn about the PIOs organizational and financial structure on the basis of the information they provide on their web site. In the absence of obvious criteria to select PIOs, we decided to restrict our sampling to non-profit PIOs that were disease-specific and were either member of the European Patients' Forum, or were within the network of the Norwegian Cancer Genomics Consortium. This was a pragmatic choice that enabled us to come in contact with a variety of PIOs. However, our sampling may not be representative of the wider spectrum of PIOs that exist, and the PIOs situation (e.g. relationship to biopharmaceutical companies) could have to some extent influenced their interest in and level of knowledge about PM.

For many of the PIO representatives, this study was the first time they discussed PM and they were therefore not able to provide any concrete examples of issues related to their experience with PM, or specific recommendations regarding their potential role in the realization of PM. More work may be needed to investigate how a larger spectrum of PIOs which have specifically endorsed the concept of PM in their strategies, and work actively toward it, envision their role in the realization of PM agenda.

Ethics approval and consent to participate

All participants in the study provided a written informed consent. The study was approved by the Norwegian Social Science Data Services (ref. 39155 / 3 / JSL).

Availability of data and materials

The study data (interview records and transcripts) are stored securely at the University of Oslo and will not be shared according to requirements from the Norwegian Social Science Data Services, and conditions outlined in the informed consent.

Abbreviations

PIO: patient and interest organizations; PM: personalized medicine.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IBL conceived of the study and JRH participated in its design. IBL carried out the interviews, analysed the data and drafted the manuscript. IBL and JRH critically revised the manuscript. Both authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank Mrs Camille Bullot, Membership Officer at the European Patient's Forum (EPF) for informing the EFP members about our study; the PIO representatives for participating in our study and providing useful and qualified insights on PM; Professor Jan Helge Solbakk and Postdoc fellow Viva Combs Thorsen, University of Oslo, for their comments. This work is supported by the National Research and Innovation Platform for Personalized Cancer Medicine funded by the Norwegian Research Council (NFR BIOTEK2021/ES495029).

Funding

This work is supported by the National Research and Innovation Platform for Personalized Cancer Medicine funded by the Norwegian Research Council (NFR BIOTEK2021/ES495029).

Author details

[1]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, P.O Box 1130, Blindern NO-0318 Oslo, Norway. [2]Norwegian Cancer Genomics Consortium, kreftgenomikk.no, Oslo, Norway. [3]Department of Genetics and Bioinformatics, Norwegian Institute of Public Health, Oslo, Norway.

Received: 11 December 2015 Accepted: 9 May 2016
Published online: 13 May 2016

References

1. Godman B, Finlayson AE, Cheema PK, Zebedin-Brandl E, Gutierrez-Ibarluzea I, Jones J, et al. Personalizing health care: feasibility and future implications. BMC Med. 2013;11:179.
2. Fact sheet: President Obama's Precision Medicine Initiative. https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative. Accessed 4 Dec 2015.
3. European Commission. Personalised Medicine. http://ec.europa.eu/health/human-use/personalised-medicine/index_en.htm. Accessed 4 Dec 2015.
4. Committee on a Framework for Development of a New Taxonomy of Disease. National Research Council of the National Academies. Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease. The National Academies Press; 2011. http://www.ncbi.nlm.nih.gov/books/NBK91503/. Accessed 4 Dec 2015.
5. European Science Foundation. ESF Forward Look: Personalised Medicine for the European Citizen. Towards more precise medicine for the diagnosis, treatment and prevention of diseases. http://www.esf.org/coordinating-research/forward-looks/biomedical-sciences-med/current-forward-looks-in-biomedical-sciences/personalised-medicine-for-the-european-citizen.htmlhttp://www.esf.org/index.php?eID=tx_nawsecuredl&u=0&g=0&t=1449323277&hash=084b5e4527d937f396ae7200f8e709d69f6fb34d&file=fileadmin/be_user/CEO_Unit/Forward_Look/iPM/FL_2012_iPM.pdf. Accessed 4 Dec 2015.
6. The Academy of Medical Sciences. Realising the Potential of Stratified Medicine. https://www.acmedsci.ac.uk/viewFile/51e915f9f09fb.pdf. Accessed 4 Dec 2015.
7. The President's Council of Advisers on Science and Technology. Priorities for personalized medicine. https://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf. Accessed 4 Dec 2015.
8. European Alliance for Personalised Medicine. Report from Irish Presidency Conference. Innovation and Patient Access to Personalised Medicine. http://euapm.eu/pdf/EAPM_REPORT_on_Innovation_and_Patient_Access_to_Personalised_Medicine.pdf. Accessed 4 Dec 2015.
9. Horgan D, Jansen M, Leyens L, Lal JA, Sudbrak R, Hackenitz E, et al. An index of barriers for the implementation of personalised medicine and pharmacogenomics in Europe. Public Health Genomics. 2014;17(5-6):287–98.
10. Novartis Oncology. Patient Group Perceptions of Personalized Medicine. https://pipeline.novartisoncology.com/about-us/our-viewpoint/patients-study-overview.jsp. Accessed 4 Dec 2015.
11. Budin-Ljosne I, Harris JR. Ask not what personalized medicine can do for you - ask what you can do for personalized medicine. Public Health Genomics. 2015;18(3):131–8.
12. Joly Y, Saulnier KM, Osien G, Knoppers BM. The ethical framing of personalized medicine. Curr Opin Allergy Clin Immunol. 2014;14(5):404–8.
13. Koay PP, Sharp RR. The role of patient advocacy organizations in shaping genomic science. Annu Rev Genomics Hum Genet. 2013;14:579–95.
14. Panofsky A. Generating sociability to drive science: patient advocacy organizations and genetics research. Soc Stud Sci. 2011;41(1):31–57.
15. Mavris M, Le Cam Y. Involvement of Patient Organisations in Research and Development of Orphan Drugs for Rare Diseases in Europe. Mol Syndromol. 2012;3(5):237–43.
16. Ledbetter DH. Gene patenting and licensing: the role of academic researchers and advocacy groups. Genet Med. 2008;10(5):314–9.
17. Landy DC, Brinich MA, Colten ME, Horn EJ, Terry SF, Sharp RR. How disease advocacy organizations participate in clinical research: a survey of genetic organizations. Genet Med. 2012;14(2):223–8.
18. Marcus AD. Patients with rare diseases work to jump-start research. Wall Street journal. http://www.wsj.com/articles/SB115257685637802872. Accessed 4 Dec 2015.
19. Bromley RL. Financial stability in biobanking: unique challenges for disease-focused foundations and patient advocacy organizations. Biopreserv Biobank. 2014;12(5):294–9.
20. Wexler NS. Huntington's disease: advocacy driving science. Annu Rev Med. 2012;63:1–22.
21. Norwegian Cancer Genomics Consortium. http://kreftgenomikk.no/en/. Accessed 4 Dec 2015.
22. National Human Genome Research Institute. Talking Glossary of Genetic Terms. http://www.genome.gov/glossary/index.cfm. Accessed 4 Dec 2015.
23. European Patients' Forum. http://www.eu-patient.eu/. Accessed 4 Dec 2015.
24. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs. 2008;62(1):107–15.
25. European Medicines Agency. Adaptive pathways. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp. Accessed 4 Dec 2015.
26. Shih YC, Smieliauskas F, Geynisman DM, Kelly RJ, Smith TJ. Trends in the Cost and Use of Targeted Cancer Therapies for the Privately Insured Nonelderly: 2001 to 2011. J Clin Oncol. 2015;33(19):2190–6.
27. Walker J. High Prices for Drugs Attacked at Meeting. The Wall Street Journal. http://www.wsj.com/articles/high-prices-for-drugs-attacked-at-meeting-1433119411. Accessed 4 Dec 2015.
28. Dolgin E. Big pharma moves from 'blockbusters' to 'niche busters'. Nat Med. 2010;16(8):837.
29. Genetic Alliance UK. Genome sequencing: What do patients think? Patient Charter. http://www.geneticalliance.org.uk/docs/patient-charter-genome-sequencing-what-do-patients-think.pdf. Accessed 4 Dec 2015.
30. European Alliance for Personalised Medicine. Affordable and sustainable patient access to personalised medicine. http://euapm.eu/pdf/EAPM_Affordable_and_sustainable_patient_access_to_PM.pdf. Accessed 4 Dec 2015.
31. Brock DW, Wikler D. Ethical Issues in Resource Allocation, Research, and New Product Development. In: Jamison DT, Breman JG, Measham AR,

