The creation and management of innovation in healthcare

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-
THE EXAMPLE OF PERSONALISED MEDICINE

SEBASTIAN SCHEE GENANNT HALFMANN

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Abbreviations

ADRs	Adverse drug reactions
CEO	Chief executive officer
CDs	Common Diseases
CSA	Coordination and Support Action
CSRs	Clinical Study Reports
DG	Directorates-General
DNA	Deoxyribonucleic acid
DTC-PG	Direct-to-consumer personal genomics
EAMS	Early Access to Medicines Scheme
EAPM	European Alliance for Personalised Medicine
EBM	Evidence-based medicine
EC	European Commission
EMA	European Medicines Agency
EFPIA	European Federation of Pharmaceutical Industry Association
ERNS	European Reference Networks
EU	European Union
FDA	Food and Drug Administration
GDPs	Gross Domestic Products
GPs	General Practitioners
HCPs	Healthcare professionals
HDC	Health Data Cooperatives
HGP	Human Genome Project
HLS-EU	European Health Literacy Project
HLS-EU-Q	European Health literacy survey
HTA	Health Technology Assessment
IC	Innovation Camps
ICH GCP	International Conference on Harmonisation Good Clinical Practice
IC PerMed	International Consortium Personalised Medicine
ICT	Information and Communication Technologies
IMI	Innovative Medicine Initiative
IP	Intellectual property
IPD	Individual patient data
IVDs	In vitro diagnostics
LCS	Low-Coverage Sequencing
MAPPS	Medicines Adaptive Pathways to Patients pilots
MS	Member States
NCDs	Non-communicable diseases
NGOs	Non-governmental organizations
NGS	Next generation sequencing
PM	Personalised Medicine
PPPs	Public-private partnerships
RCTs	Randomized control trials
RDs	Rare diseases
R&D	Research and Development

REFIT	Regulatory fitness and performance programm
SED	Systematic early dialogue
SDGs	Sustainable Development Goals
SMEs	Small-medium sized enterprises
SNS	Social network sites
SRIA	Strategic Research and Innovation Agenda
STI	Science, technology and innovation
SWOT	Strengths, Weakness, Opportunities and Threats
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UN	United Nations
USPTO	US Patent and Trademark Office
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing

CHAPTER 1

Introduction

In the last two decades, most countries around the world have been challenged by economic, social and environmental crises. The global financial crisis that started in 2008 was followed by a public debts crisis [1] and put immense economic pressure on governments around the world [1]. The consequences included: stagnating economic growth, reduced gross domestic product's (GDP), increasing public debts and unemployment rates as well as increasing poverty. Furthermore, the financial crisis evoked major threats to global public health [3].

In addition to recovering from the financial crisis, the Member States (MS) of the European Union (EU) are challenged by stagnating population growth and the resulting demographic change. It is expected that the aging population will negatively impact economic productivity due to the increasing the old-age dependency ratio (declining ratio of working-age population compared to the total population) [4]. Furthermore, an ageing society will lead to skill mismatches and even skill shortages which will negatively impact the economies and create financial pressure. It is estimated that by 2025, approximately 20% of the European population will be aged 65 years or older [5]. Besides the aging society, European healthcare systems are challenged by the increasing burden of non-communicable diseases (NCDs) and infectious diseases. NCDs are one of the major causes of morbidity and premature mortality in the EU. Evidence shows that more than 4,000 Europeans die every day of cancer [6]. The costs to address those health(care) challenges are tremendous. It is estimated that every day close to 4 billion Euros are spent by the European Member States on healthcare and this amount will increase in the next year [6] .

Whereas most western countries are challenged by an aging society, other parts of the world are challenged by quickly growing populations. It is expected that Asia, Africa and Latin America will experience an immense growth of their populations. The urban population in Asia will increase from 1.3 billion in 2010 to more than 2.6 billion in 2030; in Africa from 294 millions to more than 740 millions and in Latin America from 394 million to over 600 million [4]. The growing world population poses major societal challenges which need to be addressed.

The countries around the world are facing resource challenges. With an increasing world population, the demand for natural resources will significantly increase and for some natural

resources, the current demand is already outstripping available supply, causing severe shortages of natural resources [4]. In addition, climate change is a major threat to all sectors of the economies around the world. The increasing average temperatures, caused by the rising presence of greenhouse gases, are pressuring governments to move away from current technologies and ways of find new sustainable solutions [4].

The need for innovation

To overcome those challenges which we are currently facing, it is of great importance to find new sources of economic growth [4]. To achieve long-term economic growth, it is widely believed that innovation plays a crucial role. According to the OECD (2015) "Innovation provides the foundation for new businesses, new jobs and productivity growth and is a key driver of economic growth and development" [4]. In addition to the impact innovation has on economic growth, it also reaches out to other important policy areas affecting the well-being of the citizens such as healthcare and the environment [4]. In light of the many challenges we are currently facing, it is not surprising that innovation is receiving more attention and is increasingly becoming a top priority on the agendas of policy makers, industry and the civil society [4]. For the purpose of this thesis, innovation is defined according to the 3rd edition of the Oslo Manual of the OECD (see Box 1).

Over the last two decades, the understanding of innovation has drastically changed [7]. In the beginning, innovation was seen as linear process following discrete steps It started with the production of new knowledge, followed by the creation of a new product based on the new knowledge and the commercialization and marketing of the new product [7,8]. However, this understanding has since been widely criticized as oversimplifying the innovation process by not taking into account the complexity and diversity of innovations [7]. Over the years the understanding of innovation has evolved and nowadays innovation is seen as something which occurs in a complex ecosystem. In this innovation ecosystem, different actors including large and small companies, universities and research institutes, venture capital companies and governments all participate, cooperate and exchange skills, ideas and knowledge on a local, national and increasingly global level [9].

Box 1: Definition 'Innovation'

"[…]the implementation of a new or significantly improved product (good or service), or process, a new marketing method, or a new organizational method in business practices, workplace organization or external relations. […].

Innovation, thus defined, is clearly a much broader notion than R&D or technological change and is therefore influenced by a wide range of factors, some of which can be influenced by policy. Innovation can occur in any sector of the economy, including government services such as health or education. However, the current measurement framework applies to business innovation, even though innovation is also important for the public sector […]." (page 46) [2]

Furthermore, policies and regulations are playing a crucial role in the innovation process. Since the understanding of innovation has changed and is no longer seen as a linear process, it became clear that innovation is influenced by more than just R&D policies. In order to create innovation friendly environments and an innovation ecosystem, policy makers have to take into account a large variety of different policy measures ranging from education and regulatory reforms to both labour and financial markets. Furthermore, incentives to perform R&D and a strong knowledge infrastructure need to be established in order to successfully innovate [7].

Countries around the world greatly differ in their innovation process, potential and innovation performance. Societies differ in their perception and beliefs towards innovation and new technologies and have often mixed feelings towards innovation which has great impact on the innovation process. Over the last years it became clear that fresh and open mindsets and a willingness to change are needed to improve the innovation process [7].

The many parameters and differences in attitudes towards innovation influence the innovation process and highlight that there is no 'one-size fits all' solution. Innovation policies should take the regional, local, national and international specific contexts and circumstances more into account in order to be fully effective [7].

Innovation policies not only matter for economic growth, but also for healthcare, the environment and many other areas. However, the relation between innovation and economic growth has been studied in more detail than the other policy areas [4]. Therefore, the focus of the thesis is on innovations in healthcare and the impact innovations can have on healthcare systems and the well-being of the citizens. For the purpose of the thesis, the approach of Personalised Medicine (PM) will be discussed in more detail as one current example of innovation in healthcare.

Current approach

European healthcare systems predominantly apply a 'one-size fits all' healthcare approach. Patients are treated based on principles of 'evidence-based medicine (EBM)' [10,11]. According to Sackett et al. (1996) EBM means 'integrating individual clinical expertise with the best available external clinical evidence from systematic research' [11]. The individual clinical expertise is understood as the competencies and faculties medical professionals have acquired over time through their clinical experiences and practices. The second pillar of EBM is external clinical evidence which is the application of basic sciences of medicine, including patient centered clinical research, to improve the accuracy of diagnostic tests and treatments [11]. In practice, the vast majority of patients are treated with pharmaceuticals which have proven to be effective and safe in well-designed randomized control trials (RCTs). Over the last decades, RCTs have been seen as the 'golden standard' in clinical research [12]. RCTs have reshaped clinical practice by reducing bias and improving the accuracy of clinical trials [13].

However, the approach of EBM is being increasingly criticized, especially the fact that RCTs are considered to be superior to any other study design and that clinical decisions are mainly based on RCTs results and not on a variety of different research outputs [14]. Moreover, in the scientific literature the generalizability of RCT results to clinical practice has been widely criticized and is seen as a major limitation [15]. According to Sultana et al. (2013) the main limitations of current RCTs are "limited study population size and duration of study, the selective recruitment of patients with resulting limited heterogeneity and the consideration of few predefined ADRs" [15]. Furthermore, drugs are often tested in RCTs among patients,

who are not representative of the patients who will receive the medicine and who might have a higher risk of suffering from adverse drug reactions (ADRs) [15].

Since diagnostic tools and medicines are based on population averages, millions of patients receive drugs which do not fit their needs and do not help them to recover [16]. Those patients will either continue to suffer the burden of their current health condition or will develop even more serious health conditions caused by side effects or adverse drug reactions and will eventually die [6]. Evidence has indicated that in oncology treatment the current 'one-size fits all' approach is only effective in less than 25% of the cases [17]. That leaves 75% of cancer patients who receive medicines which are not effective for them causing severe ADRs. Consequently, patients and their families suffer from a loss of quality of life during the course of treatment [17]. Approximately 6% of all acute hospital admissions are attributable to severe ADRs [18].

Not only is the current approach causing harm to millions of patients, it also creates an immense economic burden on European healthcare systems due to additional care that is needed and higher rates of hospitalization, amounting to more than EUR 100 billion each year [6,19]. It becomes clear that the current 'one-size fits all' healthcare approach has its limitations and that new innovative approaches are urgently needed that make healthcare more effective and healthcare systems more efficient. One innovative approach which is challenging the conventional 'one-size fits all' approach is 'Personalised Medicine' [10,19].

Innovation in healthcare – the example of Personalised Medicine

PM is a new promising approach to make healthcare more effective by reducing the burden of ADRs making healthcare systems more efficient by providing "the right treatment for the right person at the right time" [20] .

Over the last decade, the new paradigm has received a lot of attention from policy makers, industry, academics and the media and became a widely used buzz word voiced in public discussions regarding medicine and healthcare [12]. Consequently, PM is defined and understood in many different ways among different stakeholders [21]. Currently, several

terms such as ‘precision medicine’, ‘genomic medicine’, ‘individualized medicine’ and ‘stratified medicine’, are often used interchangeably to describe the approach of PM [12,22]. The challenge with the many different terms which are used interchangeably is that they arouse hopes among different stakeholders and citizens even though it is not fully clarified what PM actually means. Furthermore, since there is no uniform definition of PM, healthcare professionals understand the concept of PM differently, which often leads to misunderstandings and miscommunications [23]. Some healthcare professionals believe that personalised medicine are treatments which are exclusively based on genetic analysis and the application of biomarkers [24], whereas others perceive PM as a healthcare approach in which the doctor makes the treatment decision based on both the health status and the individual circumstances of the patient [25].

For the purpose of this thesis the definition of PM of the Horizon 2020 Advisory Group for Societal Challenge ‘Health, Demographic change and Wellbeing’ of the European Commission is applied, because the definition, is based on the understanding that the current healthcare approaches move away from the common ‘one-size fits all’ healthcare approach. According to the Advisory Group of the European Commission, Personalised Medicine is defined as “a medical model using characteristics of individual phenotypes and genotypes (e.g. molecular profiling, medical imaging and lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention”[26]. This definition will be used as the working definition for the dissertation.

From DNA sequencing to Personalised Medicine

The foundation of PM was already laid around 60 years ago. In 1953, the researcher James Watson and Francis Crick successfully deciphered the structure of the deoxyribonucleic acid, also known as DNA, for the first time in history [27] and initiated a revolution in healthcare. Since that breakthrough, which is seen as the foundation of today’s molecular biology, technological developments and innovation have changed many medical research areas and have led to the possibility of sequencing the whole human DNA for the first time. The

sequencing of the human genome is seen as another major landmark in modern molecular biology and was achieved during the Human Genome Project (HGP) [28].

The HGP, initiated in 1990, was a 13-year long public funded international collaborative research program "whose goal was to complete mapping and understanding of all the genes of human beings" [29]. In 2001, 11 years after the HGP started, the International Human Genome Sequencing Consortium published the first initial sequencing and analysis of the human genome [30]. The full sequencing of the human genome was achieved in 2003, at a cost of more than US $ 2-3 billion [31].

Since 2003, the emergence of new technologies such as 'omics technologies' made it possible to cut the costs of the human genome sequencing from more than US $ 100 million in 2003 to less than US $ 1000 in 2013 [10,31]. This breakthrough discovery initiated a new era in medicine and laid the foundation for the approach of PM [31-33].

Application of Personalised Medicine

PM applies 'omics-technologies' including "genomics, transcriptomics, epigenomics, proteomics, metabolomics, lipidomics" [34] and integrates a large variety of real-life data, also known as 'big data', in order to classify the molecular characteristics of the patients and their predispositions to specific diseases as well as their responses to medicines [35,36].

Currently, the traditional 'one-size fits all' healthcare approach differentiates between common diseases and rare diseases [37]. In the era of PM this differentiation between common and rare diseases is no longer applicable. 'Omics-technologies' and the sequencing of the human genome made it evident that each tumour is unique and that each patient has a unique molecular make-up [6]. Based on this new understanding of the complexity of diseases, they can be classified more accurately by taking into consideration the individual molecular characteristics [38]. Consequently, the new emerging understanding does not differentiate between common and rare diseases. Since every patient is unique, PM utilizes the understanding that all diseases will become rare diseases [12,39].

According to National Institutes of Health Biomarkers Definitions Working Group, biomarkers are defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [40]. Biomarkers are applied for a long time in healthcare to better understand diseases and to predict and monitor patient responses to medications. A common biomarker is 'prostate-specific antigen' (PSA) for the diagnosis and screening of prostate cancer [41]. Another common biomarker is blood pressure for the diagnosis of heart diseases [42]. Over the last few years, the interest in biomarkers has been rapidly increasing. New discoveries such as 'static biomarkers' are being increasingly used and are challenging the current traditional healthcare approaches. Due to the emergence of 'omics-technologies', thousands of new biomarkers have been identified [43] and which are shifting from "a reactive 'one-size-fits-all approach to one which is more proactive, and increasingly 'personalised'."[44]. Biomarkers are often divided into the following three subcategories: "predictive, prognostic and pharmacodynamic biomarkers" [43,45]. Pharmacodynamic biomarkers are used to measure the interaction between a drug and a disease including adverse drug reactions and therapeutic effects [43]. Predictive biomarkers are used for making treatment decisions, since they indicate the potential benefits of a specific drug to a specific patient [45]. Prognostic biomarkers indicate the potential outcome of a disease regardless of treatment [43]. Biomarkers play a pivotal role in PM, since they provide insights into the individual molecular characteristics of patients, which are of great importance to provide the right treatment, in the right dose at the right time to the patient [43]. The rapidly growing number of biomarkers has a high potential to develop more effective medicines that are targeted to the patient needs and to make healthcare more efficient (see Figure 1).

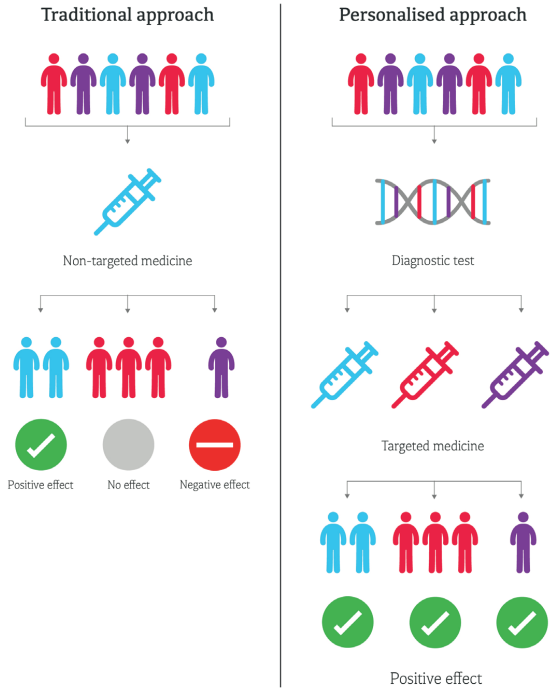

Figure 1: Traditional healthcare approach vs. personalised medicine approach [46]

PM can no longer be seen as an abstract healthcare approach since it is already successfully applied in a large variety of healthcare areas. The application of PM has had its greatest impact in the field of oncology [22]. Cancer has become the leading cause of death in Europe. Approximately 4000 people die every day in Europe of cancer [6]. In addition, ineffective and inefficient cancer treatments and related ADRs are presenting a great economic burden for European governments. The technological advances over the last decades showed that each person and tumour are different and that the current 'one-size fits all' approach in cancer treatment is no longer applicable [10]. Therefore, most examples of the application of PM that are presented in this dissertation are related to oncology in order to highlight the impact PM can have in making healthcare systems more effective and efficient.

The impact of PM goes beyond the application in oncology. PM is increasingly being applied in other medical areas such as cardiovascular diseases [22], diabetes [47] and the treatment of infectious diseases [48].

Even though PM, 'omics-technologies' and 'static biomarkers' are challenging traditional healthcare approaches and are increasingly applied to provide more effective personalised treatments, there is still room for improvement to further strengthen the role of PM. Healthcare systems often still prefer to apply the traditional 'one-size fits all' approach instead of the new promising technologies and discoveries [10]. This can be explained by the resistance of healthcare systems to change and the slow moving and complex nature of healthcare systems [12]. However, evidence from many different areas shows that 'one-size fits all' is increasingly becoming a thing of a past. Currently, a 3D printed wheelchair is disrupting the market and has the potential to replace 'one-size fits all' wheelchairs. New technologies allow to completely personalize the wheelchair based on the patient's disability and the biometric information. Thus, providing maximum comfort for the patient and improving the quality of life [49]. Another field which shows that 'one-size fits all' comes to an end is the nutrition sector which is increasingly moving towards more personalised approaches [50].