Alleyne G, Claeson M, Evans DB, Jha P, Mills A, Musgrove P, editors. Disease Control Priorities in Developing Countries. 2nd ed. Washington (DC): World Bank; 2006. Chapter 14.
32. Daniels, Norman, "Justice and Access to Health Care", The Stanford Encyclopedia of Philosophy (Spring 2013 Edition), Edward N. Zalta (ed.). http://plato.stanford.edu/archives/spr2013/entries/justice-healthcareaccess/. Accessed 25 Feb 2016.
33. Fleck LM. Just caring: assessing the ethical and economic costs of personalized medicine. Urol Oncol. 2014;32(2):202–6.
34. Guindo LA, Wagner M, Baltussen R, Rindress D, van Til J, Kind P, Goetghebeur MM. From efficacy to equity: Literature review of decision criteria for resource allocation and healthcare decisionmaking. Cost Eff Resour Alloc. 2012;10(1):9.
35. Rogowski WH, Grosse SD, Schmidtke J, Marckmann G. Criteria for fairly allocating scarce health-care resources to genetic tests: which matter most? Eur J Hum Genet. 2014;22(1):25–31.
36. Daniels N. Accountability for reasonableness. BMJ. 2000;321(7272):1300–1.
37. NHS Scotland. Scottish Medicines Consortium. http://www.scottishmedicines.org.uk/Home. Accessed 4 Dec 2015.
38. Vogt H, Hofmann B, Getz L: The new holism: P4 systems medicine and the medicalization of health and life itself. Med Health Care Philos. 2016. pp 1-17
39. Sorensen K, Pelikan JM, Rothlin F, Ganahl K, Slonska Z, Doyle G, Fullam J, Kondilis B, Agrafiotis D, Uiters E et al: Health literacy in Europe: comparative results of the European health literacy survey (HLS-EU). Eur J Public Health 2015; 25(6):1053-58.
40. U.S. Food and Drug Administration. Targeted Drug Development: Why Are Many Diseases Lagging Behind? http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM454996.pdf. Accessed 4 Dec 2015.
41. Schleidgen S, Marckmann G. Re-focusing the ethical discourse on personalized medicine: a qualitative interview study with stakeholders in the German healthcare system. BMC Med Ethics. 2013;14:20.
42. European Patients' Academy on Therapeutic Innovation. http://www.patientsacademy.eu/index.php/en/. Accessed 4 Dec 2015.
43. European Alliance for Personalised Medicine. http://euapm.eu/. Accessed 4 Dec 2015.

IV

Budin-Ljøsne et al. BMC Medical Ethics (2017) 18:4
DOI 10.1186/s12910-016-0162-9

BMC Medical Ethics

RESEARCH ARTICLE Open Access

Dynamic Consent: a potential solution to some of the challenges of modern biomedical research

Isabelle Budin-Ljøsne[1,2*], Harriet J. A. Teare[3], Jane Kaye[3], Stephan Beck[4], Heidi Beate Bentzen[1,2,5], Luciana Caenazzo[6], Clive Collett[7], Flavio D'Abramo[8], Heike Felzmann[9], Teresa Finlay[3], Muhammad Kassim Javaid[10], Erica Jones[4], Višnja Katić[11], Amy Simpson[12] and Deborah Mascalzoni[13,14]

Abstract

Background: Innovations in technology have contributed to rapid changes in the way that modern biomedical research is carried out. Researchers are increasingly required to endorse adaptive and flexible approaches to accommodate these innovations and comply with ethical, legal and regulatory requirements. This paper explores how Dynamic Consent may provide solutions to address challenges encountered when researchers invite individuals to participate in research and follow them up over time in a continuously changing environment.

Methods: An interdisciplinary workshop jointly organised by the University of Oxford and the COST Action CHIP ME gathered clinicians, researchers, ethicists, lawyers, research participants and patient representatives to discuss experiences of using Dynamic Consent, and how such use may facilitate the conduct of specific research tasks. The data collected during the workshop were analysed using a content analysis approach.

Results: Dynamic Consent can provide practical, sustainable and future-proof solutions to challenges related to participant recruitment, the attainment of informed consent, participant retention and consent management, and may bring economic efficiencies.

Conclusions: Dynamic Consent offers opportunities for ongoing communication between researchers and research participants that can positively impact research. Dynamic Consent supports inter-sector, cross-border approaches and large scale data-sharing. Whilst it is relatively easy to set up and maintain, its implementation will require that researchers re-consider their relationship with research participants and adopt new procedures.

Keywords: Dynamic consent, Participant engagement, Research communication, Ethics, Biobank, Clinical trials, Clinical research, Software tools

Background

Conducting biomedical research is essential to increase our understanding of biological and molecular mechanisms underlying disease, test the efficiency of new drugs, interventions and devices, and move toward personalised medicine [1]. Biomedical research requires the continuous collection of biological samples, health and outcome data from representative samples of patients and populations and the follow up of these groups over time [2]. As innovations in technology develop at exponential speed, researchers need to have flexibility in the conduct of their research to be able to react quickly to ongoing developments and accelerate medical discovery and the development of new treatment strategies. However, traditional approaches to the planning and conduct of biomedical research projects present a number of challenges.

First, recruiting enough participants, or reaching out to the population of interest, is often difficult [3, 4]. This is particularly true in genetic research which experiences lower recruitment rates than other types of biomedical

* Correspondence: i.b.ljosne@medisin.uio.no
[1]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, Blindern, P.O. Box 1130NO-0318 Oslo, Norway
[2]Norwegian Cancer Genomics Consortium, cancergenomics.no, Oslo, Norway
Full list of author information is available at the end of the article

research [5]. Participant recruitment may be hindered by a lack of manpower or funding to organise large information-giving and enrolment campaigns. It may also be inhibited by clinical staff's limited familiarity or understanding of research objectives and fears that it will interrupt patient care [6]. Furthermore, patients may not understand the objectives of the research, may not be willing or able to travel to the research centre [7], or may not speak the language used by researchers [8].

Second, obtaining informed consent from research participants can be demanding. The objective of the informed consent process is to ensure that research participants understand the aims and risks of the research and participate in the research voluntarily with this knowledge. However, research participants often do not understand the content of the information sheet or the consent form for the study, particularly if the consent form is lengthy and includes complex terminology [9, 10]. While some participants may be satisfied with receiving information about the research project only once during the recruitment phase, others may want to go through the information several times and may have additional questions or concerns. Assessing the participants' health literacy and understanding of the research objectives and implications can be difficult and time-consuming [11]. If new research needs arise that were not foreseen and included in the original consent document, collecting new consent from research participants may be expensive and burdensome, particularly if additional consent requires face-to-face interaction or the mailing of paper consent forms. If multiple consents are collected over time, keeping records of these consents can be complicated, particularly in cohort studies, or in projects spanning several years and multiple iterations where paper consent forms are stored in several institutions [11].

Third, retaining research participants in projects is often challenging [8, 12]. Participants may drop out because they experience changes in their condition, respond adversely to the intervention under investigation, move away from the study area or lose interest in the study. Participant drop-out jeopardises the quality of the data, the significance of research findings, and the conduct of follow-up studies [13]. In addition, clinical researchers often need to collect patient-reported outcome data over time to better understand disease symptoms and the impact on disease burden [14]. Researchers conducting population-based health surveys may want to send new health questionnaires to their participants. Regularly collecting additional data from participants may be administratively demanding and costly, particularly if paper forms have to be sent in the mail.