Despite the promising potential impact, the application of PM can have on providing more effective treatments and reducing the economic burden of inefficient healthcare systems, there are also challenges regarding PM which impact the implementation of PM.

Challenges of Personalised Medicine

Common concerns which are often voiced in discussion regarding PM include issues such as, affordability, data protection and data safety, and a lack of evidence illustrating the benefits of PM.

Affordability is one of the most widely discussed criticisms with regards to PM. Opponents are concerned that the high costs may lead to increasing health inequalities on a national and European level [51]. Targeted personalised treatments and companion diagnostic tools might make treatments costlier for both the patient and the healthcare system [52]. Many stakeholders argue that PM does not live up to their expectations with regard to being more cost-effective than current standard care [53]. However, as the past decades have shown, the costs of new technologies are expected to decrease through increased usage over time,

as can be seen with the costs of the sequencing of the human genome. This decreased from $100 million to $1000 [31] as has the cost of storing 1 GB of data which decreased from $250 million in 1971 to $0,03 in 2017 [54].

Access to PM greatly differs among the European Member States, since healthcare is a national competence. European countries also greatly differ in their pricing and reimbursement of PM and companion diagnostics which leads to great variations in access to innovative personalised treatments [10]. The fragmented landscape of health technologies assessments (HTA) and the large variety of pricing and reimbursement schemes in the EU, greatly impact the implementation of PM across Europe. HTAs are often applied in healthcare systems to make resource allocation decisions, for example, on whether a new pharmaceutical or companion diagnostic will be reimbursed by the insurance companies [10]. However, since every European country has its own methodologies to conduct HTAs, MS greatly vary in their pricing and reimbursement decisions regarding new medicines and diagnostic tools. A survey conducted by Leopold *et at.* (2013), indicated that reimbursement of new treatments greatly depends on the country in which the patients undergo or receive treatments [53]. In the survey, Leopold and colleagues analysed the reimbursement of the personalised medicine trastuzumab which is administered for the treatment of HER2* breast cancer. The results highlighted that, whereas the majority of patients are treated in hospitals in most European countries, in some countries HER2 positive breast cancer patients were treated in out-patient settings [53]. Another finding was that countries differ in their reimbursement schemes. In some countries the costs of trastuzumab and its diagnostic tools were covered by the hospitals, in others the costs were split between the hospitals which paid for the diagnostic tests and third-party payers such as insurance companies which covered the cost of trastuzumab [53]. In summary, the fragmented HTA and pricing and reimbursement schemes in the EU, greatly impact both the implementation of and the access to PM [10].

Other concerns regarding the application of PM are data protection and data safety. Estimates suggest that by 2020, the amount of digital healthcare data will accumulate to more than 25,000 petabytes (1 petabyte = 1000 terabytes) [55]. The integration of genetic data with environmental, clinical and lifestyle information, also known as ‘big data’, is one of the

main pillars of PM. Big data analytics have great potential to support the development of more effective treatments and interventions tailored to individual needs [56]. Developments in Information and Communication Technologies (ICT) have catalysed the emergence of the digital health revolution. Innovations in the ICT sector have rendered new technologies, such as mobile broadband [4] and human genome sequencing [31], easier, faster and more affordable. The spread of broadband and cloud computing has improved access to the internet on a global scale, changing the lives of millions of people [57]. The diffusion of mobile broadband "has demonstrated the most global technology uptake in human history" [58]. Some even believe that a convergence between ICT and biomedical sciences, nanoscience, and cognitive science could initiate the 'next industrial revolution'[4].

Despite the promising approach of big data analytics and ICT solutions in healthcare, concerns are rising regarding data protection and data safety. Tech giants such as Apple, Microsoft and Google show increasing interest in collecting large amounts of health data [59] but concerns are growing that the data might not be used for the purpose it was intended and that third-parties will be able to access the health data. The increasing challenge of data breaches is also undermining the trust of the citizens in the digital health economy [60]. Many citizens share concerns regarding misuse of health data which might lead to stigmatization. For example, when a health insurance company gets access to individual healthcare data it may increase the premiums based on individual risk of illness [61]. The fast emergence of new technologies means legislation can often not keep up. In order to make full use of big data analytics in the era of PM, it will be important, that on the one hand patient data is adequately protected and on the other hand research will not be hindered and slowed down through overregulation [10].

The European Commission (EC) is a major facilitator of PM. The EC has recognized the great potential of PM and has published several reports analysing the impact PM and 'omics technologies' can have on public health and health policy and the factors that are currently challenging the implementation and uptake of PM [62-64]. Since 2007, the EC has committed more than 3 billion Euros to their previous funding program, the EU 7th Framework Programme and the current H2020 funding programme, to support scientific research related to PM. It has also funded more than 370 research projects to promote personalised

healthcare, including the Coordination and Support Action (CSA) PerMed, project. The PerMed consortium received funding from the EC to develop a "Strategic Research and Innovation Agenda (SRIA)" named "Shaping Europe's Vision for Personalised Medicine". During the two years project (2013-2015) the 27 consortium partners from 14 countries including key opinion leaders from research and research policy, academics, industry partners, and healthcare and patient organizations identified five key challenges which need to be addressed in order to strengthen the implementation of PM. The identified challenges are "**Challenge 1**: Developing Awareness and Empowerment; **Challenge 2**: Integrating Big Data and Information and Communication Technology (ICT) Solutions; **Challenge 3**: Translating Basic to Clinical Research and Beyond; **Challenge 4**: Bridging Innovation to the Market; **Challenge 5**: Shaping Sustainable Health Care"[65]. Moreover, the PerMed consortium provided recommendations and research activities aiming to improve the implementation of PM [65].

Taking the aforementioned issues into account, it becomes clear that several challenges need to be addressed in order to improve the uptake of PM. To further implement PM, special infrastructures and policies are needed which support the innovation process and don't hinder the uptake and diffusion of innovative approaches in healthcare. In order to create an innovation friendly ecosystem, it is of great importance to understand the complexity of innovation and the settings in which innovation occurs and that there is no 'one-size fits all' solution to successfully innovate. Against this background, research was conducted as part of this dissertation to provide new insights into the landscape of innovation in the EU and by investigating the example of PM in more detail.

Aim of the thesis

The thesis aims to:

I. Describe the innovation process & to introduce best practice guidelines for innovation creation and management (innovation wheel) and to analyse the current landscape of innovation in healthcare in Europe
II. Evaluate the uptake of European healthcare systems for Personalised Medicine and to highlight barriers in the implementation and application of Personalised Medicine.

The thesis starts with the description of the innovation process, including the different parts, namely innovation creation and innovation management. Furthermore, the theoretical framework of the thesis is introduced, the 'innXchange innovation wheel' (see Figure 2) which was developed as part of the EU FP7 ERA-net ERAfrica project 'innXchange - increasing innovation potential by European African cooperation'. As previous highlighted, innovation is influenced by many different parameters and there is no 'one-size fits all' solution for innovation. Against this background, the developed framework provides specific guidance on the essential parts, principles and steps of innovation creation and management which can be applied to different settings and policy areas. The framework emphasizes the importance of active engagement by all key stakeholders involved in the innovation process from the, 'systematic early dialogue', to improve the creation and the management of innovations. To provide an overview, the current landscape of innovation in healthcare and ICT in Europe is analysed and factors that are both hindering and facilitating innovation are discussed.

The second aim of the thesis is to apply the theoretical framework to the innovative healthcare approach of PM. The framework is used to analyse the current situation of the adaptation and implementation of PM in Europe and to identify factors that are currently hindering or facilitating the uptake of the innovative approach. Analysing parts of the wheel in more detail highlights whether we are currently doing the right things or whether some of our actions have a negative impact on the uptake and application of PM in Europe. Furthermore, different policy tools are introduced which could play an important role in strengthening the uptake of PM by European healthcare systems.

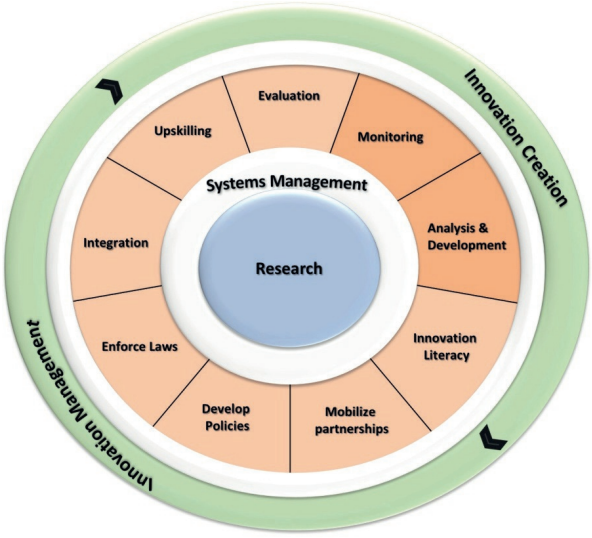

Figure 2: The innXchange innovation wheel (developed as part of the EU FP7 ERA-net ERAfrica project innXchange- increasing innovation potential by European-African cooperation).

Outline of the thesis

The dissertation has eight chapters, starting with a general introduction, followed by six chapters in which the innovation landscape is analysed. This is followed by the description of theoretical framework of this dissertation, the innXchange innovation wheel. The framework is applied in order to analyse the creation and management of PM in Europe and to provide an overview of the current status of the uptake and implementation of PM in Europe. The thesis ends with synthesising the results of the six analyses into a general discussion, to highlight the main challenges we are facing in the implementation and application of PM and to draw conclusions for future research. In total, four scientific articles published in peer-reviewed impact factor journals, one submitted scientific article, and one book chapter form the core body of this dissertation.

Chapter 2: "Best Practice Guidance for the Creation and Management of Innovation - innXchange innovation wheel"

- Wheel introduction

In Chapter 2, the innovation process and the theoretical framework of this dissertation, the 'innXchange innovation wheel' is introduced. The different parts of the framework, including innovation creation and innovation management, are described in more depth. Best practice guidelines for the creation and management of innovations are presented to overcome current hurdles we are facing in the innovation process. In addition, the concept of 'systematic early dialogue' is introduced, which is the underlying concept of the 'innXchange innovation wheel'.

Chapter 3: "The creation and management of innovation in healthcare and ICT – European – African experience"

- Wheel guideline: **Research**

In Chapter 3, research is performed to analyse the current innovation landscape in healthcare and ICT in Europe and Africa. Factors that are currently hindering or facilitating the innovation process and in particular, the creation and management of innovations, are highlighted and discussed. In addition, conclusions are drawn on how the creation and management of innovation in healthcare and ICT can be improved and barriers overcome.

Chapter 4: "**European healthcare system readiness to shift from one-size fits all to personalised medicine"**

- Wheel guideline: **Systems management**

In Chapter 4 research is performed to analyse the system readiness of European Healthcare systems to shift from 'one-size fits all' to Personalised Medicine. To assess which factors are facilitating and hindering the uptake of PM in Europe, the "Conceptual model for the determinants of diffusion, dissemination, and implementation of innovation in health service delivery and organizations" developed by Greenhalgh et al. [66], is applied. Originally, the model was developed to assess the uptake of innovation among healthcare organizations. The research applies a heuristics approach by analysing parts of the model for healthcare

systems instead of healthcare organizations, thereby assessing the readiness of European healthcare systems to shift towards PM.

Chapter 5: "Attitudes towards Personal Genomics and Sharing Genetic Data among older Swiss Adults: A Qualitative Study"

- Wheel guideline: **Innovation Literacy**

In Chapter 5, the innovation literacy of European citizens and their concerns and beliefs regarding the emergence of Personalised Medicine and new technologies is analysed. Factors that are hindering or facilitating the willingness of citizens to share genetic data for research purposes are assessed. In addition, what motivates citizens to participate in research is analysed. The research is performed among older adults since they represent a large part of the society, which will increase in the coming years and which is often underrepresented in research.

Chapter 6: "Rare diseases What's in it for Personalised Medicine?"

- Wheel guideline: **Develop Policies**

In Chapter 6, the impact of Personalised Medicine on rare diseases is analysed. In addition, the new understanding of the complexity of diseases and the ability to classify diseases more accurately is discussed and its impact on current policies. Several policy tools are introduced which will be of importance to further strengthen the uptake of PM in Europe.

Chapter 7: "Clinical Trials, Data Protection and Patient Empowerment in the Era of the New EU Regulations"

- Wheel guideline: **Enforce laws**

In Chapter 7, the current regulatory landscape of Personalised Medicine in Europe is investigated. Several legislations are discussed in more detail and how the current legislative framework of the EU impacts the uptake and implementation of PM is assessed. How the current legislations need to change in order to strengthen clinical research with regard to PM in the years ahead and to bring the benefits of PM to the patients/citizens is also discussed. The publication provides crucial insights in the application and implementation of PM from a regulatory point of view.

Due to the high relevance of the topics which are addressed and discussed in this publication and the relation to the wheel guideline 'enforce laws', the article was included in this dissertation and not added to the appendix, even though I am not first nor second author of this article.

Chapter 8: General discussion

In Chapter 8, the research findings are briefly summarized and put into the wider context of innovation in healthcare, taking the example of PM. Whether we are currently doing the right things right or whether our actions are hindering the creation and management of innovations and the uptake of PM is discussed. Furthermore, an outlook is provided on how innovation can help us address the many challenges we are currently facing and how the uptake of PM in Europe can be strengthened in the years ahead.

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CHAPTER 2

2

Evaluation

Best Practice Guidance for the Creation and Management of Innovation - innXchange innovation wheel

Manuscript submitted to Health Policy and Technology **IF 1.013 (2017)**
Schee genannt Halfmann S, Evangelatos N, Kweyu E, Steinhausen K, van der Merwe A, Brand A: Best Practice Guidance for the Creation and Management of Innovation - innXchange innovation wheel

Abstract

Objectives: Innovation will be key to address the many economic, environmental and societal challenges Europe and the rest of the world are currently facing. However, many innovations often end in the death valley of innovation and consequently the benefits of innovation do not reach the citizens. To improve the creation and management of innovation, the innXchange innovation wheel was developed, as part of the EU FP7 ERA-net ERAfrica project 'innXchange – increasing innovation potential by European – African cooperation'. The objective of the project was to develop guidelines to provide guidance on essential parts of the innovation process.

Methods: A manifold methodological approach was applied. Based on the research activities and from the various sources (narrative literature review; strength weaknesses, opportunities and threats (SWOT) analysis; survey; innovation camps, a general framework for an optimized innovation process was developed.

Results: The innXchange wheel provides systematic guidance on the essential steps of the innovation process and building capacity for the creation and management of innovation. The framework emphasizes that innovative thinking and the creation of marketable ideas can be enforced by active engagement of all key stakeholders from the very beginning also referred to as "systematic early dialogue".

Conclusion: Following the essential steps outlined in our generic framework and best practice guidelines and incorporating systematic dialogue as key concept in the innovation process can help to overcome the current barriers and consequently bring breakthrough discoveries and innovative ideas to the people.

Keywords

Innovation Creation, Innovation Management, Healthcare & ICT, Systematic Early Dialogue, Innovation Process, innXchange wheel

Best Practice Guidance for the Creation and Management of Innovations in Healthcare and ICT
–
The innXchange Innovation Wheel

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Keywords:

Innovation Creation, Innovation Management, Healthcare & ICT, Systematic Early Dialogue, Innovation Process, innXchange wheel

Introduction

Many economies are still recovering from the aftermath of the 2008 financial crisis which was followed by a debt crisis. The crisis put countries around the world under tremendous economic pressure (1, 2). Economies suffered from increasing unemployment rates and public debts as well as reduced gross domestic products (GDPs) (3). Developed countries and middle- and low-income countries greatly differed with regard to the impact the crisis had on them and also in the way they responded to the crisis (4). Moreover, the crisis not only put countries under immense economic pressure, it also caused threats to the global public health (5).

Furthermore, countries around the world are increasingly being challenged by changing demographics and continuing population growth mainly in Africa, Asia, Latin America and the Caribbean (6). Those emerging economies will face challenges due to rising migration flows within countries and urbanization (7). Growing population and increasing urbanization create great societal challenges especially with regard to healthcare. On the other hand, the European Member States and many other western countries are facing challenges due to stagnating population growth and aging societies (6). Aging populations will put governments under immense pressure with regard to economic productivity, increasing the burden of disease and its impact on healthcare systems (7, 8).

In addition, governments are facing acute resource challenges. The demand for natural resources is increasing around the world and is already outpacing the available supply (7). As a consequence, shortages in natural resources will challenge governments even more. Moreover, climate change, caused by the rising presence of greenhouse gases, adds another major challenge for governments which requires immediate actions and solutions (9).

Science, technology and innovation (STI) are seen to be the keys to address those challenges (10). In addition to creating new jobs and business, improving processes and existing products and consequently leading the foundation for long-term economic growth (7), the impact of innovations reaches out to other policy fields that are crucial for the well-being of the society, such as healthcare (7). Thus, it is obvious that STI will be pivotal to achieve the Sustainable

Development Goals (SDGs) (10). The overall aim of the SDGs is to improve the well-being of all world citizens and to ensure a sustainable future by addressing the many challenges we are facing (11). Therefore, it is not surprising that innovation is high on the agendas of politicians, academics, industry, and non-governmental organizations. Moreover, innovation is receiving continuously more attention by the civil society (7).

According to relevant literature, innovation appears within a complex ecosystem, where a variety of different actors such as large, small and medium enterprises, politicians/governments, investors and academic institutions participate and collaborate on local, regional, national and more often on international level (12). Factors such as infrastructure, skilled workforce, regulation and legislation, innovation funding schemes and norms and values and trust of the society have been shown to be of great importance for the innovation process and determine to a large extent the success of innovations (7, 12, 13). Furthermore, those factors can either hinder or facilitate the diffusion of innovations (14). Therefore, it becomes clear that due to the complexity of innovation, continents and countries greatly differ with regard to their innovation performance.

The last years, developments in Information and Communication Technologies (ICTs) have catalyzed the emergence of the digital economy. Indeed, innovations in the ICT sector have rendered access to new technologies (7, 15, 16), such as mobile broadband (17) or human genome sequencing (18), easier, faster and more affordable. The spread of broadband and cloud computing has improved access to the internet on a global scale, changing the lives of millions of people (7, 19). The diffusion of mobile broadband 'has demonstrated the most global technology uptake in human history'(15).