A number of innovative strategies have been developed which aim to offer practical solutions and tools to facilitate the processes described above. For instance, clinical research projects have developed in-home clinical trial support programs to enable patients who cannot travel long distance to clinical sites to participate in research [12]. Projects are coordinating efforts between research teams and infrastructure support at clinical sites to improve recruitment rates [15]. The use of new technologies such as mobile phones and applications is also explored to facilitate ongoing data collection [16]. In addition, large efforts have been made to investigate designs for informed consent that both facilitate the conduct of biomedical research and protect the interests of research participants. A strategy that has received considerable attention is the use of broad consent. Broad consent is an alternative to the more customary specific consent; many consider specific consent too difficult to apply in biobank research where biological sample collections are built as research resources for multiple uses [17]. Definitions of broad consent vary and span from "consent to a wide (broadly specified) range of options" [18] to consent to "an unspecified range of future research subject to a few content and/or process restrictions" [19]. In general, broad consent can be described as a tool that enables research participants to consent to a variety of research projects. Blanket consent, that is consent to an unlimited range of options, has also been suggested as a potential strategy to facilitate the conduct of research [18]. More recently, meta-consent, an approach which enables individuals to express preferences regarding which type of consent they want to give for which type of research (for example, blanket consent to research on biological samples, specific consent to research led by industrial actors) has been described as a solution that may positively affect people's willingness to participate in research [20].

In principle, broad and blanket consent may facilitate the conduct of research as researchers do not have to consent research participants each time new research questions or situations arise. However, there is some controversy regarding the extent to which these approaches to consent enable research participants to be truly informed about the objectives and details of the research and are respectful of the participants' values and personal preferences [18, 21]. Furthermore, it remains unclear whether broad consent may help address some of the challenges described earlier. For instance, it is unlikely that the use of broad consent facilitates reaching out to populations that would not normally participate in research because they do not have easy access to research facilities or do not understand why they should participate. In addition, the use of broad consent may not provide any protection against unforeseen events such as regulatory changes. The difficulties that the Swedish population biobank Lifegene encountered are illustrative of this issue. Although the biobank had already

recruited many participants and collected their broad consent, in 2013, the Swedish Data Inspection Board decided to temporarily suspend the biobank's activities as it considered that broad consent did not describe the biobank research in a way that would satisfy the requirements of forthcoming regulation [22, 23]. Similarly, it is unclear whether meta-consent may positively impact participant retention or facilitate ongoing health data collection in research projects.

Another strategy to facilitate the conduct of biomedical research while protecting the interests of research participants is Dynamic Consent. Dynamic Consent is a term used to describe personalised, online consent and communication platforms [3]. Such platforms are primarily designed to achieve two objectives: 1) facilitate the consent process and 2) facilitate two-way, ongoing communication between researchers and research participants. It should be noted that Dynamic Consent is not the same as specific consent. Rather, it can be setup to accommodate different types of consent depending on the research objectives and context [24]. For instance, biobank research participants may give their broad consent to research through a Dynamic Consent platform. Later in time they may use the platform to give their new consent to new research activities that were not foreseen in the original consent (e.g. feedback of genetic research results), or they may alter their consent choices in response to their changing circumstances [3]. Although a central objective of Dynamic Consent is to offer some flexibility to the consent process, Dynamic Consent platforms may also be used for communication in both clinical and population-based research projects. For instance, researchers may use the platform to give participants regular updates about the research, or ask participants to upload new health data throughout the duration of the research project. Research participants may use the platform to set up their preferences regarding access to their health data by third parties or how often they would like to be contacted by the researchers. In recent years, several clinical and population-based research projects have tested online Dynamic Consent platforms [25–31], initiatives welcomed by research participants [29, 32]. Also in health care settings, projects are exploring the use of online platforms for patient consent to the re-use of electronic patient records for research [33].

In the literature, there is emphasis on discussing how Dynamic Consent may enhance the research participants' right to make autonomous choices regarding their participation in research, improve their comprehension of the consent process and promote their engagement in the research endeavour [11, 24, 34–37]. Less attention has been given to exploring specific ways that Dynamic Consent may facilitate the conduct of medical research. The key purpose of this paper is to explore how Dynamic Consent can help researchers address the challenges encountered (in population-based and clinical research) when inviting individuals to participate in research and following them up over time in a continuously changing environment.

Methods

In October 2015, the Centre for Health, Law and Emerging Technologies (HeLEX) [22] at the University of Oxford and Working Group 1 of the COST Action CHIP ME IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives" [23] (a European Union Framework which brings together European experts) conducted an interdisciplinary two-day workshop at the University of Oxford to share experiences of implementing Dynamic Consent within research projects. Representatives from a range of disciplines contributed to the workshop including ethicists, lawyers, clinicians, researchers, research nurses and research participants. First, the workshop members discussed Dynamic Consent approaches that are implemented in clinical and biobank research projects and identified key elements in these projects that characterise Dynamic Consent. Several workshop members reported how Dynamic Consent had been designed and applied in their projects. Second, the workshop members mapped a process flowchart describing the main tasks that researchers have to complete in order to include and follow up individuals in research projects. For each task, the workshop members identified challenges encountered that may delay or render task completion difficult. Then a discussion followed as to how Dynamic Consent may facilitate the conduct of each task, particularly in terms of increased requirements for transparency, information-sharing and participant engagement. The workshop members were made aware that the findings from the workshop would be published and were offered the opportunity to contribute to the writing of this paper. Notes were taken during the workshop; the workshop organisers summarised and analysed the data using a content analysis approach with an inductive approach [38]. First, the notes were sorted and the data categorised according to the main tasks that had been listed in the process flowchart. Then the data were condensed to reflect the main points made by the workshop members. A preliminary paper summarising the workshop findings was shared with workshop members for validation. Their comments and corrections were integrated into the results. This research did not require informed consent or approval from an ethics board.

Results

Discussions at the workshop demonstrated that Dynamic Consent can provide practical solutions to the conduct of four main tasks: participant recruitment, collection of informed consent, participant retention and

consent management as summarised below and described in Fig. 1. For each task, we provide concrete examples from research projects to describe how Dynamic Consent can address these challenges.

Participant recruitment

A Dynamic Consent platform can be set up to provide most of the information about a research project online in a user-friendly and standardised way across research sites (including video, podcast, web, or mobile applications). The information can be given in as many languages as necessary by use of subtitles, dubbed soundtracks and translated text, and at a level of detail that satisfies the specific needs of participants [16, 18]. In principle, the information is accessible to large groups regardless of their geographical location since it is on the Internet, thus potentially broadening the research population. This may be particularly useful in rare disease research where the number of cases is often low and patients are geographically scattered. An example of this is the website for RUDY, a study in rare diseases of the bones, joints and blood vessels headed by a research team at the University of Oxford [39]. The website provides simple information about the research and explains how patients diagnosed with a relevant rare disease, or their relatives, may register to become a research participant in the study. Individuals who would like to register are invited to use the online secure registration system and are informed that they will be contacted after registration for completion of the consent process, usually by telephone, by a research team member [27]. Patients can consult information sheets and consent forms on the website. Since most of the information about the project is available online, the time needed for individual discussions with potential research participants is reduced.

To reach out to populations who are not entirely familiar with the use of online technologies or do not have access to them, the use of a Dynamic Consent platform may be accompanied with conventional methods such as paper leaflets or local information-giving meetings. This strategy was used in the Cooperative Health Research In South Tyrol (CHRIS) study [40], a population-based study aiming to investigate the genetic and molecular basis of age-related common chronic conditions and their interaction with life-style and environment in the general population [28]. To recruit participants from rural areas to the study, village information meetings, broadcasts of information to the public through the local media and web-based recruitment were combined to maximise family participation. However, it is anticipated that the use of multiple methods may become less important as people's access and familiarity with the Internet improves and they become acquainted with Dynamic Consent platforms. Once participants are recruited, the platform may also be used to regularly update them about recruitment progress and how they can improve awareness of the research within their communities.

Collection of informed consent

Although standard ethical practice is to have face-to-face dialogue with potential research participants at least for the attainment of the original consent, Dynamic Consent may challenge such practice. In the RUDY study, potential participants discuss the study with the research team in telephone consultations. Then, the participants may choose to download the informed consent form from the website, sign it and send it to the research team by postal mail or email, or they may give their electronic sign-off [27]. Research projects may use mechanisms to assess the participants' level of comprehension of the research online, for instance by asking research participants to correctly answer interactive questions before providing their consent [33]. As an illustration, potential participants in the Harvard Personal Genome

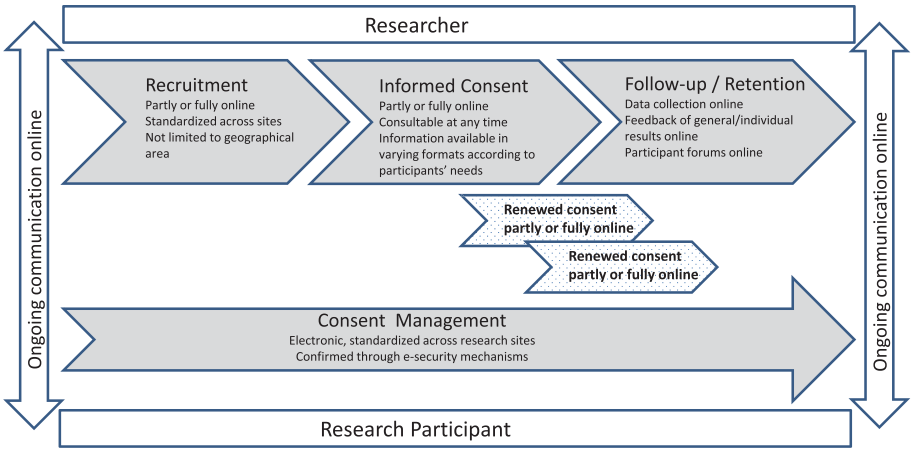


Fig. 1 Dynamic Consent's contribution to phases of research

Project (PGP) [41], a project aiming to publicly share the genome, health and trait data of thousands of volunteers, are required to complete an online enrolment examination to demonstrate their comprehension of the risks and protocols associated with being a member of the project before they can give their informed consent to participate in the research [42]. Individuals who fail the examination or do not complete it are not eligible to participate in the research.

A Dynamic Consent platform enables researchers to refine consent in a more nuanced way that the traditional 'all or nothing' approach (either participate in the research or not) [43]. For instance, researchers may give participants the choice to consent to some or all aspects of the research depending on their personal preferences and beliefs. Researchers may also ask research participants which types of data access by third parties are acceptable to them. For example, in the Platform for Engaging Everyone Responsibly (PEER) [44], a tool developed by the Genetic Alliance [45] and Private Access [46], research participants may indicate the type of access that they approve and do not approve of, in a matrix. Researchers may also ask participants to consent to a range of other activities at any time; these include data deposit in public research databases [47], data sharing with drug companies and privately-funded institutions [48, 49], or the use of biological samples in case of death or incapacity. This solution enables researchers to know exactly which levels of privacy risks research participants are willing to take and which data may or may not be used in the research. Access preferences can be updated at any time depending on the specific needs and preferences of each research participant and may be directly connected to the databases [50]. Rather than creating potential restrictions on data sharing, such a strategy may enhance data sharing. This is because research participants often consider that the altruistic benefits of sharing their data for research outweigh potential risks [33, 51, 52] but anticipate being consulted about how their data are used and expect transparency regarding such decisions [51, 53].

A Dynamic Consent platform may also enable participants to consent online to the feedback of genetic research results, even years after a project starts. For instance, participants in the CHRIS study may indicate in their personal settings whether they would like to be contacted if results are produced in the research which may offer "chances of therapy or prevention", and by whom (for example the hospital which recruited them in the research or their general practitioner) [50]. Enabling participants to consent to the feedback of their genetic research results may be useful in research projects planning to recruit participants in future follow-up studies on the basis of their genotype [54]. In principle, the results could be fed back through the platform if the necessary requirements in terms of genetic counselling are met. As an illustration, private actors such as the direct-to-consumer genetic testing company 23andMe combine user-friendly online feedback services with genetic counselling by telephone to those customers who want it [55].

Participant retention

Dynamic Consent enables researchers to provide participants with regular updates about early findings, follow-up studies, key outcomes, presentations and publications, or invite them to information meetings or follow-up consultations. A recent survey conducted among participants in the CHRIS study shows that ongoing communication motivates research participants to continue with the research [50], an observation also made in previous studies [29, 32]. Importantly, researchers may use a Dynamic Consent platform to ask participants to upload additional health data online. This may become a critical feature of Dynamic Consent as researchers are increasingly moving away from traditional, large-scale randomised controlled trials under which measurements from thousands of people are harvested, to trials conducted on smaller patient groups that are stratified based on presence or absence of specific biomarkers [56]. In these trials, relying solely on statistical methods or average responses to assess new treatment strategies is hardly optimal since the numbers are too small to quantify positive and negative uncertainties such as benefit and risk [57]. Researchers need to rely more on patients' experiences by regularly collecting data from them regarding health outcomes, quality of life, side effects and personal utility of interventions over time [43]. In the RUDY study, participants use the online platform to fill in health questionnaires, manage their history of illness as well as diagnostics, prescriptions and surgical interventions. The information uploaded in the platform is not only useful to researchers but also to individual research participants who can use it, for instance, in their consultations with physicians [27].

The Dynamic Consent platform may be designed to enable participants to initiate communication with researchers or among themselves, for example via online discussions, forums and webinars. For instance they may do so to comment on recruitment and assessment processes or to identify new research questions that may be relevant to them, thus helping researchers to identify future research opportunities [58]. The use of the platform may enhance participants' understanding of research and positively impact their willingness to remain in a research project as their scientific literacy increases, as illustrated by low withdrawal rates in the Harvard Genome Project [42] and the CHRIS study (Mascalzoni D, De Grandi A, Pattaro C, D'Elia J, Pramstaller P, Goegele M, et al.

Dynamic Consent: building trust through ELSI improvements. Six years of Dynamic Consent in the CHRIS study. Submitted). Participants may also use the platform to indicate when, how, and by what means (e.g. telephone, letter, e-mail, SMS, website) they wish to be notified about new events and in what circumstances, thus mitigating concerns that they may feel overwhelmed by continual communication, or conversely feel insufficiently informed [59].

Consent management

The Dynamic Consent platform allows consent records to be stored and updated electronically, providing researchers with a reliable and fully tracked overview. Research participants may consult their current and previous consent decisions at any time. The electronic storage of consent details enables researchers to confirm easily the consent status of participants and to audit and review procedures without the need to refer to individual paper records. This can significantly reduce the time taken for audit and improve reliability of the record trail. The technology to gather and securely store Dynamic Consent records can be developed so that it is durable despite rapid software advances and meets security expectations similar to requirements for electronic health records [60]. For instance, online consent may be valid only if provided with an official e-identity or unique user name and password given by public services [30]. In principle, the Dynamic Consent platform can also be linked to other information systems such as Laboratory Information Management Systems in biobanks [24] and electronic patient records [33]. These systems can be automatically updated with the consent preferences of research participants as these are electronically "tagged" to each biological sample and/or data [50]. Participants can enter the platform at any time to review their consents, print a copy, or ask for a copy to be sent by electronic mail or post [31].

Discussion

The use of Dynamic Consent may facilitate the conduct of specific research tasks, positively impact recruitment and retention and simplify the collection and management of participants' consent. It may also potentially contribute to reducing costs as many activities (such as sending out information to research participants in the mail) are conducted online, permit greater operability across different organisations if built using recognised national standards [11] and provide researchers with a practical tool to meet forthcoming legal requirements for transparency and precise information-giving to participants [61]. Importantly, Dynamic Consent may offer an opportunity for researchers and research participants to engage in long-term dialogue in a way that goes beyond the traditional one-off consent process, which may benefit both parties. Our results are supported by recent recommendations to explore online tools and multimedia interventions as these have the potential to improve consent processes and increase participants' level of comprehension of the research [62, 63]. Establishing a culture of ongoing communication between researchers and research participants is increasingly demanded by patient advocacy groups [64] and research participants [53] who would like to be consulted about third party access to their data [51, 65] and the management of genetic research results [66]. Increased researcher-research participant communication is also encouraged by research funders and policymakers to improve the usefulness and accuracy of research, facilitate the development of research projects within areas of medicine that have been given little priority (such as rare diseases) and accelerate the translation of research findings to clinical practice [1, 67]. As an illustration, the recently launched Precision Medicine Initiative Cohort Program [68] which aims to build a national cohort of one million participants across the United States, recommends the development of an online platform for "dynamic information sharing" that enables participants to "actively engage in an informed, voluntary, and ongoing manner", including setting consent preferences or consulting information whenever needed, and providing "requested data when it is convenient for them" [69].

Dynamic Consent platforms are still under development and only limited empirical data report experiences from their use or hurdles to their implementation [27, 29, 31, 32]. However, several elements need to be considered by researchers before implementing Dynamic Consent platforms in their project.