Ubiquitous mobile devices and ICT applications have generated large amounts of data, also known as big data, which is seen as a major resource to innovation (7, 16, 20). Some believe that a convergence between ICT and biomedical sciences, nanoscience, and cognitive science could initiate the 'next industrial revolution'(7). Developments in the ICT sector and the biomedical sciences have been changing the economic and societal landscapes more than any other sector and are a promising approach to addressing the current economic, environmental as well as social and public health challenges.

Even though innovation is high on the agendas of policymakers, many mature markets, which have been ranked as top innovators over decades, are facing challenges to remain on top of the leaderboard due to the changing landscape of innovation. Countries such as China have immensely increased their innovation capacity and are catching up quickly with Europe and the US (7). Europe is currently struggling to keep up with the innovation capacity of emerging countries and does no longer enjoy the old monopolies in fields of science and technology (12). In order to remain a top innovator, Europe needs to understand the quickly changing landscape of innovation and needs to refine its innovation strategy.

In most western countries innovation mainly appears in highly regulated, research and development (R&D) intensive predefined settings. Top-down approaches are often applied which leaves the vast majority of the society out (10). However, the last years new emerging innovation approaches such as frugal innovation and grassroot innovation, which focus on inclusiveness, have been increasingly disrupting the current innovation processes of mature markets (21). Those innovations are designed to address specific daily problems at low-cost and thus are affordable and accessible also for the lower socioeconomic groups. The emergence of new bottom-up, low-cost innovations highlights that innovation can appear without high R&D expenditures and in less pre-defined settings (21). Thus, being a top investor in R&D does not guarantee to be a top innovator anymore. Moreover, frugal innovations have the potential to address the many societal and environmental challenges we are currently facing (22).

Evidence has indicated that many innovations are failing during the developing process and are often ending in the 'Death Valley of Innovations'(23). Findings of our previous study have indicated that clear coordination and engagement of the stakeholders involved in the innovation process were often lacking in healthcare and ICT in both innovation creation and innovation management, which greatly impacts the success of the innovation process (14). In addition, it is important to understand that there is no 'one-size fits all' innovation approach and that an innovation approach which works in one setting might fail in another. This can to large extend be explained by the complexity and diversity of the phenomenon of innovation as such. Furthermore, the success of the innovation process is not exclusively depending on R&D investments, but rather on the interplay of many different factors such as creativity,

norms and values and attitudes towards innovation, education systems, legislation and many more (12).

Against this background, the interdisciplinary EU FP7 ERA-net ERAfrica project 'innXchange – increasing innovation potential by European – African cooperation' was initiated. The project aimed at providing systematic guidance on the essential steps of the innovation process and building capacity for the creation and management of innovation through international cooperation between African (Kenya, South Africa) and European partners (The Netherlands, Germany). The participating countries are members of the ERA-net ERAfrica scheme and shared the same enthusiasm and interest to allocate funding in order to develop best practice guidelines for the creation and management of innovation in healthcare and ICT. These fields were chosen due to their immense innovation potentials. Over the last years, traditional healthcare approaches have been increasingly challenged by the emergence of new technologies (18). And as mentioned before, especially the conjunction of healthcare and ICT has the potential to initiate the next 'industrial revolution' (7).

The unique approach of innXchange was to first compare countries from Africa and Europe in order to gain new insights into existing innovation systems by exchanging perspectives and comparing the state-of-the-art of existing innovation approaches in healthcare and ICT on two different continents (14). Based on those findings, the project consortium was able to develop guidelines and to provide guidance on essential parts of the innovation process in these areas.

Methods

In order to the develop the best practice guidelines, a manifold methodological approach was applied. For the purpose of the study, we defined innovation according to the 3rd edition of the Oslo Manual. Innovation here is defined as "the implementation of a new or significantly improved product (good or service), or process, a new marketing method, or a new organizational method in business practices, workplace organization or external relations" (24). Furthermore, the project consortium agreed to divide the innovation process into two

parts, namely innovation creation and innovation management. The first part, innovation creation, refers to the steps from the *first idea (the invention) to market.* Innovation management is the part which covers the *technology transfer/ uptake of innovation from market to implementation*.

As first step a narrative literature review was conducted to determine the status quo with regard to innovation in healthcare and ICT in the four participating countries from the ERA-net ERAfrica. Based on the information derived from the literature search, the project partners designed semi structured interviews in the format of a strengths, weaknesses, opportunities and threats (SWOT) analysis. Furthermore, a complementary survey was developed, consisting of 22 open and closed questions addressing innovation creation and innovation management with regard to healthcare and ICT. The SWOT analysis was conducted to retrieve insights about factors facilitating or hindering the innovation process. The survey and interviews were adjusted after detailed input from the members of the scientific advisory board of the project. In total, 40 experts from the four participating project countries, representing different stakeholders such as policy makers, industry, academia, civil society and non-governmental organizations, were invited to participate in the interview and survey in person or via phone.

For the second part of the guideline development process, the consortium organized 'innovation camps' in each of the four countries. High level representatives and key opinion leaders of the different stakeholder groups were invited to participate in the innovation camps. Between 15-20 experts participated in the two-day events. During the innovation camps, experts were asked to discuss case studies, which were developed during the course of the project based on the outcomes of the literature search. The four case studies addressed the two different parts of the innovation process, the creation and the management part. In order to be able to make cross-country comparisons, the consortium decided to have a European and an African country in each part of the innovation process. Therefore, two case studies covered the innovation creation process in South Africa and Germany while innovation management was addressed in the case studies from the Netherlands and Kenya.

During the last part of the project the partners organized together with the scientific advisory board of the project an 'innovation creator'. During the innovation creator, all data collected during the different research activities and from the various sources (literature research, innovation camps, interviews and survey) were brought together, clustered and analyzed. Based on those findings of the analysis, a general framework for an optimized innovation process – the 'innXchange innovation wheel' was developed. The framework emphasizes that innovation thinking, and the creation of marketable ideas or concepts can be enforced by active engagement of all key stakeholders from the very beginning, also referred to as 'systematic early dialogue'. Summarizing the results of the project in an innovation wheel was inspired by the 'Public Health Wheel' created by the Institute of Medicine, 1988 (25). The Public Health Wheel was used to derive the 'European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies', which had been endorsed by the EU Member States in 2012 (PHGEN II, coordinator: Maastricht University, The Netherlands) (26).

Results

The 'innXchange innovation wheel' is depicted in figure 1. The wheel consists of 11 tasks which together address the whole complexity of the innovation process. The wheel tasks 'Monitoring and Analysis & Development' are addressing the innovation creation process. The other tasks are focusing on innovation management. Research and systems management are underlying and cross-cutting tasks which apply to the whole innovation process. For each wheel task specific guidelines and recommendations were formulated to improve the innovation process and to strengthen 'systematic early dialogue'.

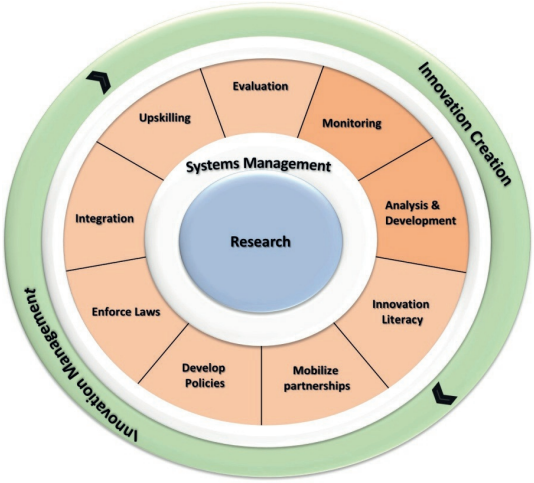

Figure 1:The 'innXchange innovation wheel' – adapted from the Institute of Medicine (25) and PHGEN II (26)

Research

- Keep up with new insights from different scientific fields
- Strengthen the role of universities and research institutions in the innovation process
- Support basic and applied sciences
- Strengthen the role of science as catalyzer for innovation
- Promote open access to research
- Promote creativity, design-driven thinking & living labs
- Promote sustainable funding for research to stimulate the innovation process

Systems management

- Develop innovation friendly infrastructures
- Comply with and support international intellectual property rights and support technology transfer
- Support and promote the modernization of governance structure
- Support digitalization and integrate it as main pillar of the innovation process
- Provide adequate funding schemes for innovation

- Support the concept of open innovation 2.0 and open governance
- Exchange knowledge and know-how with others and be open to learn from others and their mistakes
- Be flexible to adjust to specific circumstances
- Take cultural and gender aspects into consideration while composing innovation ecosystems
- Support systematic early engagement of the key stakeholders from the very beginning and on all levels

Monitoring

- Monitor shifts in markets to leverage new opportunities and to find the niche
- Assess the impact of innovation including emerging innovation approaches
- Identify barriers which might appear during the innovation process
- Compose innovative ideas to answer societal, economic and environmental problems
- Ensure interoperability of ICT systems on a local, national and international level to support collaboration and exchange of knowledge
- Ensure objective monitoring which is not influenced by large economic players
- Promote the importance of monitoring in the policy development process

Analysis & Development

- Create innovation roadmaps that address identified problems
- Ensure that innovations can be scaled up, diffused or transferred to different settings
- Identify the technology or tools to use in the development of the innovation-based given infrastructures

Innovation Literacy

- Promote innovation literacy among all stakeholders
- Communicate in a clear, understandable and transparent language to all stakeholders
- Introduce emerging innovation approaches such as frugal innovations to the society
- Identify specific groups within the society which are skeptical towards innovation and open constructive dialogues to promote innovation
- Promote a better understanding of innovation and the different types of innovation– from a pure technological innovation towards alternative areas of innovation such as social or process innovation
- Share your experience of challenges you faced and support others who face similar challenges
- Provide support and education on how to use, apply and understand new technologies/innovations

Mobilize Partnerships

- Develop an innovation diplomacy agenda
- Support Public-Private Partnerships
- Be open to learn from others and to build international partnerships
- Ensure that home grown talent becomes actively involved in the innovation process
- Support collaborations on local, regional, national and international level

Develop Policies

- Develop policies supporting science, technology and innovation
- Develop policies to support innovators and reduce bureaucratic burdens for innovators
- Develop polices which cover the whole complexity of innovation
- Develop policies to support and ensure funding for innovation
- Develop polices to support innovation creation and management

- Support coherence of policies
- Reinforce collaboration between countries / continents to develop joint innovation policies and policy agendas to address societal challenges
- Act more promptly as new things emerge (big data, blockchain etc.)
- Ensure that policies meet the demands of the society and increase trust in policies among the society

Enforce Laws

- Ensure that innovations and their use meet applicable legal standards
- Ensure that fast emerging technologies and their implications are addressed more promptly
- Embed innovation as a fundamental principle in regulation and laws
- Find the right balance between protecting the society and promoting innovation

Integration

- Communicate in a clear way and take into account that different stakeholders use different jargon to describe the same product or process
- Ensure that responsibilities of the involved stakeholders are clearly defined in an understandable manner from the early beginning
- Support technology transfer offices
- Take cultural, ethical and gender perspectives into consideration while innovating
- Support innovation throughout the whole society and include those parts of the society which have been left out until now in the innovation process i.e. elderly or lower social economic groups

Upskilling

- Integrate innovative thinking into training programs and workshops
- Emphasize the importance of lifelong learning

- Support cross-sectoral and cross-cultural collaborations
- Adjust skills to new emerging technologies
- Support out of the box thinking and reward creativity
- Emphasize that creativity will be the key driver for new technologies and innovations
- Conduct innovation awareness campaigns
- Reduce the gender divide
- Make innovative thinking a core value of your company, institute, research group

Evaluation

- Conduct frequent evaluations of your innovation systems, policies and agendas
- Introduce feedback loops from the early beginning and ask actively for feedback while innovating
- Critical reflect on previous experiences to develop best practices and to learn from mistakes
- Include the end-users in evaluating the innovation in order to maximize the benefits associated with the innovation

Discussion

This study was conducted to provide systematic guidance on the essential steps of the innovation process and building capacity for the creation and management of innovation in healthcare and ICT through international cooperation between African and European countries. As described in our previous article (14) and highlighted by others (27-29), systematic early dialogue between the different stakeholders involved in the innovation process in healthcare and ICT is often lacking or even missing. As a consequence, many promising healthcare inventions/discoveries are at high risk of ending in the Death Valley of innovations and fail to bring improvements to the healthcare system (30).

Scientific literature, published over the last two decades, emphasized the importance to understand the changing landscape of innovation (21) and the need for a well working

innovation ecosystem (12). Both determine to a large extent the success of the innovation process.

According to Madelin et al (2016) "(…). Traditionally, innovation has taken place in centralized, closed and inward-looking elite circles" (12). In the past, R&D investments have been seen as the main driver for innovation (31). However, in times of resource constraints, the demand for low-cost solutions is drastically increasing throughout Europe and around the world. Based on the demand for affordable solutions, new innovation approaches, such as frugal innovation and grassroot innovation have emerged and are currently challenging the traditional innovation approaches in mature markets (21, 32). Mainly those new innovation approaches emerge in developing economies and are stemmed from the urgent need to find immediate, cheap solutions to address local needs and to improve the economic opportunities of the poor segments of the society (33). Frugal innovation, according to Hossain et al (2016), "comprises innovative mixtures of available knowledge and technologies to solve urgent local needs" (32). Frugal mindsets and ideas of individuals are the main drivers for those innovations which appear in less predefined settings and without immense R&D investments. The last years, the new innovation approaches have changed the lives of millions of people (mostly of the poorest in the society) around the world (34).

Especially with regard to healthcare and ICT, the new innovation approaches have a great potential to help to address the many challenges and several success stories are already evident (33). According to Rosca (2017) "frugal innovations in healthcare involve simple, affordable, robust and easy to use technologies that doctors or patients themselves can use in resource-constraint environments to either avoid, identify or treat health issues" (33). Not only have frugal innovation the potential to improve the quality of life of millions of people, they also improve economic productivity through decreasing mortality and a consequently healthier more productive workforce (33, 35). Notwithstanding, the great potential frugal innovations might have to address the many healthcare challenges around the world, it will be important to ensure that they comply with international safety standards. This will be a key challenge that needs to be addressed in the years ahead to offer solutions that are accessible and affordable for everyone that are proven to be safe for the users and that safety is not sacrificed to lower the costs (33).

It is widely discussed among scholars, that frugal innovations bear a great opportunity to address the many challenges the world is currently facing (33, 34). Not only do those innovations have great impact on developing countries, frugal innovation can also play an important role for developed markets (21, 31). However, to make full use of this potential, changes in mindsets of innovators in developed countries are needed. To keep up with emerging markets and to ensure to remain top-innovators, western mature markets need to increase their willingness to learn from developing markets and to shift their mindsets away from believing that they can teach the rest of the world (21, 35). As highlighted by Crisp (2014), mutual learning will be a crucial part in the future to make full use of the potential's new innovation approaches bear (35).

The second important pillar which determines the success of the innovation process is the innovation ecosystem. The ecosystem is a complex construct which is built on many different pillars. In order to create pro-innovation environments, governments play a crucial role in providing the fundamental perquisites such as education, legislation and regulation, innovation funding schemes, and integrating innovation throughout the whole policy landscape (7, 10, 12). Governments need to ensure that the provided infrastructures meet the demands of the 21st century and that digitalization will be incorporated and supported on regional, national and international level. Digitalization and the emergence of new technologies such as big data, 'omics-technologies' and artificial intelligence can be key drivers for new breakthrough discoveries in healthcare and can greatly contribute to make healthcare systems more efficient and effective (10, 36).

However, our findings highlighted that the given infrastructure often hampers innovation instead of supporting it. Regulations and legislations are often outdated and do not address emerging technologies in healthcare and ICT adequately. In some cases, the regulatory framework is even too restrictive for emerging technologies to evolve and diffuse. This is in line with scientific literature (37). In order to facilitate innovation and not hindering it, legislations and regulations need to adapt faster to emerging technologies such as 'omics-technologies' and the use of big data in healthcare and that the digitalization will become a main pillar of regulatory frameworks. Digitalization is not only a key enabler for innovation in

healthcare, its impact reaches out to other areas such as agriculture (38), banking (39) and education (40).

Furthermore, norms and values of the society, trust in institutions, mindsets, and openness towards innovation are also important pillars of the innovation ecosystems (41). Creativity and changes in mindsets will be important to keep up with emerging economies. Furthermore, governments need to act in more transparent way to gain the trust of the society. Governments are often criticized to be not transparent, to think and act in silos and to support their own interests and not the interest and rights of the society. It will be of great importance for governments to be more transparent and responsive (12, 41). As highlighted by Zhu et al (2018) "innovation is incubated as long as people show a constant trust in institutions" (41).Especially in healthcare and ICT trust is an important pillar which needs to be adequately addressed. Data misuse and data protection in times of 'omics-technologies' and big data are major concerns of the society which greatly impacts the diffusion and adaption of new technologies. Governments need to provide regulatory frameworks that ensure the protection of the citizens and patients and on the other hand support science and research and not restricting them.

We belief that the proposed list of guidelines and the application of the 'innXchange innovation wheel' and the underlying concept of 'systematic early dialogue' will be crucial to improve the innovation creation and management process in healthcare and ICT. The framework will help to assess whether we are doing the right things right in the innovation process.

The framework is not only providing guidance for innovators, it also emphasizes the inclusion of all stakeholders involved in the innovation process. Stressing the importance of dialogue and collaboration between all stakeholders from the early beginning reduces the risk of innovation to end in the Death Valley of innovation. Since the framework emphasizes the inclusion of all parts of the society, it will enable more openness towards innovation and that current skepticism will be shifted towards optimism and inclusiveness.

The proposed guidelines and recommendations which cover the different parts of the innovation process, address the whole complexity of innovation and the many different aspect that are influencing the innovation creation and management process. Following the 11 different steps outlined in the innovation wheel will help to address the crucial parts of the innovation process to ensure a successful innovation process.

The framework is designed to help innovators to analyze the innovation creation and innovation management process in more detail. This will allow innovators to identify as well as to overcome common barriers and hurdles at the different stages of the innovation process. This will allow them to bring improvements and breakthrough ideas and technologies to the citizens/patients/ healthcare systems and thus improving the lives of millions of people. In addition, the framework will support new innovations to diffuse and to bring breakthrough discoveries to the market by emphasizing the importance of the innovation ecosystem, the emergence of novel innovative approaches and systematic early dialogue.

Furthermore, it is important to mention that there are no 'one-size fits' all innovation and that the innovation process might vary between different sectors and also on local, national and especially international levels. Therefore, we developed the generic framework which can be applied to all different levels. In addition, we belief that wheel can also be applied to other sectors than healthcare and ICT.