Cost and maintenance

Designing, implementing and maintaining a Dynamic Consent platform requires staff with good communication and IT-skills and, in some cases, equipment if potential participants cannot use their own device [16]. However, such costs can reasonably be expected to decrease in the future as online solutions are likely to become more standardised, user-friendly and automatic. If researchers are able to use existing software or are provided with access to a national platform for Dynamic Consent, as was recently proposed in Norway [11], this may also reduce investments in IT-infrastructure [24]. Similarly, links can be provided in the platform to publicly available tools such as educational videos, thus limiting the need to produce information material. Researchers should identify key individuals who may help them develop a Dynamic Consent platform, investigate collaborations with other projects to facilitate platform sharing or establish whether there is a national platform that could be used. A budget for the development or use of a platform should be included in research funding applications.

Collaboration with research ethics committees

Research ethics committees may not be familiar with Dynamic Consent solutions, although this is gradually changing [70]. The implementation of Dynamic Consent in research projects requires research ethics committees assessing research projects to adapt from expectations of participants' binary yes/no consent status to one that varies both in scope and across time. Research ethics committees may need to put greater emphasis on evaluating the functionalities of the tools that are made available to participants in a research project rather than scrutinising the type of consent they may give. In the CHRIS study, the research ethics committee approved the whole process of Dynamic Consent along with the informational material. A presentation of the concept had been provided a few weeks earlier. The committee agreed that once a participant was informed about the procedure and gave initial consent in person, he or she could deal with subsequent consent requests online (provided security checks and identification means were in place) [50]. As the use of Dynamic Consent develops, researchers could collaborate with research ethics committees to agree upon required criteria for a platform to qualify as an approved Dynamic Consent platform.

Accessibility of the platform

Some research participants may not have access to the Internet, may not be the owner of a mobile device, or may not have the ability to use these technologies [33]. This may be particularly true for the elderly, the disabled and individuals in socially deprived communities. Recent experiences from the use of online platforms for consent show that populations enrolling electronically are less diverse in terms of ethnicity and education than populations enrolled through other means [31]. The positive effects of using multimedia platforms in the informed consent process also remain unclear for socio-economically disadvantaged groups [71]. Furthermore, it is unknown whether the use of a Dynamic Consent platform fully addresses participants' needs in terms of human interaction [32]. Researchers should ensure that education in the use of online tools is provided to participants who request it and that alternative solutions including face-to-face meetings are available for those who cannot use the platform or are not likely to benefit from its use. Younger people are often experts in the use of online communication tools; their input to the design of a Dynamic Consent platform may therefore be useful in addition to contributions from older people who would be potential users.

It is inevitable that some research participants will not want to use the Dynamic Consent platform even if it is user-friendly and easily accessible. As an illustration, some patients who are recruited to research through their clinician may fully trust the clinician's judgment and prefer to give a one-off broad consent to participation in research considering a Dynamic Consent interface unnecessary. Thus it is important to note that the objective of using a Dynamic Consent platform is not to force people to engage in research and communicate with researchers, but rather to offer them an opportunity to do so. Results from a recent empirical study aiming to investigate biobank participants' experiences of the use of a Web 2.0 Dynamic Consent interface suggest that once introduced to using an online platform, participants recognise its benefits and find the functions offered by the platform useful [32]. Disseminating information about the platform and enabling participants to discuss the platform together, may indirectly encourage some reluctant participants to consider its use.

Personal responsibility

Dynamic Consent respects differences between research participants. Researchers must ensure that this empowering feature of the platform does not lead to undesirable side effects [59]. Research participants should not have to take responsibility for making decisions regarding complex issues that they do not fully grasp or are not in a position to assess properly [59, 72]. For instance, as data sharing spans several years and a variety of projects, research participants may struggle to decide which data sharing scenarios are or are not acceptable to them. Researchers may use the platform to educate research participants in the general implications of research including the benefits or risks of data sharing, using short information videos or frequently asked questions. Research participants who have a better understanding of what is at stake are more likely to be able to make informed decisions about data sharing. Finally, participation in genetic and genomic research may have implications not only for the individuals recruited to the project but also for their family. In the future, researchers may need to take this into consideration when designing communication interfaces for participants [73].

Conclusion

Dynamic Consent, through transparent information exchange and ongoing consent, aims to reinforce the informational, societal and relational value of research and implies a powerful change in the participant's role from passive 'subject' to active 'participant' [74]. With Dynamic Consent, informed consent is not restricted to a functional or legal instrument, but also becomes a social agreement between researchers and research participants [75]. Such change is essential to the creation of new knowledge, the development of new and adaptive research designs, and the realisation of personalised medicine [1]. It may however generate some anxiety in the

research community as the active role of participants is sometimes perceived as potentially threatening [36]. Similar concerns were raised when the Harvard Personal Genome Project (PGP) implemented an online platform for Open Consent in 2005 [41]. Open consent means that participants give their consent to unrestricted disclosure of their genotype-phenotype data and are made fully aware of the risks of participation in the project, including loss of confidentiality and privacy through public disclosure or identification [76]. In the project, ongoing communication is maintained with participants to collect knowledge regarding the consequences of participation. Experiences from the first ten years of the project show that ongoing communication is perceived as meaningful both by the research participants and the researchers [42].

When engaging participants in research through a Dynamic Consent platform, researchers need to be open-minded, accept that research participants may raise critical questions and make suggestions, and be prepared to take these into consideration in the design of the research. In return, researchers will benefit from having more engaged, committed and productive participants in their research; such participants are useful as demonstrated by the successful contributions to research made by online communities of patients [77]. Dynamic Consent could provide a tool that enables researchers to fully benefit from increased interaction with participants.

Abbreviations

CHIP ME: Citizen's health through public-private initiatives: public health, market and ethical perspectives; CHRIS: Cooperative health research in south tyrol; COST Action: European cooperation in science and technology; PEER: Platform for engaging everyone responsibly; PGP: Harvard personal genome project

Acknowledgments

The authors would like to thank all the workshop participants for their fruitful contributions, and Professor Jan Helge Solbakk, University of Oslo, for his comments.

Funding

This article is based upon work from COST Action IS1303 "Citizen's Health through public-private Initiatives: Public health, Market and Ethical perspectives", and is supported by COST (European Cooperation in Science and Technology) (http://www.cost.eu) which funded the workshop. IBL receives support from the National Research and Innovation Platform for Personalized Cancer Medicine funded by The Research Council of Norway (NFR BIOTEK2021/ES495029). HBB receives support from Legal Regulation of Information Processing relating to Personalized Cancer Medicine (LegRegPCM) funded by The Research Council of Norway (NFR BIOTEK2021/238999). MKJ receives support from the Oxford NIHR Musculoskeletal BRU. JK is funded under Wellcome Trust Award 096599/2/11/Z. DM has received funding from the Innovative Medicines Initiative project BT-Cure (grant agreement number 115142–1) and the Biobanking and Molecular Resource Infrastructure of Sweden project, RD Connect FP7 (grant agreement No. 305444).

Availability of data and materials

Notes from the workshop are stored at the University of Oslo and will not be made publicly available.

Authors' contributions

IBL, HJAT, JK and DM organised the workshop, conceived the paper and drafted the first version of the manuscript. IBL, HJAT, SB, HBB, LC, CC, FD, HF, TF, MKJ, EJ, VK, AS, JK and DM participated in the workshop discussions. IBL revised the manuscript according to comments from all authors, and finalised the manuscript. All authors critically read, revised and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

No ethics approval or informed consent was necessary. Participants at the workshop were informed that the results from the workshop would be used to write a paper and were invited to contribute to its production.

Author details

[1]Centre for Medical Ethics, Institute of Health and Society, University of Oslo, Blindern, P.O. Box 1130NO-0318 Oslo, Norway. [2]Norwegian Cancer Genomics Consortium, cancergenomics.no, Oslo, Norway. [3]Centre for Health, Law and Emerging Technologies (HeLEX), Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom. [4]UCL Cancer Institute, University College London, London, United Kingdom. [5]Norwegian Research Center for Computers and Law, Faculty of Law, University of Oslo, Oslo, Norway. [6]Università degli Studi di Padova, Padova, Italy. [7]Health Research Authority, London, United Kingdom. [8]Focus Area DynAge, Freie Universität, Berlin, Germany. [9]Centre of Bioethical Research & Analysis, NUI Galway, Galway, Ireland. [10]NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom. [11]School of Medicine, University of Rijeka, Rijeka, Croatia. [12]Genetic Alliance UK, London, United Kingdom. [13]Centre for Research Ethics and Bioethics, Uppsala University, Uppsala, Sweden. [14]Centre for Biomedicine, EURAC, Bolzano, Italy.

Received: 9 June 2016 Accepted: 26 December 2016
Published online: 25 January 2017

References

1. European Science Foundation. ESF Forward Look: Personalised Medicine for the European Citizen. http://archives.esf.org/fileadmin/Public_documents/Publications/Personalised_Medicine.pdf. Accessed 25 Nov 2016.
2. Anderson N, Bragg C, Hartzler A, Edwards K. Participant-Centric Initiatives: Tools to Facilitate Engagement In Research. Appl Transl Genom. 2012;1:25–9.
3. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. BMJ Open. 2012;2(1):e000496.
4. Johnsson L, Helgesson G, Rafnar T, Halldorsdottir I, Chia KS, Eriksson S, et al. Hypothetical and factual willingness to participate in biobank research. Eur J Hum Genet. 2010;18(11):1261–4.
5. Matsui K, Kita Y, Ueshima H. Informed consent, participation in, and withdrawal from a population based cohort study involving genetic analysis. J Med Ethics. 2005;31(7):385–92.
6. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol. 1999;52(12):1143–56.
7. Newington L, Metcalfe A. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC Med Res Methodol. 2014;14:10.
8. Boden-Albala B, Carman H, Southwick L, Parikh NS, Roberts E, Waddy S, et al. Examining Barriers and Practices to Recruitment and Retention in Stroke Clinical Trials. Stroke. 2015;46(8):2232–7.
9. Perry J, Wohlke S, Hessling AC, Schicktanz S. Why take part in personalised cancer research? Patients' genetic misconception, genetic responsibility and incomprehension of stratification-an empirical-ethical examination. Eur J Cancer Care (Engl) 2016.
10. D'Abramo F, Schildmann J, Vollmann J. Research participants' perceptions and views on consent for biobank research: a review of empirical data and ethical analysis. BMC Med Ethics. 2015;16:60.
11. Budin-Ljosne I, Bentzen HB, Solbakk JH, Myklebost O. Genome sequencing in research requires a new approach to consent. Tidsskr Nor Laegeforen. 2015;135(22):2031–2.

12. Khaleel SL. In: Clinical Leader. Rare Disease Patient Recruitment And Retention. http://www.clinicalleader.com/doc/rare-disease-patient-recruitment-and-retention-0001. Accessed 25 Nov 2016.
13. Penckofer S, Byrn M, Mumby P, Ferrans CE. Improving subject recruitment, retention, and participation in research through Peplau's theory of interpersonal relations. Nurs Sci Q. 2011;24(2):146–51.
14. Bronstein MG, Kakkis ED. Patients as key partners in rare disease drug development. Nat Rev Drug Discov. 2016;15(11):731–2.
15. Nicholson LM, Schwirian PM, Klein EG, Skybo T, Murray-Johnson L, Eneli I, et al. Recruitment and retention strategies in longitudinal clinical studies with low-income populations. Contemp Clin Trials. 2011;32(3):353–62.
16. Pugliese L, Woodriff M, Crowley O, Lam V, Sohn J, Bradley S. Feasibility of the "Bring Your Own Device" Model in Clinical Research: Results from a Randomized Controlled Pilot Study of a Mobile Patient Engagement Tool. Cureus. 2016;8(3):e535.
17. Hansson MG, Dillner J, Bartram CR, Carlson JA, Helgesson G. Should donors be allowed to give broad consent to future biobank research? Lancet Oncol. 2006;7(3):266–9.
18. Hofmann B. Broadening consent–and diluting ethics? J Med Ethics. 2009;35(2):125–9.
19. Grady C, Eckstein L, Berkman B, Brock D, Cook-Deegan R, Fullerton SM, et al. Broad Consent for Research With Biological Samples: Workshop Conclusions. Am J Bioeth. 2015;15(9):34–42.
20. Ploug T, Holm S. Going Beyond the False Dichotomy of Broad or Specific Consent: A Meta-Perspective on Participant Choice in Research Using Human Tissue. Am J Bioeth. 2015;15(9):44–6.
21. Caulfield T, Upshur RE, Daar A. DNA databanks and consent: a suggested policy option involving an authorization model. BMC Med Ethics. 2003;4:E1.
22. Lind A-S. In: Uppsala Universitet. New law for Biobank researchers http://www.crb.uu.se/biobank-perspectives/item/?tarContentId=496836. Accessed 25 Nov 2016.
23. Lind A-S. LifeGene - a Closed Case? In: Information and Law in Transition: Freedom of Speech, the Internet, Privacy and Democracy in the 21st Century. Edited by Lind AS RJ, Österdahl I. Stockholm: Liber; 2015. p. 339–50.
24. Kaye J, Whitley EA, Lund D, Morrison M, Teare H, Melham K. Dynamic consent: a patient interface for twenty-first century research networks. Eur J Hum Genet. 2015;23(2):141–6.
25. Wilbanks J, Friend SH. First, design for data sharing. Nat Biotechnol. 2016;34(4):377–9.
26. Dixon WG, Spencer K, Williams H, Sanders C, Lund D, Whitley EA, et al. A dynamic model of patient consent to sharing of medical record data. BMJ. 2014;348:g1294.
27. Javaid MK, Forestier-Zhang L, Watts L, Turner A, Ponte C, Teare H, et al. The RUDY study platform - a novel approach to patient driven research in rare musculoskeletal diseases. Orphanet J Rare Dis. 2016;11(1):150.
28. Pattaro C, Gogele M, Mascalzoni D, Melotti R, Schwienbacher C, De Grandi A, et al. The Cooperative Health Research in South Tyrol (CHRIS) study: rationale, objectives, and preliminary results. J Transl Med. 2015;13(1):348.
29. Teare HJ, Morrison M, Whitley EA, Kaye J. Towards 'Engagement 2.0': Insights from a study of dynamic consent with biobank participants. Digital Health. 2015;0(0):1–13.
30. Thiel DB, Platt J, Platt T, King SB, Fisher N, Shelton R, et al. Testing an online, dynamic consent portal for large population biobank research. Public Health Genomics. 2015;18(1):26–39.
31. Boutin NT, Mathieu K, Hoffnagle AG, Allen NL, Castro VM, Morash M, et al. Implementation of Electronic Consent at a Biobank: An Opportunity for Precision Medicine Research. J Pers Med. 2016;6(2):17.
32. Coathup V, Teare HJ, Minari J, Yoshizawa G, Kaye J, Takahashi MP, et al. Using digital technologies to engage with medical research: views of myotonic dystrophy patients in Japan. BMC Med Ethics. 2016;17(1):51.
33. Spencer K, Sanders C, Whitley EA, Lund D, Kaye J, Dixon WG. Patient Perspectives on Sharing Anonymized Personal Health Data Using a Digital System for Dynamic Consent and Research Feedback: A Qualitative Study. J Med Internet Res. 2016;18(4):e66.
34. Kaye J, Curren L, Anderson N, Edwards K, Fullerton SM, Kanellopoulou N, et al. From patients to partners: participant-centric initiatives in biomedical research. Nat Rev Genet. 2012;13(5):371–6.
35. Cañada JA, Tupasela A, Snell K. Beyond and within public engagement: a broadened approach to engagement in biobanking. New Genet Soc. 2015;34(4):355–76.
36. D'Abramo F. Biobank research, informed consent and society. Towards a new alliance? J Epidemiol Community Health. 2015;69(11):1125–8.
37. Williams H, Spencer K, Sanders C, Lund D, Whitley EA, Kaye J, et al. Dynamic consent: a possible solution to improve patient confidence and trust in how electronic patient records are used in medical research. IMIR Med Inform. 2015;3(1):e3.
38. Elo S, Kyngas H. The qualitative content analysis process. J Adv Nurs. 2008;62(1):107–15.
39. The Rudy Study. https://research.ndorms.ox.ac.uk/rudy/. Accessed 25 Nov 2016.
40. The CHRIS Study (Cooperative Health Research In South Tyrol). In: EURAC Research. http://www.eurac.edu/en/research/health/biomed/projects/Pages/default.aspx. Accssed 25 Nov 2016.
41. Harvard Personal Genome Project. http://www.personalgenomes.org/. Accessed 25 Nov 2016.
42. Ball MP, Bobe JR, Chou MF, Clegg T, Estep PW, Lunshof JE, et al. Harvard Personal Genome Project: lessons from participatory public research. Genome Med. 2014;6(2):10.
43. Melham K, Moraia LB, Mitchell C, Morrison M, Teare H, Kaye J. The evolution of withdrawal: negotiating research relationships in biobanking. Life Sci Soc Policy. 2014;10(1):16.
44. Platform for Engaging Everyone Responsibly (PEER). In: Genetic Alliance. http://www.geneticalliance.org/programs/biotrust/peer. Accessed 25 Nov 2016.
45. Genetic Alliance. http://www.geneticalliance.org/. Accessed 25 Nov 2016.
46. Private Access, Inc. https://www.privateaccess.info/. Accessed 25 Nov 2016.
47. Haga SB, O'Daniel J. Public perspectives regarding data-sharing practices in genomics research. Public Health Genomics. 2011;14(6):319–24.
48. Nilstun T, Hermeren G. Human tissue samples and ethics–attitudes of the general public in Sweden to biobank research. Med Health Care Philos. 2006;9(1):81–6.
49. Critchley C, Nicol D, Otlowski M. The impact of commercialisation and genetic data sharing arrangements on public trust and the intention to participate in biobank research. Public Health Genomics. 2015;18(3):160–72.
50. Mascalzoni D. ELSI of Psychiatrics in Population projects. In: European Biobank Week: 13–16 September 2016; Vienna, Austria. 2016.
51. Ludman EJ, Fullerton SM, Spangler L, Trinidad SB, Fujii MM, et al. Glad you asked: participants' opinions of re-consent for dbGap data submission. J Empir Res Hum Res Ethics. 2010;5(3):9–16.
52. Burstein MD, Robinson JO, Hilsenbeck SG, McGuire AL, Lau CC. Pediatric data sharing in genomic research: attitudes and preferences of parents. Pediatrics. 2014;133(4):690–7.
53. Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB, Burke W. Genomic research and wide data sharing: views of prospective participants. Genet Med. 2010;12(8):486–95.
54. Budin-Ljosne I, Soye KJ, Tasse AM, Knoppers BM, Harris JR. Genotype-driven recruitment: a strategy whose time has come? BMC Med Genomics. 2013;6(1):19.
55. 23andMe. https://www.23andme.com/. Accessed 25 Nov 2016.
56. Biankin AV, Piantadosi S, Hollingsworth SJ. Patient-centric trials for therapeutic development in precision oncology. Nature. 2015;526(7573):361–70.
57. Wynne B. Uncertainty and environmental learning. Glob Environ Chang. 1992;2(2):111–27.
58. Dove ES, Joly Y, Knoppers BM. Power to the people: a wiki-governance model for biobanks. Genome Biol. 2012;13(5):158.
59. Steinsbekk KS, Kare MB, Solberg B. Broad consent versus dynamic consent in biobank research: Is passive participation an ethical problem? Eur J Hum Genet 2013.
60. Fernandez-Aleman JL, Senor IC, Lozoya PA, Toval A. Security and privacy in electronic health records: a systematic literature review. J Biomed Inform. 2013;46(3):541–62.
61. Baker DB, Kaye J, Terry SF. Governance Through Privacy, Fairness, and Respect for Individuals. EGEMS (Wash DC). 2016;4(2):1207.
62. Beskow LM, Dombeck CB, Thompson CP, Watson-Ormond JK, Weinfurt KP. Informed consent for biobanking: consensus-based guidelines for adequate comprehension. Genet Med. 2015;17(3):226–33.
63. Sonne SC, Andrews JO, Gentilin SM, Oppenheimer S, Obeid J, Brady K, et al. Development and pilot testing of a video-assisted informed consent process. Contemp Clin Trials. 2013;36(1):25–31.
64. Genome sequencing: What do patients think? Patient Charter. In: Genetic Alliance UK. 2016. https://www.geneticalliance.org.uk/media/2493/my-cancer-my-dna-patient-charter-edits-sept2016.pdf.Accessed 25 Nov 2016.
65. Trinidad SB, Fullerton SM, Bares JM, Jarvik GP, Larson EB, Burke W. Informed Consent in Genome-Scale Research: What Do Prospective Participants Think? AJOB Prim Res. 2012;3(3):3–11.