Conclusion

Undoubtedly, innovation has great potential to address the many challenges that we are currently facing. Especially, new emerging innovation are seen as drivers for sustainable growth. The potential innovations bear is widely discussed among scholars, however, to make full use of this potential several barriers have been discussed in this article that need to be addressed to successfully innovate.

To improve the innovation process, the right infrastructures and a well-functioning innovation ecosystem need to be in place. Governments can play a crucial role in this by providing the right policy frameworks, that are supportive for innovation and that address the whole

complexity of innovation. In addition, western countries need to be open to learn from developing countries to adequately address the need for affordable solutions in healthcare and ICT and to ensure that all parts of the society can participate in the innovation process. To ensure that the aforementioned issues are addressed we emphasize the importance of systematic early dialogue. Following the essential steps outlined in our generic framework and best practice guidelines and incorporating systematic dialogue as key concept in the innovation process can help to overcome the current barriers and consequently bring breakthrough discoveries and innovative ideas to the people.

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CHAPTER 3

3

Research

The creation and management of innovations in healthcare and ICT – the European and African experience

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Abstract

The purpose of the study was to gain new insights into innovation systems by comparing state-of-the-art of existing approaches of innovation creation and innovation management in healthcare and ICT. It is unique, in that it compares countries in Africa with countries in Europe in order to identify similarities and differences regarding the creation and management of innovations. The main similarity is that early dialogue between different stakeholders was underrepresented during the whole innovation process in all countries. Our results also indicated that the various stakeholders often work in silos. The main difference was that the countries face problems at different stages of the innovation process. Whereas European countries face more problems in the innovation creation process, African countries experience difficulty sustaining and managing innovation. To overcome barriers, we suggest the application of systematic early dialogue between all key stakeholders.

Keywords

Innovation Creation, Innovation Management, Frugal Innovation, Healthcare and ICT, Systematic Early Dialogue

Introduction

The 2008 financial crisis and the economic and public debt crises that followed [1, 2] put countries around the globe under immense economic pressure [1], with many facing a reduced gross domestic product (GDP), increasing public debt, a higher unemployment rate, reductions in recourses, and increasing poverty. Furthermore, the crisis caused major threats to global public health [3]. The impact it had on national economies and the responses it evoked greatly differed between developed countries and middle- and low-income countries [4].

In addition to recovering from the 2008 crisis, the European Union (EU) member states are challenged by stagnating population growth [5]. An aging population is expected to negatively impact economic productivity. An aging society also poses challenges to healthcare systems [6]. Conversely, African countries are facing challenges due to growing populations. It is expected that half of the global population growth until 2050 will occur in Africa [5] as its population is predicted to increase from 294 to 742 million by 2030 [7]. There, the rapid change in demographics is set to present challenges to healthcare, too.

To overcome the challenges the world is currently facing, there is a pressing need to find new sources of growth [7]. Innovation is seen as the key to achieving long-term economic growth since it provides the foundation for new businesses, creates new jobs, improves processes and products, and contributes to poverty reduction [7, 8]. It also impacts health, the environment, and other policy areas that are important to the well-being of citizens [7]. Therefore, innovation can play a pivotal role in addressing many of the developmental challenges [9] and is considered an important pillar of development [10]. It is thus not surprising that policy makers, researchers, the industry, and civil society place innovation high on their agendas [7].

Our understanding of innovation has changed dramatically over the last decades. It is no longer seen as a linear process limited to national borders [7, 11] but as something that occurs in a complex ecosystem, in which different actors, such as large and small companies, universities and research institutions, venture capital and funding organizations, and

governments continuously participate and interact on a national and increasingly global stage [7, 12]. Despite the challenges that countries have in common, their innovation performance differs greatly. Mature innovators, such as the USA and Europe, are challenged to keep up with the innovation performance of new emerging markets, especially in east Asia.

Differences in the diffusion of innovations between countries and continents highlight the fact that innovation appears in open and innovation-friendly environments and is determined by infrastructure, workforce, and values as well as attitudes towards innovation and new technologies. Legislation, governmental support, the capacity to invest in research and development (R&D), and the success of funding schemes are also critical [11, 13]. Governments can play a crucial role in creating an innovation-friendly environment by promoting effective resource allocation in R&D while considering factors such as workforce quality, financial markets, knowledge creation and diffusion, and avoiding blanket cuts to public expenditure [7, 11].

Study Background

Since innovation is the key for improving quality of life and maintaining competitiveness on the national and global market, the interdisciplinary research project *innXchange* (Increasing Innovation Potential by European-African Cooperation) aimed at building the capacity for innovation creation and innovation management in African (i.e., South Africa and Kenya) and European partner institutions (Germany and The Netherlands). Countries were chosen based on their innovation performance. The Netherlands and Germany are ranked in the top 10 most innovative countries in the world (in 2nd and 9th place, respectively); South Africa and Kenya are the highest-ranked of the Sub-Saharan African countries (58th and 78th, respectively). It is important to point out that the countries chosen do not represent the 2 continents, but rather specific blocks of countries with similar rankings [14]. The 4 participating countries are members of the ERA-net ERAfrica scheme that funded this project. They had a shared interest in allocating funding to study specifically interfacing challenges in innovation in healthcare and ICT, and therefore decided the collaborate on this project to assist the relevant organizations to improve their capacity and/or their enabling environment for research and innovation.

The innovative approach of *innXchange* was to gain new insights into existing innovation systems by exchanging perspectives and comparing state-of-the-art current innovation creation and innovation management approaches in the healthcare and ICT sector in African and European countries.

Our hypothesis was that differences exist in the way innovations are created and managed in African and European countries. Healthcare and ICT were chosen as study fields due to their high innovation potential. The conjunction of healthcare and ICT, in particular, has changed the landscape of traditional healthcare approaches in recent years. New ICT solutions allow the generation of large amounts of data, also known as "big data", which are increasingly used to improve the understanding, diagnosis, treatment, and prevention of diseases. Furthermore, ICT solutions have enabled patients and citizens to take an active role in the treatment process. New ICT solutions in healthcare are seen as promising tools to make healthcare systems more efficient and effective, with substantial benefits for both public health and the economy.

Methods

A manifold methodological approach was applied to collect information to provide an inclusive and detailed picture of how innovations in the ICT and healthcare sector are created and managed in the participating countries from Europe (Germany and The Netherlands) and Africa (Kenya and South Africa). We defined innovation according to the 3rd edition of the Oslo Manual as: "…the implementation of a new or significantly improved product (goods or services), or process, a new marketing method, or a new organizational method in business practices, workplace organization or external relations…" [15]. For the purpose of the study, the project partners agreed to divide the innovation process into 2 parts. The first is the creation part, from first idea (to invention) to innovation to market, hereafter referred to as innovation creation. The second part is called innovation management, which covers the technology transfer/uptake from market to implementation.

The project started with a narrative literature review to determine the status quo of innovation creation and innovation management in the 4 countries. Based on the literature

review, semi-structured interviews and a survey were conducted. The interviews were designed as an analysis of strengths, weaknesses, opportunities, and threats (SWOT). The survey was conducted to highlight gaps and needs in the innovation process in these countries. To retrieve insights from different points of view, 40 experts, representing different key stakeholders (Table 1) from the 4 participating countries, were invited to participate in the interview in person or via phone. These experts were asked to fill in a complementary survey consisting of 22 open and closed questions related to innovation creation and innovation management. Verbal informed consent was obtained from all participants before the interview and survey.

Table 1. Methods and experts' profile

Innovation camps (case studies)	Innovation camps were organized in all countries at the same dates (a 2-day workshop) There were 15–20 participants per innovation camp in each country Experts were invited based on their expertise in innovation and healthcare and ICT Participants discussed the 4 different case studies and shared their expertise on innovations in healthcare and ICT **Topics:** M-health/e-health tools to overcome the shortage of healthcare professionals (South Africa) Uptake of digital solutions by healthcare systems (Kenya) Diffusion of "-omics" technologies and personalized medicine (The Netherlands) Acceptance of emerging ICT and healthcare technologies (Germany) **Expert Profiles:** Senior researchers, CEOs of SMEs, policy-makers (incl. the European Commission), medical doctors, experts in big data and data science, HTA experts, representatives of pharmaceutical companies, NGOs, funders, and PhD students
SWOT analysis and complementary survey	In total, 40 invitation e-mails were sent to selected experts in the field Ultimately, 23 out of the 40 invited experts from the 4 countries participated (a response rate of 57%) We aimed for equal gender representation but according to the availability of the experts, more men participated in the study There was an age range of 25–60 years Interviews and complementary surveys were conducted via phone or in person over 2 weeks (07.03.2016–18.03.2016) Interviews were conducted by the country project coordinators, following a semi-structured questionnaire **Expert Profiles:** Senior researchers, CEOs of SMEs, policy-makers (incl. European Commission), medical doctors, experts in big data and data science, HTA experts, representatives of pharmaceutical companies, NGOs, and PhD students

For the second part of the project, the project partners organized "innovation camps" (ICs) in each participating country. High-level representatives from the different key stakeholder groups were invited to participate in the camps, and 15–20 experts (Table 1) participated in the ICs in each country. The project partners developed 4 case studies (for topics, see Table

1), which addressed different parts of the innovation process in the healthcare and ICT sectors. Two case studies addressed the process of innovation creation in South Africa and Germany while the other 2 focused on innovation management in Kenya and The Netherlands. Participants were asked to share their beliefs and suggest potential solutions for the problems presented in the case studies. The project partners decided to have a European and an African country in each part of the innovation pipeline, in order to be able to make cross country comparisons.

Results

To present the findings from the semi-structured interviews and ICs, the project partners decided to present the main similarities and differences between the 4 participating countries in both phases of the innovation process separately. They divided the process into innovation creation and innovation management (Table 2). In total, 23 of the 40 invited experts participated in the interviews and survey (a response rate of 57%).

Table 2. *innXchange* key findings

	Africa		EU	
	South Africa	*Kenya*	*Germany*	*The Netherlands*
Innovation Creation	Frugal innovation (local needs) Innovations mostly appear in undefined settings outside of industry Silo thinking A lack of governmental support A lack of financial support Gaps in education A lack of innovation literacy and empowerment	Frugal innovation (local needs) Innovations mostly appear in undefined settings outside of industry Silo thinking A lack of governmental support A lack of financial support Gaps in education A lack of innovation literacy and empowerment	Innovations appear in predefined settings (mainly in industry) A lack of creativity (society is often sceptical about innovation) Silo thinking Unsupportive innovation environment A lack of financial support/inappropriate funding schemes Inappropriate regulation/ overregulation A lack of governmental support	Innovations appear in predefined settings (mainly in industry) A lack of creativity Old Boys' networks Power on innovation agenda Silo thinking A lack of financial support/ inappropriate funding schemes Inappropriate regulation A lack of governmental support
Innovation Management	Silo thinking Corruption A lack of governmental support A lack of IP rights infrastructure/regulation Complex bureaucracy Gaps in education A lack of innovation literacy and empowerment	Silo thinking Corruption and mismanagement A lack of governmental support A lack of IP rights infrastructure/regulation Gaps in education Failure to sustain innovations A lack of innovation literacy and empowerment	Silo thinking Inappropriate regulation A lack of financial support/ inappropriate funding schemes A lack of governmental support	Silo thinking Inappropriate regulation A lack of financial support/ inappropriate funding schemes A lack of governmental support

Innovation Creation

By analyzing the results of the interviews and the ICs, the following similarities were identified. Participants believed that there are great opportunities in both African countries to innovate, especially in the healthcare and ICT sectors. Furthermore, the African participants highlighted the importance of frugal innovations and frugal mindsets to address the challenges the countries are facing. Particularly in environments with resource constraints, frugal innovations are urgently needed. Despite the discussed potential for innovation in Africa, several barriers were indicated. The main barriers to innovation creation that all countries had in common were a lack of government and financial support and a silo mentality. In Kenya and South Africa, the low level of innovation literacy and citizen empowerment were highlighted as factors hindering or slowing down the innovation creation process. The African countries also experienced a lack of regulatory and legal frameworks that would support innovators in bringing innovations to the market.

Most of the European study participants shared the opinion that, in comparison to Africa, the EU seems to be less creative and that mindsets are often too traditional. It was also indicated that the problems the countries are facing and the environments in which innovations appear could not have been more diverse. It was emphasized that this must be taken into account when comparing the 4 countries. In both European countries, the regulatory frameworks and funding schemes were often criticized by the participants of the ICs and interviews and deemed inappropriate and often outdated. Participants stressed that regulatory and legal frameworks need to adapt to new technologies quicker and regulate effectively without hindering innovation by overregulation. An example of the latter is the heavily regulated genomics research in Germany, which slows down innovation processes. Participants indicated that Germany will be left behind in many research areas such as "-omics" technologies due to restrictive regulations thought to have been introduced mainly for historical reasons. Another barrier that was identified in Germany was that the society is often skeptical about innovation and prefers current ways of working to being open to new solutions and technologies. The power of large companies and "Old Boys' networks" was criticized in The Netherlands; it was thought that the innovation agenda was shaped in the interests of a few companies, making it difficult for SMEs to innovate and bring new products

to the market. Moreover, lacking active stakeholder engagement, missing systematic dialogue, and silo mentality were also identified as barriers which negatively impact innovation creation.

Innovation Management

Similar to innovation creation, all participating countries experience barriers to innovation management related to silo thinking, a lack of governmental and financial support, and issues related to legal and regulatory frameworks.

Rather than problems with the creation process, as European countries have, African countries experience difficulties in later stages of the innovation process, namely in managing and sustaining innovations. First, participants indicated that the regulation of intellectual property (IP) rights has a huge impact on the innovation management phase in Kenya and South Africa, and that IP regulations are often inappropriate and poorly developed in African countries. Innovators are concerned that their products can be copied by international competitors because IP protection is often weak. In South Africa, in particular, applying for IP rights was thought to be too bureaucratic and innovators often lack the knowledge required to apply for patents. The second barrier shared by the 2 African countries was corruption and mismanagement, where capital is often not used as intended. Third, South Africa and Kenya have immense gaps in education and skills are often lacking to sustain or manage innovations. Participants highlighted that both countries experience a low level of innovation literacy. Finally, both countries also experience problems regarding the scaling-up of frugal innovations because skills, money, and legal frameworks are lacking.

Germany and The Netherlands face similar barriers to innovation management: silo thinking, inappropriate regulation, and a lack of government and financial support. Compared to African countries, IP rights and applying for IP rights were not seen as problematic in European countries. Moreover, the results indicated that there is no need for more regulation in the EU. However, there is a clear need to update regulations and make them “smarter” and to adapt to new technologies and innovative solutions quicker.

Discussion

This study was conducted to gain new insights into existing innovation systems by exchanging perspectives and comparing state-of-the-art of existing innovation approaches in the healthcare and ICT sectors in 2 European and 2 African countries.

The main difference was that the countries experienced barriers to innovation at different stages of the innovation process. Whereas the European countries face problems in the innovation creation process, African countries face problems in sustaining and managing innovations. The main similarity was that there is no well-developed systematic approach for how innovations are created and managed in all 4 countries. Furthermore, systematic and active engagement among the stakeholders are often missing or underrepresented.

Before discussing the findings in detail, it is important to keep in mind the circumstances and ecosystems of the studied countries in which innovations are created and managed. The settings could not have been more diverse. Furthermore, it is necessary to point out that our findings address issues regarding healthcare and ICT, and that this may be different for other sectors which were outside of the scope of this study.

Innovation Creation

As the results of the ICs and interviews highlighted, the creation of innovation was often not seen as a problem in African countries. Moreover, it was discussed how the Western world can learn from Africa's creativity. Most of the participants shared the opinion that many African countries have great innovation potential to address challenges, e.g., in healthcare or agriculture. However, this potential can only be realized when barriers are removed. Our results are in agreement with the relevant literature which indicates that, despite major deficits in skills [16], a lack of resources [17], and poorly developed infrastructure [18], African people develop products or improve processes to meet their specific local needs [19]. Often, innovations stem from urgent needs to find forthright and sustainable solutions to address the multiple challenges the continent is facing [19]. Many of these innovations are mainly driven by the ideas of individuals with a frugal mindset, and they evolve from the bottom up,

often being referred to as “frugal innovations” [20]. According to Hossain et al. [20], frugal innovations “comprise innovative mixtures of available knowledge and technologies to solve urgent local needs.” Instead of being re-engineered solutions, frugal innovations are often disruptive and based on new product architectures [21]. The novel approach of frugal innovation emerged to improve the economic opportunities of the poor [22]. Particularly in Africa, frugal innovations in the banking [23], healthcare [24], agriculture [25], and energy [26] sectors have the potential to change the lives of millions of people [22].

One main facilitator of frugal innovation was the diffusion of mobile broadband, which has enabled the emergence of the digital economy and increased the innovation potential in Africa [27–29] as illustrated by the example of Kenyan’s mobile money system, M-PESA (M for “mobile” and PESA being the Swahili word for “money”) [22]. The idea of M-PESA was to increase access to financial services and offer financial inclusion for the poor and unbanked [29]. Based on this frugal idea, M-PESA has disrupted the existing banking and financial institutions by forcing them to lower prices and speed up the process of check clearance [23]. Not only did M-PESA diffuse to other countries, it also spilled over to other sectors and enabled innovations such as the agriculture microinsurance, Kilimo Salama [17, 23]. The implications of M-PESA are explained in more detail elsewhere [22, 23, 30, 31].

As highlighted in the results, frugal innovations in healthcare can greatly contribute to improve the well-being of citizens in Africa. This finding is in agreement with the international literature [32]. There is evidence that frugal innovations are already successfully used in several countries around the globe to improve access to healthcare for under-served patients [32, 33]. Frugal innovations can enable doctors or citizens to use simple, low-cost, and easily operated technologies in low-income settings. Furthermore, applying such technologies means that health threats can be prevented, diagnosed, and treated [24, 34].

Beside the discussed potential that innovations can have in Africa, several barriers were highlighted which impact the creation of innovations. In accordance with the literature [35], silo thinking and a lack of stakeholder engagement were often mentioned as challenges with a huge impact on innovation creation.

As our results highlighted, most of the European participants of the study shared the opinion that certain European countries display a lack of creativity and a frugal mindset. Furthermore, it was indicated that innovations in the healthcare and ICT sectors mainly occur in industry in predefined settings and are associated with high R&D spending.