66. Tabor HK, Stock J, Brazg T, McMillin MJ, Dent KM, Yu JH, et al. Informed consent for whole genome sequencing: a qualitative analysis of participant expectations and perceptions of risks, benefits, and harms. Am J Med Genet A. 2012;158A(6):1310–9.
67. Presidential Commission for the Study of Bioethical Issues: Privacy and Progress in Whole Genome Sequencing. 2012. http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf. Accessed 25 Nov 2016.
68. Precision Medicine Initiative Cohort Program. In: National Institutes of Health. https://www.nih.gov/precision-medicine-initiative-cohort-program. Accessed 25 Nov 2016.
69. The Precision Medicine Initiative Cohort Program – Building a Research Foundation for 21st Century Medicine - Precision Medicine Initiative (PMI) Working Group Report to the Advisory Committee to the Director, NIH. https://www.nih.gov/precision-medicine-initiative-cohort-program/pmi-working-group. Accessed 25 Nov 2016.
70. Faglig prioriterte områder i 2016: Interessekonflikter, samtykke og vitenskapelig integritet. In: De nasjonale forskningsetiske komiteene. https://www.etikkom.no/hvem-er-vi-og-hva-gjor-vi/komiteenes-arbeid/faglig-prioritert-omrade-i-2016-interessekonflikter/. In Norwegian. Accessed 25 Nov 2016.
71. Nishimura A, Carey J, Erwin PJ, Tilburt JC, Murad MH, McCormick JB. Improving understanding in the research informed consent process: a systematic review of 54 interventions tested in randomized control trials. BMC Med Ethics. 2013;14:28.
72. Shabani M, Borry P. Challenges of web-based personal genomic data sharing. Life Sci Soc Policy. 2015;11:3.
73. Johnsson L, Eriksson S. Autonomy is a Right, Not a Feat: How Theoretical Misconceptions have Muddled the Debate on Dynamic Consent to Biobank Research. Bioethics 2016.
74. Mascalzoni D, Hicks A, Pramstaller P, Wjst M. Informed consent in the genomics era. PLoS Med. 2008;5(9):e192.
75. McCormack P, Kole A, Gainotti S, Mascalzoni D, Molster C, Lochmuller H, et al. 'You should at least ask'. The expectations, hopes and fears of rare disease patients on large-scale data and biomaterial sharing for genomics research. Eur J Hum Genet. 2016;24(10):1403–8.
76. Lunshof JE, Chadwick R, Vorhaus DB, Church GM. From genetic privacy to open consent. Nat Rev Genet. 2008;9(5):406–11.
77. Free the data. http://www.free-the-data.org/. Accessed 25 Nov 2016.

APPENDICES

Appendix A. COST Action CHIP ME e-mail survey, July-August 2014

Appendix B. Case study for COST Action CHIP ME workshop, University of Coimbra, October 2014

Appendix C. Request for participation in a research study

Appendix D. Study approval from the Norwegian Social Science Data Services (NSD)

Appendix E. Study extension approval (NSD)

Appendix F. Interview guide patient and interest organizations, 2014/2015

Appendix A. COST CHIP ME e-mail survey, July-August 2014

1. Please provide 3 to 5 principles which you think should apply for the return of genetic research results to research participants (e.g. equity, quality) and shortly explain why you choose these principles.

2. Please describe the current legal framework that applies in your country for the return of genetic research results to research participants. Refer to specific laws when relevant.

3. Please describe which results could be returned in your country according to applying legal and ethical frameworks (e.g. actionable results only), and under which conditions they could be returned (e.g. by genetic counsellor only).

4. Please describe any project/initiative in your country that is currently returning research results to research participants or planning to do so, or developing frameworks for such return. If any web sites or literature can be consulted, please provide URL.

5. Please describe current challenges and practical issues that may impede the return of results in your country (e.g. financial and administrative hurdles, privacy protection regulation, and lack of genetic counsellors).

6. Please shortly outline potential steps that could be taken to facilitate the return of results in your country.

7. Additional comments and ideas

Appendix B. Case study for CHIP ME workshop, University of Coimbra, October 2014

Returning genetic research results to research participants has been the subject of intense debate within the scientific community and many arguments for and against such return have been brought forward. Imagine that the debate is now closed and that the general consensus is that genetic research results should be returned to research participants. You are a researcher (conducting clinical research or population-based research). Your Ministry of Health asks you to take the necessary steps to enable such return on the basis of the core need for citizen-centred policies, but does not provide you with any specific guidelines or recommendations. You have a few months ahead of you to set up a plan. How would you set up your priorities? How would you organize yourself? What do you need to be able to return such results? What are the hurdles and possibilities that you identify? With whom would you need to talk or ally? Which rules or set of criteria would you set up for returning genetic research results to research participants?

Appendix C. Request for participation in a research study

UiO : University of Oslo
Institute of Health and Society, Faculty of Medicine

Request for participation in the research study:

How to bring personalized medicine to patients and citizens?
Strategies and recommendations of patient advocacy organizations

Background and Purpose

Rapidly enabling personalized medicine (PM) is seen as critical by funders of health care. This study investigates the views of patient advocacy organizations (PAOs) on PM, strategies and tools that PAOs may be developing to facilitate access to PM, and potential recommendations from PAOs for the rapid adoption of PM. This study is part of the PhD project "Ethical challenges of personalised medicine" conducted at the Centre for Medical Ethics, University of Oslo, Norway. Representatives from PAOs which have a particular interest in PM are invited to join the study.

What does participation in the study entail?

As a PAO representative, you will be interviewed by phone to answer a short list of questions. Each interview is expected to last approximately one hour. The interview will be recorded.

What happens to your information?

Interview data and personal information (Name, position, affiliation and professional email) are treated confidentially and stored separately. Interview data and personal information are accessed by the project manager only.

The project is scheduled to end September 2017. Personal data will be deleted after that date.

Voluntary participation

It is voluntary to participate in the study, and you can withdraw your consent at any time without giving any reason. If you withdraw, all personal information and interview data will be deleted.

If you have questions concerning the study, please contact project manager Isabelle Budin-Ljøsne, email: i.b.ljosne@medisin .uio.no, tel: + 47 22 85 06 24

The study is reported to the Privacy Ombudsman for Research, Norwegian Social Science Data Services.

Consent for participation in the study

I have received information about the study and am willing to participate.

Study participant name, signature and date

Postal address: P.O box 1130Blindern - 0318 OSLO, Norway
E-mail: i.b.ljosne@medisin.uio.no
www.uio.no

Appendix D. Study approval from the Norwegian Social Science Data Services (NSD)

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr: 985 321 884

Isabelle Budin Ljøsne
Institutt for helse og samfunn Universitetet i Oslo
Postboks 1130 Blindern
0318 OSLO

Vår dato: 03.07.2014 Vår ref: 39155 / 3 / JSL Deres dato: Deres ref:

TILBAKEMELDING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 27.06.2014. Meldingen gjelder prosjektet:

39155	*How to bring personalized medicine to citizens? Strategies and recommendations of patient advocacy organizations*
Behandlingsansvarlig	*Universitetet i Oslo, ved institusjonens øverste leder*
Daglig ansvarlig	*Isabelle Budin Ljøsne*

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger er meldepliktig i henhold til personopplysningsloven § 31. Behandlingen tilfredsstiller kravene i personopplysningsloven.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/meldeplikt/skjema.html. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://pvo.nsd.no/prosjekt.

Personvernombudet vil ved prosjektets avslutning, 01.09.2017, rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

Katrine Utaaker Segadal

Juni Skjold Lexau

Kontaktperson: Juni Skjold Lexau tlf: 55 58 36 01
Vedlegg: Prosjektvurdering

Dokumentet er elektronisk produsert og godkjent ved NSDs rutiner for elektronisk godkjenning.

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 39155

Utvalget informeres skriftlig om prosjektet og samtykker til deltakelse. Informasjonsskrivet er godt utformet. Vi ber likevel om at følgende endres:
- Følgende setning slettes: "Recordings from the interviews will be stored anonymously". (Setningen skal slettes da lydopptakene trolig inneholder personopplysninger. Videre er det oppgitt i meldeskjemaet at lydopptak skal slettes ved prosjektslutt).

Revidert informasjonsskriv skal sendes til personvernombudet@nsd.uib.no før utvalget kontaktes.

Personvernombudet legger til grunn at forsker etterfølger Universitetet i Oslo sine interne rutiner for datasikkerhet. Dersom personopplysninger skal sendes elektronisk , bør opplysningene krypteres tilstrekkelig.

Forventet prosjektslutt er 01.09.2017. Ifølge prosjektmeldingen skal innsamlede opplysninger da anonymiseres. Anonymisering innebærer å bearbeide datamaterialet slik at ingen enkeltpersoner kan gjenkjennes. Det gjøres ved å:
- slette direkte personopplysninger (som navn/koblingsnøkkel)
- slette/omskrive indirekte personopplysninger (identifiserende sammenstilling av bakgrunnsopplysninger som f.eks. bosted/arbeidssted, alder og kjønn)
- slette lyd- og videoopptak

Appendix E. Study Extension Approval (NSD)

From: audun.lovlie@nsd.no <audun.lovlie@nsd.no>
Sent: 14 September 2017 14:59
To: Isabelle Budin Ljøsne
Subject: Prosjektnr: 39155 How to bring personalized medicine to citizens? Strategies and recommendations of patient advocacy organizations

---

AFFIRMATION

Referring to status report received 11.09.2017.

The Data Protection Official has registered that the project period has been extended until 01.09.2018.
We presuppose that the project otherwise remains unchanged.
You will receive a new status inquiry at the end of the project.
Please note that in case of further extensions, the data subjects should usually receive new information if the total extension exceeds a year beyond what they previously have received information about.

Do not hesitate to contact us if you have any questions.

Best regards,
Audun Løvlie - Phone number: 55 58 23 07
Email: audun.lovlie@nsd.no

the Data Protection Official for Research,
Norwegian Centre for Research Data
Phone number (switchboard): (+47) 55 58 21 17 (enter 1)

Appendix F. Interview guide patient and interest organizations, July 2014-January 2015

Thank you for taking the time to talk to me today. The objective of this phone call is to discuss personalized medicine (PM). For the purpose of this interview, we define PM as the practice of medicine that uses an individual's genetic profile to guide decisions made in regard to the prevention, diagnosis, and treatment of disease. For instance, knowledge of a patient's genetic profile can help doctors select the proper medication or therapy and administer it using the proper dose or regimen. I would like to ask you about:

- Your organization's views on PM
- Tools that your organization may be developing to familiarize your members with PM
- Potential challenges to the realization of PM and recommendations that your organization may make for its adoption

The interview should take less than an hour. I will be taping the session because I don't want to miss any of your comments. Although I will be taking some notes during the session, I can't possibly write fast enough to get it all down. Because we're on tape, please be sure to speak up so that I don't miss your comments. All responses will be kept confidential. Do you have any questions before we start?

1. How is your organization's interest in PM (as just defined)? Please elaborate.
2. Is your organization developing specific strategies to promote PM? Please elaborate.
3. Is your organization developing specific tools to familiarize your members with PM? Such tools may for instance include educational tools to learn about genetics. If yes, how would you describe these tools?
4. How do you experience that these tools are working? For instance, do you have information regarding their use? Please elaborate.

5. What recommendations would you make for the development of such tools? Please elaborate.

6. According to you, what are the biggest challenges in your country to make PM (as defined) accessible to as many patients and citizens as possible?

7. What are your biggest concerns, if you have any, regarding the potential adoption of PM in health care?

8. According to you, what should policy makers do in priority in order to make PM accessible to as many patients and citizens as possible?

9. How would you describe co-operation between your organization and policy-makers regarding the promotion of PM?

10. Does PM mean anything else to you that what we have discussed?

11. Is there anything more you would like to add?

I will analyze the information that you and other representatives gave me and write a draft report that I will send to you for comments.

Thank you for your time!