Europe has always been characterized as being a world-leading inventor [11]. Science, technology, and innovation (STI) are top priorities of European governments. However, countries from other continents, especially east Asia, have increased their innovation capacities in recent years and are catching up with the mature innovators like the USA and Europe [11]. It can no longer be said that Europe enjoys "old monopolies of know-how and technology or dominates the ownership of planetary resources" [11]. Moreover, the EU is facing challenges to attract and retain global inventors since many innovators and inventors rather go to the USA, Canada, and Australia, than to Europe [11].

Even though Europe, and especially the 2 participating countries which are ranked among the top innovation performers globally [36], is still seen as top innovator, our study participants highlighted several barriers which greatly impact the innovation creation process. Many of the participants of the ICs and interviews expressed criticism and concerns regarding the innovation ecosystems. The main problem that was identified was that innovations in Europe mainly occur within the formal sector and in highly regulated and predefined settings. Participants shared the opinion that creativity is driven by ideology and there is a lack of open mindsets in Europe. Rather than thinking outside the box, many Europeans prefer to work in traditional ways. This expressed need for more creativity is also highlighted in the literature and policy reports [8, 11]. Europe needs to understand the changing landscape of innovations [37]. Due to the emergence of frugal innovations, innovation no longer has a linear association with R&D spending [38]. Therefore, being a top R&D investor does not necessarily make one a top innovator [38]. For instance, as Heeks [39] highlighted, the traditional mindsets and the lack of creativity have led to a situation where Europe is lagging behind Africa in certain areas such as m-money. He also indicated that changes in mindset and ways of working in the USA and EU "may be particularly difficult given legacy attitudes towards the Third World." Due to stagnating economies and restrained resources, the demand of lower-cost solutions is increasing in Europe. There is the risk that Europe will lose these market

segments of lower-cost solutions to emerging markets if mindsets do not change and stakeholders do not leave their comfort zone. Pansera [40] pointed out that Western countries "should learn from emerging countries how to be frugal and competitive at the global market." Crisp [41], furthermore, stated that instead of teaching the rest of the world, the West should start considering learning from others and that mutual learning will benefit all.

Next to the lack of creativity, regulation and legislation were highlighted by most of the participants as barriers which greatly impact the creation of innovations in the EU. Specifically, it was criticized that legislations are often outdated, inappropriate, and do not address new digital technologies and innovations appropriately. Similar challenges are also discussed in the literature and policy reports [11, 42]. Particularly in healthcare, a sector with a strong ethical dimension, regulation can either enable or constrain innovation [43]. For example, several participants from Germany criticized how the regulation of the application of "-omics" technologies in healthcare is restrictive. It was argued that if legislation does not adapt quicker to digitalization and new emerging technologies, Germany will face the increased risk of falling behind other countries in research. It is obvious that regulations need to facilitate innovation rather than hinder it [11]. However, it is important to find the right balance between protecting citizens (e.g., by data protection) and not hindering research with outdated and inappropriate legislation [44].

Participants from The Netherlands criticized that large companies often do not want new innovative solutions because they are afraid of losing power and market shares. Young and small businesses, in particular, often experience difficulty obtaining resources to scale-up their innovations and expand [35, 45]. In order to remain a top performer, a stronger involvement and recognition of small and medium-sized enterprises (SMEs) will be important, because SMEs have great innovation potential and provide creative solutions to problems [45, 46]. The government needs to provide a supportive infrastructure for SMEs, since it is argued that they can contribute greatly to initiating change and creating new technologies [46].

Innovation Management

As presented in the results, African innovators are often faced with challenges when managing and sustaining innovations. Poor infrastructure, gaps in education, weak protection of IP rights, and silo thinking were highlighted by the African participants as major barriers to innovation management. These are also discussed in the literature [17].

It is widely accepted that education is a key driver of innovation, and that without a well working education system new ideas and technologies are less likely to scale-up and diffuse [17, 27]. In agreement with the literature, our study shows that Kenya and South Africa experience major gaps in education [17, 47, 48]. Even though many African countries have had an immense improvement in primary-school attendance, the gross secondary-school and tertiary education enrollment rates are still the lowest worldwide [17]. Evidence indicates that innovative approaches are already being successfully implemented in several African countries, drastically improving the education systems [17, 27, 49]. A recent example is an e-learning program developed in Kenya. The program aims to provide training and education for nurses in the treatment of severe diseases, such as malaria, HIV, and tuberculosis [49]. By applying this e-learning program, almost 12,000 nurses can be trained in 1 year compared to the traditional classroom-based approach, with which, due to the lack of resources, only 100 nurses can be trained [49].

The African participants highlighted the importance of IP rights with regard to innovation management, which is consistent with the literature [50]. Many African countries still apply outdated legislation to protect IP rights [51]. Furthermore, legislation differs significantly in different countries, making collaboration between countries even harder [52]. Only a small number of judges and experts have expertise in IP regulation, making its application difficult, costly, and time-consuming [52]. Many inventors and innovators are working in secrecy and are not asking for feedback because they are afraid that their ideas will be picked up and then scaled-up by others [52]. This is in line with the *innXchange* study findings that innovators are often working in silos. The above-described problems partially explains why African countries account for only 0.1% of the world share of patents submitted to the US Patent and Trademark Office (USPTO) [16]. There is a clear need to update IP legislation according to the

TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement and invest in education about IP rights management [52].

Participants also indicated that corruption, mismanagement, and weak political systems greatly impact innovation management in Africa. Those problems are also widely recognized in the literature [53, 54]. As highlighted by Oluwatobi et al. [55], increased control of corruption, improved effectiveness of governments, and robust regulatory frameworks will improve rates of innovation in Africa.

In contrast to Africa, the management of innovation was not seen as a major problem among the European participants in our study. The majority shared the opinion that Europe is relatively well-positioned with regard to the management of innovations. However, they stressed the importance of breaking down silos in healthcare. Particularly when looking at the emergence of "-omics" technologies, a silo mentality in legislation often hinders the innovation process. This is also discussed in the literature [56]. Often, regulations address only certain aspects instead of covering the whole complexity of new technologies and approaches. To successfully innovate and manage innovations, the traditional health science R&D silos and big data silos need to be broken down [44]. Rather than acting with reserve, governments and the EU need to be more forthright when new technologies or products emerge [11].

Overall, many European countries are relatively well-positioned where innovation management is concerned. However, in the global environment, rather than just offering guidance, European countries should share their experiences and also their failures with other countries. By learning from others' mistakes, African countries can avoid repeating the mistakes that Europe has made in the last decades.

Recommendations

TO overcome and address the challenges in innovation creation and innovation management, the *innXchange* project participants emphasized the importance of systematic early dialogue (SED), proinnovation environments, and public-private partnerships (PPPs).

Systematic Early Dialogue

Even though African and European countries are facing societal and economical challenges, the project identified that, in all participating countries, a systematic approach to create and manage innovations is missing. Often, early dialogue and collaboration between different stakeholders from different areas are lacking. To overcome the problems described above that attend innovation creation and innovation management, the project participants have emphasized the importance of SED between the key stakeholders as a policy tool to improve the innovation process. Companies, universities, policy-makers, and other stakeholders are often working in silos but not collaborating with each other. To successfully create and sustain innovations, a systematic approach is needed. Stakeholders across disciplines and sectors must communicate and collaborate from the beginning and in a systematic manner.

Proinnovation Environment

It will be crucial to create innovation friendly environments. Particularly in times of financial constraint, innovations will be the key for sustainable growth and the improvement of citizens' well-being. Since new innovation approaches, like frugal innovations, are increasingly disrupting the mature (developed) markets, changes in mindset are urgently needed to keep up with the emerging markets. Western countries need to change their mentality and, instead of teaching others, should start learning from emerging economies. Moreover, regulations need to be adapted, revised, and updated, to cater appropriately for the new emerging technologies. Education is also a key parameter in the innovation process. Particularly in the African countries, gaps in education, deficits in skills, and weak protection of IP rights challenge the management of innovations. Governments need to provide prerequisites such as education, legal structures, and financial support to create a proinnovation ecosystem. On the other hand, it is important that innovators are not overwhelmed by extreme governmental bureaucratic demands while trying to introduce a new technology or product to the market.

Public-Private Partnerships

To improve a multi-stakeholder SED, PPPs can help facilitate collaborations and combine public and private funding. The Innovative Medicine Initiative (IMI) is the flagship PPP for healthcare in the EU. The IMI aims to improve the development of new and safer medicines

for patients in a timely and effective manner [44]. African countries are increasingly recognizing the importance of strategic alliances and partnerships to address the challenges they are facing. Without collaborations between stakeholders, innovation can often not be realized. In Kenya, universities and small companies are currently joining forces with government institutions and foreign international companies, such as IBM and Philips, to adapt a multidisciplinary approach to overcome challenges. Both the above companies have opened research and innovation centers in Nairobi to strengthen the development and management of innovations in healthcare. There is a clear need for more PPPs like the IMI or the examples from Africa for the improvement of the innovation process and to be able to "leapfrog" into a future of sustainable growth. Only when all relevant stakeholders, in both Africa and Europe, start learning from each other and working together from the early stages of the innovation process, can current barriers and hurdles be overcome.

Conclusion

Not only is innovation seen as a key driver for economic growth, it will also make the difference in tackling the many urgent developmental challenges currently faced by the world. This study highlights several similarities and differences concerning innovation creation and innovation management in African and European countries. SED, PPPs, and proinnovation environments can help to address the many challenges these 2 continents face with regard to innovation in healthcare and ICT.

Lessons Learned

Due to the emergence of frugal innovation, innovation is no longer in a linear association with R&D spending. Instead of only teaching the rest of the world, developed countries should start considering learning from others and that mutual learning can benefit all. To overcome barriers to innovation creation and innovation management, the project participants of *innXchange* emphasize the importance of SED, proinnovation environments, and PPPs.

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CHAPTER 4

Systems Management

European healthcare systems readiness to shift from 'one-size fits all' to Personalised Medicine

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Abstract

Personalised medicine (PM) is no longer an abstract healthcare approach. It has been become a reality over the last years and is already successfully applied in the various medical fields. Although there are success stories of implementing PM, there are still many more opportunities to further implement and make full use of the potential of PM. We assessed the system readiness of healthcare systems in Europe to shift from the predominant 'one size fits all' healthcare approach to PM. We conclude that European healthcare systems are only partially ready for PM. Key challenges such as integration of big data, health literacy, reimbursement and regulatory issues need to be overcome in order to strengthen the implementation and uptake of PM.

Keywords

Personalised medicine, European healthcare systems, System readiness, Big data, Clinical trials, Health literacy, Health data cooperatives, Systematic early dialogue

European healthcare systems and Personalised Medicine

Demographic change [1], rising morbidity and increasing premature mortality of non-communicable diseases (NCD) [2] are challenging the European Union (EU) and the healthcare systems of the Member States (MS). It is estimated that in 2025 20 % of all citizens of the EU will be aged 65 years or older [3]. Approximately 90 % of all deaths in the EU are attributable to NCDs [4]. Cardiovascular diseases are belonging to the most common causes of deaths among European citizens [5]. In 2012, more than 1.7 million people died due to cancer in Europe [5]. Every single day approximately 4,000 European citizens die of cancer [1]. The burden of NCDs, infectious diseases and the ageing society will challenge our healthcare systems in the near future even more [1, 4, 5].

Besides the ageing population and the rise of NCDs, ineffective and inefficient healthcare systems are posing a great burden on healthcare expenditures within the EU [6]. Moreover, healthcare systems are challenged by the ever growing prices for new medicines being requested by pharmaceutical companies [7]. Even high-income countries seem to struggle to fund new innovative medicines due to high prices [8]. Furthermore, healthcare systems are challenged by pharmaceutical companies exploiting orphan disease status in order to drive up their requested prices. Healthcare systems in Europe are generally based on a 'one-size fits all' health approach. Based on the principles of evidence-based medicine, patients are being treated with medicines that have been proven to be safe and efficient in Randomized Controlled Trials (RCTs), which have been the gold standard in clinical research for decades [9]. By reducing bias and enhancing the accuracy of clinical trials, RCTs have literary reshaped medical practice. However, for drugs that have been demonstrated to be the best option for a group of patients with similar characteristics, fail to take into account the individual genomic and epigenomic differences that to a large extent determine the safety and efficacy of a treatment [10].

The past has shown that 'one-size fits all' actually does not fit all patient needs. Rather, patients can vary greatly in their response rate to drugs [1, 11]. For example, the 'one-size fits all' approach in oncology is effective in less than 25 % of the cases [1, 12]. Research has proven that each tumor possesses unique molecular characteristics that, together with the tumor

microenvironment and the interactions with other tumor and host cells, determine its clinical course. This essential new paradigm in cancer research allows for better and more accurate classification of diseases based on their molecular characteristics [13]. This is where the approach of personalised medicine (PM) comes in.

PM utilizes new technologies such as 'omics technologies' and integrates all kinds of data (e.g., biological, environmental, lifestyle) in order to identify individuals' biological characteristics and predisposition to a certain disease and response to treatment [14-17].

By providing "the right intervention in the right way, in the right order, and in the right time and in the right place" [15]. PM aims to make health interventions including treatments more effective and to decrease adverse side effects [13]. In fact, PM and 'omics technologies', such as 'genomics, proteomics, transcriptomics, metabolomics, epigenomics, microbiomics' [12] are already challenging the current and traditional healthcare and public health approaches in the EU and beyond [14, 18].

Over the last decade, progression in genomic technologies made it possible to reduce the costs of the human genome sequencing from initially US $100 million per genome in 2001 to US$ 1.000 per genome sequencing in 2013 [8, 14]. Over the last couple of years PM – based on -omics knowledge – has been successfully applied in several medical fields such as cancer treatment and rare diseases [15]. Moreover, the approach of PM is used in healthcare areas such as cardiology [16], nutrition [19]and for the treatment of infectious diseases [20].

Indeed, PM is no longer an abstract healthcare approach. PM has been becoming a reality over the last decade [14]. Although there are already success stories of the implementation of personalised prevention strategies, diagnoses and therapies [21], there is still room for improvement by the national healthcare systems to further implement PM.

Currently, the use of PM is expanding throughout the EU [21]. Over the last years, the European Commission (EC) as one of the leading drivers of PM in Europe and beyond, published several reports addressing issues regarding challenges and opportunities of PM and 'the use of -omics technologies' and biobanks [22, 23]. A milestone has been the launch of

the International Consortium Personalised Medicine (IC PerMed) in June 2016, a concerted action of four EC Directorates-Generals, over 26 European MS and regions as well as Canada. Furthermore, the 12th Luxembourg Presidency of the Council of the EU published positive Council Conclusions on PM in December 2015. Since 2007, the EU has committed more than 1 billion Euros of EU funding to further develop and advance the approach of PM [22]. The approach of PM is defined in many different ways among stakeholders [24], which consequently leads to the problem that there is no common or general definition of PM. The Horizon2020 Advisory Group for Societal Challenge 'Health, Demographic Change and Wellbeing' of the European Commission refers to the approach of PM as 'a medical model using characteristics of individuals' phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' [25]. In other words, this definition moves away from the common 'one size fits all' medical model.

Therefore, in this article we assess the system readiness of European healthcare systems to shift from 'one-size fits all' to PM. As a starting point of the assessment we are referring to the outcome report of the EC consortium PerMed 'Shaping Europe's Vision for Personalised Medicine – Strategic Research and Innovation Agenda (SRIA)' published in 2015 [26]. The PerMed SRIA lists 35 recommendations for actions at national as well as EU level. These recommendations are grouped into five overarching key challenges for research that need to be overcome in order to further implement PM in the EU. The five key challenges are 'Developing Awareness and Empowerment; Integrating Big Data and ICT Solutions; Translating Basic to Clinical Research and Beyond; Bringing Innovation to the Market; Shaping Sustainable Healthcare' [26]. The IC PerMed recently stated in their report "Towards an International Consortium for Personalised Medicine" [27] that they will develop a timely roadmap structured as a list of research actions according to these five challenges.

The aim of this paper is to find out which factors are facilitating or hindering the diffusion of PM among European healthcare systems. In order to critically evaluate the diffusion and uptake of PM among European MS, we use the key challenges of PM which are presented in the PerMed report [26]. We cluster the different factors that are challenging the

implementation of PM and assign them to three categories which are taken from the 'Conceptual Model for Considering the Determinants of Diffusion, Dissemination, and Implementation of Innovations in Health Service Delivery and Organizations' developed by Greenhalgh *et al.* [28]. The model describes under what conditions innovations are implemented and was originally developed for the exploration of the uptake of innovations within healthcare organizations. For the purpose of this paper we apply a heuristic approach by adopting parts of the model for healthcare systems instead of healthcare organizations to PM. Greenhalgh *et al.* conceptualized within their model different determinants which influence the 'diffusion, dissemination and implementation of innovations' [28] in healthcare settings. This article focuses on the determinants that are influencing the 'system readiness for innovation' [28]. System readiness for innovation is defined in the model of Greenhalgh et al. to consist of the six following components: Tension for change; Innovation-system fit; Power balance (supporters v. opponents); Assessment of implications; Dedicated time/resources; Monitoring and feedback. For our purpose, we decided to evaluate three of the six determinants of healthcare system's readiness to shift to PM, namely tension for change, innovation-system fit, assessment of implications, because those three determinants are closely related to the challenges described in the PerMed SRIA report (Figure 1).

We conducted a narrative literature review to collect information regarding the main factors that are challenging the uptake of PM, as described in the PerMed report, in order to critically discuss and assign them to one of the three determinants of system readiness. We will first present the theoretical definition of the system readiness determinants according to the model by Greenhalgh *et al*. Afterward we will apply the model to discuss how ready European healthcare systems are to implement PM into daily practice. Moreover, we provide a future perspective and describe potential solutions and recommendations for the challenges.

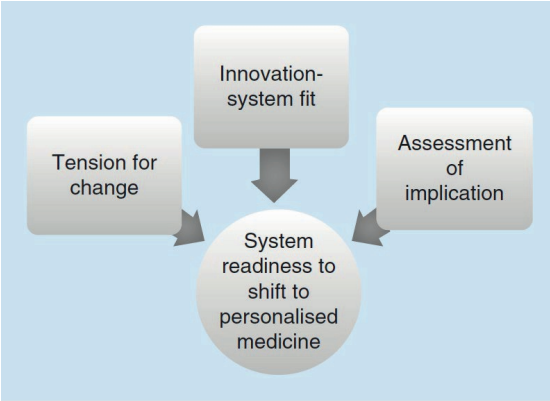

Figure 1: Determinants of system readiness.
Original figure adapted from the 'Conceptual Model for Considering the Determinates of Diffusion, Dissemination, and Implementation of Innovations in Health Service Delivery and Organizations' [28].

1. Tension for change

Referring to Greenhalgh et al. 'tension for change' occurs 'if staff perceive that the current situation is intolerable' [28]. In cases where the current situation and practices are seen as intolerable, new innovations will be adopted to improve the situation. We discuss whether the current 'one-size fits all' situation is seen as intolerable or unacceptable.

One-size fits all does actually not fit all

As previously described, patients do greatly vary in their response rates to drugs [29, 30]. The response rates vary from 80 % for analgesics (Cox-2) to 25 % in oncology [12]. Therefore, approximately 75 % of cancer therapies are not effective, which consequently leads to increasing healthcare expenditures and ineffective healthcare systems [1]. Between 20 to 95 % of adverse drug reactions (ADRs) are related to the genomic characteristics of the patient [30, 31]. Patients are not only suffering a loss of quality of life during treatment, many are also suffering on ADRs [32]. The unnecessary burden of suffering caused by ineffective therapies and ADRs not only presents a burden for the patients and their families, but also an immense economic challenge for European healthcare systems [1, 32]. Approximately 100 million are spent on ineffective treatments and ADRs healthcare systems among the EU [1].

2. Innovation-System fit

According to *Greenhalgh et al*., innovations are more likely to be adopted when the innovation 'fits the organization's existing values, norms, strategies, goals, skill mix, supporting technologies, and ways of working' [28]. European healthcare systems greatly differ in their structures, way of working and funding schemes. Therefore, it will be discussed whether the approach of PM will fit or already fits into our current systems and ways of working or whether changes or adaptations are needed to make full use of the potential of PM.

Integration of big data needed

The collection, handling, storage and analysis of increasing quantities of data are defining traits of our current society [33, 34]. Until 2020, it is estimated that the amount of data of every citizen on our planet will increase to approximately 5.200 gigabytes of data. Every 5 years the amount of health data is doubling [35, 36]. In the next years the amount of digital healthcare data will increase globally from around 500 petabytes (1 petabyte = 1000 terabytes) in 2012 to 25.000 petabytes in 2020 [37]. Almost 90 % of health data was developed and gathered over the last couple of years [35]. The immense amounts of data collected through an increasing variety of sources, is known as 'big data' [38], is offering a new understanding of the complexity of diseases. Furthermore, big data analytics can help to develop new drugs and interventions adjusted to the individual needs by taking into account the interaction between genomic data, lifestyle information and environmental factors [38] and thus turning big data into actionable data. Increasing healthcare expenditures and ineffective treatments are often caused by inaccessible medical information [6]. Since health information is collected from a large variety of sources, big data is often stored in various silos. Furthermore, health information is not only collected in different ways and stored in different silos, but can be stored in incompatible data structures [6]. In the years ahead, the further development of PM in healthcare systems will rely on the potential of integrating big data analytics and ICT solutions [26, 38]. Since health information can be gathered through a large variety of sources it becomes clear that the data generation is no longer a bottleneck for PM. However, the storage, analysis and management of health information is still

challenging the current ways of working and the performances of our healthcare systems [39, 40]. As we learned already from electronic health records and their interoperability problems, new technologies and approaches to analyse, integrate and store big data are urgently needed in order to make full use of the potential of PM.

Lacking knowledge of healthcare professionals and low health literacy in patients

Healthcare professionals (HCPs) are often not aware of new innovative therapies [21]. Even when the HCPs are aware of new innovative treatment possibilities they often feel overloaded and overwhelmed by the amount of new information and lack of tools to support their treatment decision-making process [21, 41]. The curricula for HCPs are outdated and are not adjusted to the new complex understanding of diseases [17, 42, 43]. Differences in the curricula do not only exist between the 27 EU Member States, they also occur within a country on regional and local level [44]. For example, most European curricula of physicians do not address issues which are key elements of PM such as ICT, companion diagnostics or the application of 'omics-technologies' [21]. The reviewed literature indicated that there is a clear need for change regarding empowered and literate patients and also to adjust current curricula of HCPs to new innovative therapies and diagnostic tools.

The current 'one-size fits all' healthcare approach sees the patient's role in care as passive recipient [45, 46]. Patients do have trust in their general practitioners (GPs) and their decisions and therefore are often not scrutinizing their decisions and asking questions [46]. In order to further implement and strengthen the role of PM in the EU it is of great importance to involve the patient more actively in the decision-making process of his/her treatment [15, 26, 45].

An important pillar of involving the patient more actively in his/her treatment is health literacy. In 2006, health literacy was defined by Kickbusch *et al.* as 'the ability to make sound health decision(s) in the context of everyday life, - at home, in the community, at the workplace, the healthcare system, the market place and the political arena' [47]. Over the last years health literacy has gained increasing attention by the European Commission. The concept of health literacy was included in several policy documents of the EU [48]. In 2011,

as part of the European Health Literacy Project (HLS-EU), the first European Health literacy survey (HLS-EU-Q) was conducted in order to be able to measure the level of health literacy among eight European MS [48]. Also, the initial broad definition of health literacy from 2006 was elaborated upon by identifying four dimensions of health literacy as 'the ability to access, understand, appraise and apply health information' [49].

The results of the survey HLS-EU-Q indicated that, on average, every second participant experienced or indicated a lack of health literacy. The survey also highlighted that the countries greatly vary in their level of health literacy from 28 % of lacking health literacy in the Netherlands to more than 60 % in Bulgaria. People with a lower level of health literacy are suffering more from a lower health status than people with higher levels [46, 48]. Since health literacy and patient empowerment are central concepts to further strengthen and adapt PM, changes are needed [15, 21, 26, 46].

Changes in Regulation

To make full use of the potential of PM, national and European regulations need to be revised in several areas such as data protection and medical devices [43]. The revised version of the clinical trial regulation, which was published in May in 2014, can be used as an example of how a regulation can be quickly improved though close collaboration of legislators, stakeholders and interest groups [43]. For PM, data protection is a key issue that needs to be addressed in order to further implementation across Europe. It is of great importance that the new data protection regulation takes into account the immensely increasing amount of health data and the sources by which big data is gathered [43]. Regulations must be adapted in such a way so that, on the one side the patient or citizen is protected against misuse of his or her personal information, and on the other side that research will not be hindered through overregulation [50].

Furthermore, more harmonization of regulations is heavily required within the EU [21]. Within the coming years, changes in the process of the market authorization of new drugs and tests will be needed, since current clinical trial approaches cannot be used to test personalised treatments [21]. However, approaches such as the UK's Early Access to

Medicines Scheme (EAMS), conditional approvals, market authorization under exceptional circumstances (e.g., the German "Heilversuch") or adaptive pathways pilots (e.g., the Medicines Adaptive Pathways to Patients pilots (MAPPs) of the European Medicines Agency (EMA)) are already paving the way. These approaches 'refer to flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits'. For example, MAPPs provide an early authorization of a product focused on a well-defined and targeted population with a clear safety and efficacy profile [51]. Different healthcare stakeholders are concerned regarding the use of adaptive pathway pilots of the EMA for fast track drug approvals [52-54]. Nevertheless, it needs to be mentioned that drugs which are approved under expedited authorization will not necessarily have a therapeutic added value for the patients'[55]. Stakeholders are concerned that adaptive pathways approvals will become the rule rather the expectation and those pharmaceutical companies will try to acquire orphan status licenses for their drugs by conducting MAPPs. By seeking orphan drug status for their drugs pharmaceutical companies aim to drive up the prices of their drugs [7, 8]. Many stakeholders are afraid that the rising burden of healthcare expenditures due to increasing pharmaceutical prices will bankrupt the healthcare systems [7]. Another issue that challenges stakeholders is the shift of evidence from pre-marketing to post-marketing, which means that pharmaceutical companies are required to show evidence on beneficial effects and safety of the drugs after it is placed on the market. Critics fear that agreements to provide post-marketing evidence will not be honored by pharmaceutical companies [55]. By applying MAPPs, drugs get premature licenses based on preliminary results which are also supported by advocates such as patient groups. Patient advocates will of course demand access to the best treatment as early as possible even when evidence is limited. The issue is related to the notion of 'public health right' where enabling access to experimental drugs, in order to respect the individual's right to health, violates the 'public health right' to sound and tested scientific knowledge. Despite the problems and issues discussed beforehand it is important to state that MAPPs is a pilot by EMA and that there is of course room for improvement. To learn from weaknesses in such pilots is precondition for future development.

Clinical trials

Although it is known that patients respond differently to drug treatments due to their genetic and epigenetic profile and that each tumor has unique characteristics, clinical trials often ignore this complexity of diseases [1]. The current clinical trial approaches cannot gather the complexity of necessary data which is needed to make use of the full potential of PM [15]. In order to test personalised treatments for market authorization, current clinical trials with hundreds or thousands of participants are not appropriate [21]. A shift is needed to apply the new complex understanding of diseases to trial designs in order to reduce adverse side effects of patients due to 'one-size fits all' treatments. Of course, those issues regarding the design of clinical trials in the era of PM are not unique to EU. These issues need to be addressed globally. Current designs are often not adjusted to the new complex understanding of diseases [1, 21, 56]. However, new approaches such as adaptive pathways are already in place in Europe, and beyond. These are preparing the way by recognizing the uniqueness of diseases as currently best proven in cancer.

Pricing and reimbursement

Affordability is seen as one of the major barriers with regard to further strengthening the implementation of PM. Due to the high costs of PM it is often argued that PM will even increase the burden of healthcare expenditures and health inequalities among EU Member States (MS) [57]. However, as it is with almost all technologies, the price for personalised treatments and technologies is expected to fall with increased use over time, as it is the case with sequencing of the human genome [58]. Within the EU access to innovative therapies is limited and varies among the MS [59, 60]. At the moment, European reimbursement systems are restrictive to providing access to PM [61]. For example, pricing and reimbursement for pharmaceutical products and companion diagnostics are made by the MS or even on regional level within the MS, whereas regulatory decisions are made on European level [61]. Therefore, the EU encompasses a large variety of pricing and reimbursement schemes, tools and health technology assessments (HTAs), which are seen as barriers to harmonizing the implementation PM into European healthcare systems [21, 42, 61, 62]. To manage limited health resources, HTAs are used to make resource allocation decisions, for instance on

whether new drugs will be reimbursed. The EU also needs harmonization with regard to HTA [15]. Furthermore, HTA models need to be adapted to PM in order to make sound and safe decisions [51, 63]. A survey regarding the reimbursement of Trastuzumab among 27 EU MS, indicated that reimbursement of the treatment heavily depends on the country in which the patient receives treatment. In most of the countries, HER2-positive breast cancer patients were treated in hospitals and in some countries in out-patient facilities [62]. Within the EU, the study identified two main funding mechanisms for Trastuzumab and its diagnostic tools, either the costs of the drug and the test were covered by the national or regional funded hospital, or the costs were split between the hospital and a third party payer [62]. Due to limited and lacking evidence [64] and incentives [65], health insurance companies do often not reimburse biomarker tests and PM across the EU [42]. Within the current schemes, payers in the EU are challenged to evaluate PM drugs and companion diagnostics [61]. One main hurdle that needs to be addressed in the years ahead is the issue that most payers among the EU are applying different payment and evaluations models for drugs and diagnostics [61]. Therefore, drugs and companion diagnostics are handled in silos. There is a clear need to harmonize HTA approaches among the EU MS in order to make full use of the potential of PM and also to make healthcare systems more efficient [26]. In contrast to the beforehand discussed issues and our views, some stakeholders might argue that not the different pricing, reimbursement and assessment tools are hindering the uptake of PM in Europe rather the pharmaceutical companies which seek orphan drug status for most of their new drugs to charge higher prices. They fear that the increasing expenditures on orphan pharmaceuticals will bankrupt the European healthcare systems [7].

3. Assessment of Implications

It is more likely that innovations will be adopted when 'the implications of the innovations (including their subsequent effects) are fully assessed and anticipated' [28]. It is questionable whether this is already true for PM as it is still a relatively new research area and approach to healthcare.

As discussed beforehand, PM has the potential to make healthcare systems more effective and treatments more efficient. Nonetheless, there are several methodological issues that

need to be addressed in order to assess to the greatest extent possible the implications and the added value of PM for European healthcare systems [26]. More research and studies addressing the clinical and personal utility [66] of the PM approach are required. Furthermore, there is a clear need for more evidence that will demonstrate the added benefit of PM for patients in comparison to 'one-size fits all' approaches [26]. One promise of PM that is often listed in the literature is that PM will reduce healthcare expenditures. Nevertheless, it is important to keep in mind that in order to further integrate and implement the approach of PM in our healthcare systems in the EU, investments are especially essential in the beginning of the introduction process. Since PM is still a relatively new approach, experts are still arguing and discussing about the implications of PM and the right tools and methodologies to access the added value and impact of PM. Another issue that needs to be addressed is that PM is defined in many different ways by different stakeholders and experts [24, 30]. Different definitions consequently complicate discussions concerning barriers, risks and the added value of PM. It also leads to miscommunication among stakeholders [24]. Furthermore, the vagueness of the PM definitions can lead to misunderstanding among patients [24]. As long as there is not an agreed definition of PM, it will be complicated and difficult to develop methodologies and tools to further access the implications of PM such as added value and economic assessment tools. The definition developed by The Horizon2020 Advisory Group for Societal Challenge "Health, Demographic Change and Wellbeing" of the EC seem to be a workable definition and has in the meantime been taken up in the PerMed SRIA as well as for IC PerMed.

Future Perspective

PM has the potential to make treatments and healthcare systems more effective and efficient as well as more timely. Nevertheless, the PerMed SRIA as well as our discussion indicates that the uptake of PM is still lacking across the EU and that MS differ in their adaption of PM. At the same time, we showed that there is a high capability and momentum for the diffusion and uptake of PM. Furthermore, the study demonstrated that the uptake of PM might be inadequate because the approach of PM does not fit into our current ways of working such as the methodologies we use to assess for instance drugs and tests, and that regulations at

national and European level are outdated for PM. Even though some say that PM will make treatments more effective and healthcare systems more efficient in times of limited resources, much more evidence is needed in the years ahead that will assess and prove the benefit of PM. Most of the implications of the PM on EU healthcare have systems are still not been fully assessed, moreover it will take time until assessment tools and methodologies are be harmonized across the EU and adjusted to PM. In the following paragraphs, highly innovative solutions to meet current and future needs of European healthcare systems are discussed and proposed.

Health Data Cooperatives are the right way to integrate big data and empower patients

To further integrate the approach of PM into EU healthcare systems we need not only to think about the ways of working, but also to think 'out of the box'. Particularly, the challenge of finding a successful and efficient way to integrate the immense amount of health data will be a key facilitator to increase the uptake of PM in the EU. Nowadays, data collection is no longer a problem. The problem is that most healthcare systems are working ineffectively because data from multiple sources are stored in silos.

A truly European and democratic solution could be 'health data cooperatives' (HDCs) as suggested by Hafen *et al.* [6]. Since the economic value of health data is greatly increasing, security of personal information is a major issue. European citizens are often concerned that their personal data will be misused by third parties and that they could suffer from this misuse. HDCs most important characteristic is that their data platforms are owned and controlled by its members or, in this case, by the citizens. Here, in the HDC model, the citizens are not only in the driver's seat, they really become citizens. Since the value of millions of personal datasets has been recognized as a new asset class and many commercial entities such as Google or Facebook are already competing for this new asset, the rationale behind HDCs is that the primary source and beneficiary of personal health data is solely the individual, i.e. the citizen, storing, managing and sharing her/his personal data. There is a dual benefit to society of both improved health research and its subsequent economic windfall. Furthermore, by each member having a vote, HDC members decide how the revenues generated by granting third parties access to their data that they agreed to share (respectively

the data commons), should be invested (e.g., in research, in public health, in education, in community outreach etc.) [6].

Studies on the history and sociology of medicine have highlighted the social and cognitive dimensions of the important role of the patients in the history of healing [67]**.** Indeed, as our results indicate, one of the most important pillars in the process of strengthening the uptake of PM among EU healthcare systems are empowered and health literate patients and citizens. The challenge is that the degree of health literacy greatly differs between and within European MS [48]. As a potential solution to overcome the challenge of patient empowerment and health literacy across the EU we would like to come back to the concept of HDCs. HDCs not only promise to integrate big data in an effective, efficient, timely and socially acceptable way, they also promise to empower the patients/ citizens by being part of, and actively involved in the decision-making processes of the HDC [6]. HDC will make patients/citizens proactive consumers of health, so called 'prosumers' [21]. Patients/citizens will be actively involved in research ('citizen science') and be able to actively participate in the decision-making process regarding their health and treatment ('learning by doing'). We assume that empowered and literate patients/citizens will improve the diffusion of PM within the EU and its MS.

Better health literacy of healthcare professionals and patients

As mentioned before, another reason why there is still room for improvement regarding the uptake of PM is that current curricula of healthcare professionals (HCPs) are outdated and not adapted to the new developments and innovations in biomedicine and ICT. Therefore, HCPs are often not aware of new personalised treatments and technologies. For example, over the last years, the increasing technological developments in pharmacogenomics made it almost impossible for HCPs to keep up [17, 21, 42, 68]. Although the costs for the sequencing of the human genome have immensely reduced due to major technological developments, the large majority of HCPs are not able to interpret and make use of such information for the benefit of their patients. Another issue that is hampering the uptake of PM is that HCPs are often not aware of recent developments in 'omics technologies' and PM [21, 26]. Therefore, it is not surprising that the uptake of PM is lacking due to the knowledge gap among HCPs.

Within the EU, differences regarding the curricula exist not only between countries but also on a regional and local level [44]. New academic curricula are urgently needed that take into account the complexity of diseases and that prepare young HCPs to use this new understanding and to practice PM [69]. HCPs need to be trained in the right usage of drugs including new personalised medicines [30]. Another important action for healthcare systems is to invest in the independent drug expert competence in order to ensure that enough experts are able to evaluate swiftly new costly medicines and their potential impact [30].Furthermore, we need to teach the next generation of young professionals not only the science and use of 'omics' technologies but also, equally importantly, the legal, economic and ethical implications of PM [68, 69]. Rather than blaming HCP for not making use of PM we are acknowledging their importance for the timely uptake of PM. Our perspective article indicates, that our current approaches and ways of working will no longer work and that changes and adaptations are urgently needed in order to make full use of the potential of PM.

The future of clinical trials in the era of PM

The rapid progress and developments in next generation sequencing (NGS) have had great impact on rare-disease genetic research over the last century [70]. The sequencing of the whole human genome made it possible to identify more genetic variations among individuals. The number of new identified rare genetic diseases is difficult to estimate since more and more genetic variations are being discovered. It is predicted that the total number or rare genetic diseases will be between 7,000-15,000 [71]. Genomic and epigenomic studies have led to a reconceptualization of the relationship between genotype and phenotype and, consequently, to a new human disease classification [72]. Within this context, disease taxonomy is being fragmented into many different 'orphan' diseases. To use an example, form the field of cancer research, colorectal cancer was for decades considered a homogenous entity and was treated with a number of drugs regardless of the (then still unknown) genetic and molecular characteristics or the tumour. Omics have allowed for a better molecular characterization of the colorectal cancer tumours which are since a decade now being treated with monoclonal antibodies according to their molecular status as to KRAS mutation (wild type vs mutant). But colorectal cancer is ever further better characterized so we practically end up not with one homogenous entity, but rather with many different

colorectal cancers [73]. In effect, this means that distinctive groups of these, unique, colorectal cancers can be defined as an orphan disease. It is to anticipate that this in turn will have further effects. In market terms, it will lead to a market failure as the market share for a newly developed drug will be considerably lower, as compared to the recent past. Furthermore, recruitment of patients for the conduct of randomized clinical trials will be more difficult. As a result, current models of clinical trials which require the participation of hundreds or thousands of patients will no longer be possible applicable due to the small patient numbers [21]. Therefore, as described before, we need to adopt new methodologies and new clinical trial designs such as adaptive pathways. An example is the steadily increasing number of cancer clinical trials in which several drugs are tested based on the individual's specific tumor characteristics [74]. Implementing and adopting new clinical trial methodologies will decrease the burden of ADRs among patients and will consequently lead to a higher quality of life during the course of treatment. N-of-1-trials are presenting another clinical trial approach that is often proposed for PM [21, 75]. 'N=1' trial means that each patient or citizen will act as her/his own control ('I am my own reference point'). A fundamental concept of the 'N=1' trials is the continuous collection of health information over years or even a lifetime based on the fact the health information is dynamic and changing over time and space and thus allowing intra-individual follow-up and comparisons. In order to help physicians and patients in their treatment decision-making process new analytical methodologies are needed which take the changing characteristics and dynamics of health data of an individual into account. A very helpful or even essential tool for this decision-making is the model of 'virtual twins' [1].

Public-Private Partnerships and systematic early dialogue

Another issue that is hindering the uptake of PM in EU healthcare systems is that the involved stakeholders such as industry, innovators, regulators and the end consumers including patients/citizens are working and acting in silos. To overcome this hurdle, systematic early dialogue between all stakeholders across disciplines and sectors is needed. In order to strengthen the diffusion of PM it will be necessary that regulators, the industry and decision-makers will, for example, support timely evidence-informed decisions regarding reimbursement and regulatory requirements [26]. European wide collaboration between

stakeholders will be a key enabler to provide optimal access to PM for patients/citizens. Public-private partnerships (PPP) can facilitate such European collaborations between stakeholders by combining public and private funding. The flagship PPP for healthcare in the EU is the 'Innovative Medicines Initiative' (IMI). IMI is 'Europe's largest public-private initiative aiming to speed up development and better and safer medicines for patients' [76]. IMI is a joint endeavor by the EU and EFPIA, the European Federation of Pharmaceutical Industries and Associations. IMI played an important role in the development of PM in the EU and is one of the key enablers. Furthermore, the aims and goals of IMI are aligned to the ideas of the recently launched International Consortium Personalised Medicine (IC PerMed) [77]. More PPPs based on the idea of IMI are required in the EU to further strengthen the uptake and diffusion of PM. Only when all the key stakeholders are working from the very early phase of the innovation pipeline together, can the hurdles hampering the uptake of PM be overcome in the years ahead.

Our study also highlighted that the uptake of PM is a challenge due to uncertainties regarding pricing and reimbursement across the EU. There is a clear need for more harmonization with regard to HTA within the EU. Not only is there a need for more harmonization but current HTA models need to be adapted to the approach of PM. To address the issue of reimbursement and pricing of PM, an infrastructure is required that provides (other) incentives for insurance companies. Harmonization of assessment tools is also needed because in the era of PM clinical trials with thousands of participants are no longer applicable. The number of rare genetic diseases will further increase in the years ahead, and in order to be able to design clinical trials with small patient groups, more collaboration between European MS is urgently needed. Patients with similar rare genetic conditions will be spread throughout the EU. To conduct clinical trials the European MS need to work closer together by using harmonized tools for PM such as the already existing European Reference Networks (ERNs). Furthermore, our study indicates that health professionals greatly differ in their opinion regarding methodologies to assess the economic impact and the added value of PM. As long as there is no consensus it becomes almost impossible to fully assess most of the implications of PM.

Conclusion

PM promises to improve therapies and to make healthcare systems more efficient. Since it is evident that the current 'one-size fits all' healthcare approach is not fitting the patients'/citizens' needs, a change towards PM can be observed in many areas and on various levels. However, there is still room for improvement regarding the uptake and diffusion of PM among EU healthcare systems. Challenges such as integration of big data, outdated regulation and curricula, promoting health literacy as well as financing and reimbursement issues need to be tackled in a timely manner in order to strengthen the implementation of PM in the EU. We presented several solutions to overcome certain barriers, and it will be of great importance that the EU continues to pay particular attention to the implementation of PM in healthcare systems in the years ahead, ensuring equal access to PM for the European citizens and beyond.

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Executive summary

Background

- The past has shown that 'one-size fits all' approaches do not fit all patients and citizens' needs. Personalised medicine (PM) is no longer an abstract approach. It became reality over the last decade.
- PM is already successfully implemented in several areas such as oncology. However, there is still room for improvement regarding the uptake of PM in European healthcare systems.
- Therefore, we are assessing the system readiness of European healthcare systems to shift from 'one-size fits all' to PM.

Tension for Change

- Due to large varieties in drug response rates among patients, 'one-size fits all' approaches are no longer working and therefore a shift to PM is needed.

Innovation-System fit

- Moreover, in times of big data new ways and tools to integrate health information are essential.
- Knowledge among healthcare professionals and patients' /citizens´ health literacy needs to be improved in order to make full use of the potential of PM.
- The uptake of PM is often limited due to uncertainties regarding the reimbursement and financing of PM.
- Due to outdated regulation, the timely uptake of PM is hindered. New and smarter regulation and legislation is required which take into account the new characteristics and challenges of PM.
- The current ways how clinical trials are designed are no longer applicable for PM.
- Curricula of healthcare professionals are outdated and need to take into account the new complex understanding the 'omics' technologies and big data have taught us.
- Current health technology assessment tools will no longer work for PM.

Assessment of Implications

- As long as there is no harmonization of defining PM, it will be complicated and difficult to develop methodologies and tools to further access the implications of PM such as added value and benefit for citizens.

Future Perspective

- Health data cooperatives (HDCs) could be a truly European and democratic solution to ingrate big data and to make full use of their potential. Furthermore, HDCs will empower the patient/citizen being the owner of all health-related data.
- There is an urgent need to adjust and update the curricula and education of healthcare professionals to the concepts of big data and 'omics' technologies.
- The way how clinical trials are designed needs to be changed or adapted for PM. A straight-forward approach is adaptive pathways.

- Public-private partnerships and systematic early dialogue between all involved key stakeholders across disciplines and sectors are urgently needed in order to strengthen the implementation of PM among European healthcare systems.
- The EU needs to be a leading player in order to strengthen PM across the EU and beyond. The launch of IC PerMed is already a milestone in paving the global way.

Conclusion

- European healthcare systems are partially ready for PM. Several uncertainties such as integration of big data, HCP curricula, health literacy, reimbursement issues and outdated regulation need to be addressed in the years ahead in order to strengthen the timely implementation and uptake of PM.

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CHAPTER 5

5

Develop Policies

Personalized Medicine: What's in it for Rare Diseases?

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Abstract

Personalised Medicine has become a reality over the last years. The emergence of 'omics' and big data has started revolutionizing healthcare. New 'omics' technologies lead to a better molecular characterization of diseases and a new understanding of the complexity of diseases. The approach of PM is already successfully applied in different healthcare areas such as oncology, cardiology, nutrition and for rare diseases. However, health systems across the EU are often still promoting the 'one-size fits all' approach, even if it is known that patients do greatly vary in their molecular characteristics and response to drugs and other interventions. To make use of the full potentials of PM in the next years ahead several challenges need to be addressed such as the integration of big data, patient empowerment, translation of basic to clinical research, bringing the innovation to the market and shaping sustainable healthcare systems.

Introduction

Over the last decades medical treatment in Europe has been based on the concept of evidence based medicine (EBM), which intends that decision making in medical practice is informed by the most reliable scientific information combined with individual expertise of the health professional, as well as patient preferences [3]. In practice, patients mainly receive treatments and medication that have been assessed and tested regarding efficiency and safety in well-designed Randomized Clinical Trials (RCTs), the gold standard in clinical research [52]. Nevertheless, this approach does not take into account the individual molecular characteristics of the patients, which are of great importance for the effectiveness and safety of therapies. Patients do not respond to therapies and drugs in the same way [24,32,49] due to differences in genomic and epigenomic profile [36]. Therefore, the traditional approach of EBM has been critizied as an ineffective 'one-size fits all' healthcare approach [32]. Furthermore, patients who receive drugs that do not fit their needs will either continue to carry the burden of the current health condition or even suffer from more severe health problems due to the accompanied side effects such as adverse drug reactions (ADRs). For example, evidence indicated that the 'one-size fits all' approach in cancer treatment is effective in 25 per cent of the cases [57], however 75 per cent of cancer therapies and treatments are not effective and patients suffer from ADRs and a loss of quality of life during treatment [57].

Not only do the patients suffer from ineffective treatments or even ADRs, the current approach also results in economic inefficiency of healthcare systems across Europe. In addition to the rising morbidity, demographic changes and the burden of non-communicable diseases (NCDs), the low treatment response rate creates an economic burden of more than EUR 100 billion each year [32].

Another traditional approach in health care is the classification of diseases into common diseases (CDs) and rare diseases (RDs) [45]. In Europe diseases that affect less than 5 patients per 10,000 citizens are defined as rare diseases. Across the EU, approximately 30 million European citizens are suffering from RDs. However, emerging 'omics technologies' which

enable sequencing of the human genome have first proven that patients have unique molecular characteristics [33] and second, that each mutation of a tumor is different [55]. Therefore, this new understanding of the complexity of diseases allows to classify diseases more accurate based on their genetic characteristics [44] using next generation sequencing. This results in a new understanding of diseases which makes no differences between CDs or RDs. Finally, according to Boycott et al [4] the large majority of disease causing gene mutations will be discovered by 2020.

At this point, the approach of personalised medicine (PM) joins the discussions. Emerging technologies such as Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES) or Low-Coverage Sequencing (LCS) identified the need for better understanding of the molecular basis of disease and evened the path for PM. Based on molecular interindividual differences, PM applies an understanding that all diseases become rare diseases due to the uniqueness of each patient. For the purpose of the article, we apply this understanding and we do not differentiate between CDs and RDs.

What does personalised medicine mean?

Lately, PM is an often-used buzz word mentioned in discussions regarding healthcare and medicine. PM is an approach that is defined in many different ways among stakeholders and healthcare professionals [18]. Within the literature terms such as genomic medicine, stratified medicine or precision medicine are used interchangeably to describe the approach of PM [55]. Those terms arouse expectations of great medical advances even it is not fully clarified what personalised medicine means.

Since there is no uniform definition of PM, professionals differ in their understanding of the approach of PM, which consequently leads to misunderstandings and miscommunications [53]. While some experts only perceive treatments that are based on genetic analysis and biomarkers as PM [48], others describe PM as an approach in which the healthcare professional bases his treatment decision by taking into account the health status of the

patient and the individual circumstances of the patient. In those cases, it is often referred to as individualized medicine [47].

For the purpose of this paper we refer to the definition of PM of the Horizon2020 Advisory Group for Societal Challenge "Health, Demographic Change and Wellbeing" of the European Commission. The Advisory group defines the concept of PM as 'a medical model using characteristics of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention' [15]. This definition implies the understanding that the healthcare approaches are moving away from the traditional 'one-size fits all' approach.

Potentials of Personalised Medicine

By adjusting treatments to the unique molecular characteristics of the patients, PM has the potential to make treatments more effective and to decrease the economic burden. In order to identify the biological characteristics of the patient and their predispositions to a certain disease, PM applies 'omics technologies'[1,36] such as 'genomics, epigenomics, proteomics, metabolomics, lipidomics' and incorporates real life data of the patients such as environmental and lifestyle information [7,25]. All together, environmental, biological and lifestyle information adds up to an explosion of data soon reaching dimensions of "big data" [2].

PM is already applied successfully in various different healthcare fields [36] and therefore no longer seen as an abstract approach. Over the last decade 'omics technologies' and PM have had the greatest impact on oncology and cancer therapies [55] as well as other medical fields including rare diseases [36,47], cardiology [59] and also for the treatment of infectious diseases [20].

Nevertheless, there is still potential for healthcare systems across Europe to further strengthen the uptake and implementation of PM [47]. Healthcare systems are not making

full use of the potential of PM due to several barriers [25,33,47] and prefer to apply the traditional healthcare approach rather than PM. One reason is the complex and slow moving nature of health care systems as well as the lack of illustrating evidence that is needed to demonstrate the benefit of the PM approach.

Personalised medicine on the European Union Agenda

As one of the main drivers of PM across Europe and beyond, the European Commission (EC) addresses challenges regarding PM, biobanking and 'omics-technologies' in several reports that have been published since 2013 [14,13]. Furthermore, over the last ten years, the European Commission committed around 1 billion Euros of funding to advance 'omics technologies' and PM [14].

One milestone that has been achieved regarding PM, is the launch of the 'Council Conclusions on Personalised medicine for patients' in December 2015 by the Luxembourg Presidency of the Council of the European Union (EU).

Furthermore, with the launch of the 'International Consortium of Personalised Medicine (ICPerMed)' in November 2016, European countries aim to coordinate health research policy to advance the implementation of PM [12]. The initiative brings together the EC, and health research funders and policy making organisations from 28 countries and five regions across Europe and Canada. Within the next few years a roadmap of research action will be defined, which is based on the 'Strategic Research and Innovation Agenda (SRIA)' developed by the EC funded Coordination and Support Action (CSA) PerMed: 'Shaping Europe's Vision for Personalised Medicine' [47]. The CSA PerMed consisted of partners representing European and national key decision makers in research and research policy, healthcare and industry, as well as patient organisations. The PerMed SRIA lists five key challenges and provides 35 recommendations at national and EU level to address those challenges. The following five key challenges for the implementation of PM were identified: 'Developing Awareness and Empowerment, Integrating Big Data and ICT Solutions; Translating Basic to Clinical Research and Beyond, Bridging Innovation to the Market, Shaping Sustainable Healthcare' [12,47].

Challenges to implement Personalised Medicine into healthcare systems

The five key challenges of the PerMed SRIA need to be tackled and solved to promote the effective, efficient and timely implementation of PM in European healthcare systems in a socially acceptable manner. At the moment, aspects such as the integration of big data, the design of clinical trials, financing and reimbursement mechanisms and the active role of the patient/citizen in the decision-making process need to be addressed [9,25]. In this book chapter, we present the five PerMed challenges and discuss the impact of PM on rare diseases (RDs). Furthermore, we suggest potential solutions.

Challenge 1 – Developing Awareness and Empowerment

„Successful implementation of PM will be achieved only if all stakeholders, including patients and healthcare professionals, are empowered and develop the required awareness about PM. The crucial first step is to provide the best available evidence that supports the clinical and personal utility of PM, as well as its economic value to health systems, and to enable better understanding of how the changes brought by PM will impact public health for the benefit of individual citizens and society. Models that enable sharing, ownership and the development of a sense of responsibility towards personal health data, as well as the improvement of PM health literacy, will need to be generated along with suitable common principles, appropriate policy and regulatory frameworks.“[47].

Innovative treatments and therapies emerging in the field of PM are often challenging healthcare professionals (HCPs). HCPs feel overwhelmed and overloaded by the amount of new information, tools and technologies, which PM provides, to support their decision making process [27,36]. This is due to the fact that across the EU, most of the curricula for HCPs are not up-to-date and do not include the new insights and understandings of the complexity of diseases arising from PM [9,25,46]. Issues that are elementary components of PM such as ICT solutions, companion diagnostics, the use of ‘omics’ technologies are often not addressed [36]. Furthermore, great differences and variations occur between the EU Member States and differences exist at national, regional and local level [27]. Thus, there is

not only an urgent need to update current curricula to the new understanding of the complexity of diseases to new innovative therapies and diagnostic tools. Of similar importance is that HCPs are also trained in the legal, economic and ethical implications of PM.

Besides the essential role of HCP education in the implementation of PM, patients and citizens are the key stakeholders that need to be empowered and health literate. The patient is often seen as a passive recipient within the healthcare system [5,43]. For example, patients are rarely scrutinizing the decisions of their general practitioners (GPs) since they trust in their GPs [5]. To strengthen the uptake of PM it is of great importance to change the role of the patient from a passive recipient to an actively involved stakeholder of the decision-making process of his/her health interventions including prevention, diagnostics and therapies [8,43,47]. Health literacy is an important component of the approach of PM. Kickbusch and colleagues (2006) defined health literacy as 'the ability to make sound health decision (s) in the context of everyday life, - at home, in the community, at the workplace, the healthcare system, the market place and the political arena' [31]. Health literacy has gained increasing recognition by the European Institutions and is included in several of their policy documents [56]. The first European health literacy survey was conducted in 2011 as part of the European Health Literacy Project (HLS-EU) in order to measure the level of health literacy within eight Member States (MS) of the EU [56]. The results of the survey highlighted that the level of health literacy greatly differs among the participating countries. One key result of the survey was that people with a lower health literacy level are more likely to suffer from a lower health status compared to people with higher levels of health literacy [5,56]. Patient empowerment and health literacy are key components of the approach of PM.

Solution – Good governance via Health data cooperatives

As potential solution to overcome the challenge of patient empowerment and health literacy across the EU we would like to propose the concept of health data cooperatives (HDC). In order to empower and literate patients to strengthen the uptake of PM, HDCs could be a democratic solution as it is suggested by Hafen and his colleagues [24]. HDCs not only promise to integrate big data in an effective, efficient, timely and socially acceptable way, it also promises to empower the patients/ citizens by being part of and actively involved in the

decision-making processes of the HDC. HDC will make patients/citizens proactive consumers of health also called 'prosumers'. Patients/citizens will be actively involved in research ('citizen science') and be able to actively participate in the decision-making process regarding their health and treatment ('learning by doing'). It can be expected that empowered and literate patients/citizens will be the key in improving the diffusion of PM within the EU and its MS. Furthermore, in comparison to already existing health registers as for example rare disease registries, HDCs are owned and controlled by its members or in other words it is controlled by the citizens. By joining the HDC model, the citizen are not only in the driver's seat, citizens become citoyens. Since the economic value of personal data is immensely increasing and the world largest companies show increasingly interest in the collection of personal data and health data, the risk to suffer from misuse of the data by third parties, HDCs give the patient/ citizen the responsibility for the storing, analyzing and sharing of their health data [24]. As a collective, society as such is the beneficiary of both the economic as well as the health value of the health related data and information. Furthermore, by each member having one vote, HDC members decide how the revenues generated by granting third parties access to their data that they agreed to share (respectively the data commons), should be invested (e.g., in research, in public health, in education, in community outreach etc.) [24].

Challenge 2 – Integrating Big Data and ICT Solutions

„The development of PM will rely heavily on integrated 'big data' analytics and ICT solutions to generate the required knowledge and infrastructure to support the new approaches. Technologies for data capture and management and development of high quality databases will be instrumental, but there will also be a requirement for strategies to make sense of this big data for known and future purposes. Translational research infrastructures and data harmonisation of structured, semi-structured and unstructured data will be a central component of such strategies and should lead to new analytical methods and modelling approaches as well as innovative decision support tools such as in silico simulations to support physicians' decisions. To integrate all these aspects, further European big data and 'big science' frameworks need to be created and supported by suitable legislation." [47].

The world is challenged by a flood of information. In 2020, there will be approximately 5.200 gigabytes of information of each individual across the globe [50]. The European Commission describes this flood of information as 'the big data paradigm' [11]. According to the European Commission 'a defining characteristic of today's data-rich society is the collection, storage, processing and analysis of immense amounts of data' [11]. The world's largest companies such as Apple, Microsoft and Google are more and more interested in the collection and storage of health data [23]. The economic value of personal information is steadily increasing in Europe and beyond [24,51].

By applying 'big data' in healthcare and public health a new understanding of the complexity of diseases did evolve over the last year [1,37]. The analytics of big data make it possible to develop new medicines and drugs which are based on the individual molecular characteristics by integrating genomic information, lifestyle data and environmental information [37]. However, there is still room for improvements to make full use of the potential of big data because the majority of information is unstructured [29], inaccessible and stored in silos [24]. Since health and 'omics data are collected by an increasing variety of sources, the data collection is no longer seen as problem. The storage, analysis and integration of big data is currently challenging the professionals and healthcare systems traditional ways of working [1].

Big Data is commonly defined through its four V's: Volume, Velocity, Variety, Veracity [39]. According to a study by IDC [21,28] the volume of data will double about every two years and will reach 40,000 Exabyte in 2020. This will be more than 5,200 gigabytes per person in 2020. 500 petabytes are currently generated in medicine only due to medical imaging and it is predicted that this number increases 50-fold until 2020 [42]. The 'omics revolution adds to the exponentially increasing data volume and given mobile technologies and sensors, the amount of data per person that can be captured in the future is expected to be in the order of 1,100 terabytes during the person's lifetime [40]. Only 10 % of this data will be clinical data, 30% are 'omics data and the majority with 60% will be associated with exogenous data that captures lifestyle data, environmental data, behavioral data etc. The exponential increasing volume of data also indicates the speed that data is being generated, the second V of big data. Just a simple example illustrates that data is generated in real time: Each patient in an

intensive care unit generates continuous, real time data through all monitoring devices [41]. In our daily lives, mobile sensors are already capturing real time data continuously. The speed in which next generation sequencing can measure the human genome has increased drastically. Furthermore, continued progress in 'omics technologies' and new technological developments that allowed to drastically reduce the costs of the sequencing of the human genome [33]. Since 2001, the costs were cut from US $ 100 million per human genome to around US $ 1.000 in 2013 [55]. The increasing speed and lower costs now enable clinical routine use of the technology [60].

However, the other two V's of Big Data are currently posing the largest challenge. The Variety of medical data has a wide spectrum as indicated before ranging from doctor's letters, radiology reports, laboratory reports, 'omics data to mobile sensor data and even social media. To integrate and correlate all this data with the published knowledge and guidelines as well as best practices and human expertise poses a very large challenge to gain meaningful insight from big data. The more we can integrate lifestyle data from wearables for example as well as social media data or environmental data, the 4th V, Veracity should be considered when carrying out the analysis, e. g. it should be asked how much a twitter feed or google search data can be trusted.

A Solution – Creating fuzziness and making Big Data Analytics actionable

Considering the characteristics and value of Big Data in medicine, it's application is an essential step towards individualized medicine. Cognitive computing and computer tools in general become unreplaceable in how we treat patients especially in the context of rare disease. Mechanistic models with predictive power will soon be able to simulate clinical trials and predict the associated benefits for patient welfare and economy. Many other areas (e.g. the automobile and aviation industries) have already transformed towards a data driven mindset and rely on modelling techniques to improve quality, decrease costs, accelerate development and reduce risks. Often, undiagnosed patients and patients with rare disease suffer from lack of democratization of knowledge meaning that every doctor should have the wealth and expertise of the medical profession at their fingertips. Furthermore, an increased virtualisation of the drug development process – with virtual clinical trials as one of the key

components as well as more personalised therapy and prevention strategies based on patient modelling – might, in our ageing societies, very well be the only alternative to increased rationing of health care provision [32]. At the same time, services and data bases like Orphanet, OMIM, FindZebra, Isabel Healthcare and the IBM Watson technology, to name but a few, will support the physicians in finding the correct diagnosis and serve as assistants to accelerate differential diagnostics in individuals where there is no choice but to look at PM to diagnose and treat the rare disease.

Furthermore, also in this context good governance frameworks such as health data cooperatives (HDCs) will not only improve health literacy and empower patients, the integration of big data into a single system will improve the drug development process for rare disease and consequently will improve access to treatments for RDs.

Challenge 3 – Translating Basic to Clinical Research and Beyond

„In order for PM to reach its anticipated impact on human health and wellbeing, translation of discoveries and communication across the continuum of research are required. A Europe-wide process to evaluate and validate biomarkers, together with longitudinal and in-depth studies to further characterise diseases and their progression would support on-going efforts towards this integration and reclassifcation. The development of new clinical trial designs that are adapted to these new approaches and the integration of preclinical testing with innovative clinical trials may further improve the effectiveness of interventions. Collaborative pre-competitive and transdisciplinary research and cross-sector collaborations need to be promoted and supported by suitable funding mechanisms in order to truly bridge all steps of the PM research continuum.“ [47].

The new understanding of the complexity of diseases and that individuals show unique molecular characteristics is challenging the ways of working regarding the design of clinical trials. Clinical trials have been seen as the gold standard for many years but the traditional design of clinical trials is not applicable for the era of personalised medicine [36]. The traditional approach of designing clinical trials ignores the complexity of diseases [32] and the importance of the integration of big data [8], even in cases when it is known that patients

differ in their response rates to drugs. Developments in epigenomic and genomic studies have led to a new human diseases classification [38]. Since patients' pools are becoming smaller, current clinical trial designs with up to thousands of participants cannot be sustained. N-of-1-trials are often seen as new design for clinical trials in the era of PM [36,54]. The idea of N=1 trials is that each individual/ patient will be used as his/her own control/ reference point. Since each patient will act as his/her own reference point, continuous data collection of health information over years or when it is possible lifelong is needed. Data collection is a dynamic and changing process and therefore it allows intra-individual follow ups and comparisons [36].

As already mentioned above, many of the common conditions we know will be broken down into small subsets of disease with small patient populations that may fit into the definition of rare diseases. This will be possible due to the better understanding of the molecular causes of disease, the development of new biomarkers –static and dynamic- to define the characteristics of each patient, the possibility to integrate different data sources from each individual patient, and other scientific and technological developments. Therefore, we will no longer speak of "cancer" but "triple negative breast cancer", or "PIK3CA mutated squamous cell lung cancer". Centuries ago infectious diseases were considered as one big pot of diseases and nowadays we differentiate very clearly each of them with their differing pathogens and their dramatic differences, the same is already happening or will happen soon in oncology and many other diseases that are still clustered.

Rare or orphan diseases have been facing the challenge of small populations for all long time. They were challenged by clinical trials with low statistical power, the impossibility to gather enough evidence for marketing authorization applications, the indifference from drug developers due to the limited market and disseminated patients with difficulty to establish contact, between each others. In the cluster of rare diseases, all stakeholders joined forces and learned from each other to establish new pathways and overcome these challenges. Instead of reinventing the wheel, we should look at sources and methods developed in the field of rare diseases and apply them to PM, as for example rare disease registers and registries. Such registries make it possible to pool data to gather a sufficient sample size for epidemiological and clinical research even in times of smaller patient populations.

A Solution – Making use of registries

Traditional diseases registries in the sense of 'common disease regisistries' such as cancer registries and rare disease registries have been used many years to collect data and information about diseases and rare diseases and their treatments across Europe. Furthermore, they have served as key tool to assess clinical outcomes and for the assessment of technologies. Rare disease registries are often built up on national or local level to map RDs in certain areas and to collect information regarding the incidence and prevalence of different RDs in those selected areas. Beside general rare disease registers which are holding information and data on many different RDs, registries which are focusing on one specific rare disease also exist in the EU. Data for those disease registries are mostly obtained on a voluntary basis, observational studies and clinical data.

Traditional disease registries and rare disease registers are important tools for making use of PM and further strengthen the implementation of PM in healthcare systems across the EU. For example, often patients that are suffering from rare conditions are lacking access to adequate care. Further, their obtain health data is collected and stored in silos and accordingly inaccessible or incompatible with other data sources.

Pancreatic cancer can be placed at the interface between rare and common diseases. Its incidence is increasing due to factors including demographic change. Pancreas cancer, (still) defined as a rare cancer, has the lowest survival rate of any cancer. Death rates from pancreas cancer are rising across Europe and beyond while those from all other cancers continue to fall. It is predicted that in 2030 pancreas cancer will be the second most frequent cancer. There is no option to control pancreas cancer incidence or mortality by primary or secondary (screening) prevention and only minor advances have been done recently in tertiary prevention under the umbrella of personalised treatment. Recently, the EC identified pancreas cancer as a tracer in bridging "rare" and "common diseases".

As demonstrated for the case of pancreas cancer, harmonized registries including the traditional disease registries as well as rare disease registries, will be major facilitators to understand the complexity of diseases, to conduct clinical trials, to improve the drug

development process and to strengthen the uptake of PM across the EU.

Challenge 4 – Bringing Innovation to the Market

„Bringing innovative PM solutions to the market presents a new set of challenges, including the issue of uncertainty. There will be opportunities to support the development of new risk-based approaches for the evaluation of PM in a context that encourages systematic early dialogue with all stakeholders, including regulators, funders and innovators, providing guidance for companies to enter the market for PM. As is the case for the research continuum, partnerships and innovation networks need to encourage cross-disciplinary and cross-border collaboration, and these would benefit from a transparent 'open Innovation'. Finally, research on appropriate policy, regulatory and legal frameworks would ensure that the new challenges associated with PM are adequately addressed from these perspectives." [47].

In order to place an innovative product in a timely effective way on the market, the inherent uncertainties of innovation need to be considered. The implementation of an innovation to the market has traditionally been seen as a liner process "from research and development to regulatory approval, and then to health technology assessment (HTA) and on to the final reimbursement and implementation decision" [47].

However, the traditional market authorization processes, are not suitable for the approval of PM. The standard development process of drugs takes in average more than 10 years and costs up to a billion dollars [35]. The new understanding of the complexity of diseases makes it possible to design drugs that are more targeted to the patient's needs and therefore more effective than 'one-size fits all' drugs.

A Solution – flexible market authorization methods

Since large phase III clinical trials are not feasible, requirements for marketing authorizations need to adapt to the characteristics of PM. Approaches such as the adaptive pathways pilot launched by the European Medicines Agency (EMA) in 2014 open the way to promising new flexible marketing authorization methods for PM drugs. Furthermore, the consortium

working on 'Medicines Adaptive Pathways to Patients pilots (MAPPs)', lead by the EMA, are evaluating important open questions for the further development and application of flexible marketing authorization methods [35]. MAPPs 'refer to flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits' [16].

Currently underlying outdated regulation is one of the main bottlenecks for the implementation of PM. Most of the relevant legislations and regulations such as for example the data protection regulation and medical devices regulation are currently under revision or have been recently revised. Hopefully the updated versions help to strengthen the uptake and implementation of PM [8, 9]. However, this may be a protracted process, since the revision and regulation in Europe is often an extremely complicated and complex task [9].

In contrast, the clinical trial regulation, which was released in 2014, is a perfect and rare example, how a regulation can be quickly revised. Improved and close collaboration and systematic early dialogue between all relevant stakeholders such as legislators, industry and other interest groups, made this possible [9].

Another regulation that is currently under revision is the data protection regulation [25]. During the time when the data protection regulation was published, it was not foreseeable how fast 'omics technologies' and the sequencing of the human will change the landscape of collecting, storing and analyzing personal data. To strengthen the uptake of PM, it is of great importance that the revised data protection regulation considers the increasing amount of available data and the different technologies by which the data is collected [9]. On the one hand the revision needs to take into account the protection of individuals and their personal information against misuse and stigmatization by third parties [26] and on the other hand research needs to be conducted without being hindered by overregulation. Moreover, harmonization of regulations and legislation is an essential step that is needed to strengthen the uptake of PM [36].

Furthermore, regarding the regulation of rare diseases, we should go one step beyond and asks ourselves if rare diseases should still be considered as a special group of diseases needing

special pathways in the future? As we have seen, many conditions will divide into smaller clusters of disease and fit into the definition of rare diseases. Therefore, we will no longer need to develop special regulations for rare diseases. If we develop and apply them for the entire spectrum of new sub-conditions they will in any case be applicable for rare diseases.

A Solution - Systematic early dialogue

Systematic early dialogue (SED) is of great importance to bring the innovation in a timely effective way to the market. SED between the innovators, the end-users and the decision-makers ensures that innovators consider regulatory issues and reimbursement evaluation needs during the development process and will consequently lead to a more efficient innovation process [36]. SED between all stakeholders decreases the risk of duplication and misalignment of expectations and decreases the time to bring the innovation on the market. In conclusion, by applying SED, the risk that the innovation will end in the 'Death Valley of innovations' will decrease [35]. Furthermore, it brings the view of patients and HCPs into the review process and it provides guidance and clarity for the innovators throughout the whole innovation process.

Challenge 5 - Shaping Sustainable Healthcare

„PM needs to rely on a knowledgeable healthcare system that is able to adapt to these new approaches in a timely and socially acceptable way, and that enables the participation of all stakeholders to increase PM's effectiveness and effciency. Patients and the citizen will play an increasingly important role in adopting and controlling the use of data from electronic health records and in developing prospective surveillance and monitoring systems for personal health data. To ensure the effectiveness of the healthcare system, health economics research relating to PM needs to be supported. In addition a flexible framework for pricing and reimbursement equitable for all patients needs to be developed, leading to an overall healthcare nancing strategy that covers all aspects of PM. "[47].

Reimbursement questions and quality and data integration are important factors, which need to be considered to build and shape sustainable healthcare systems.

Not only is there a need to change the design of clinical trials, to revise outdated regulation and to find ICT solutions to better ingrate big data, there is also an urgent demand to adapt financing and reimbursement mechanisms across Europe and beyond [36]. The traditional reimbursement and pricing mechanisms which are currently in place are making the uptake and diffusion of PM often difficult. Moreover, it is argued by critics that PM will impose rather a higher economic burden for healthcare systems than making healthcare systems more efficient due to the high costs of PM [58]. Since reimbursement systems across Europe are restrictive to pay for PM, EC Member States greatly vary in their ability to provide access to innovative therapies and medicines [17,22,30].

There is a clear lack of harmonization across the EU, due to the fact that the decisions with regard to pricing and reimbursement of pharmaceutical products and diagnostic tools are the responsibilities of the Member States and therefore made on a national or local level [22]. On the other hand, regulatory decisions are the responsibility of the EU [22]. Consequently, the EU is challenged 27 different pricing and reimbursement mechanisms and health technology assessments [34]. Even within countries different mechanisms exist such for example as it is the case in UK. To further strengthen the uptake of PM, harmonization is urgently needed regarding pricing and reimbursement tools across the EU, as proposed in the ENVI report on a harmonized EU assessment of the Added Therapeutic Value of Medicines [6].

A Solution - Managed Entry Agreements

One of the big question marks remains the issue of pricing and reimbursement. For this area, we still need to develop new methods beyond the ones existing for orphan drugs. The sustainability of healthcare systems will be challenged if the incentives and pricing strategies developed for orphan drugs are extrapolated to all PMs. New risk methods must be developed for pricing and reimbursement. The Managed Entry Agreements negotiated between individual EU countries and pharmaceutical companies offer good examples of possible risk-sharing mechanisms. However, their results should be evaluated and they must become transparent before they can be implemented on a larger scale [19].

A Solution - European Reference Networks

The European Commission established for rare diseases so called 'European reference networks' (ERNs) to integrate information on rare disease into one single system across the EU. According to the European Commission those ERNs "should serve as research and knowledge centres, updating and contributing to the latest scientific findings, treating patients from other Member States and ensuring the availability of subsequent treatment facilities where necessary. The definition of ERN should also reflect the need for services and expertise to be distributed across the EU" [10]. The Directive 2011/24/EU on the application of patients' rights in cross-border healthcare sets the rules for patients right to access safe and good quality treatment across the European borders and reimbursement roles. The directive provides a firm basis for increased cooperation between national health authorities. Some provisions address rare diseases. Article 12 foresees enhances cooperation of Member States including the criteria and conditions for ERNs for healthcare providers. The directive aims to identify already established centres of expertise and to encourage voluntary participation of healthcare providers in the future of ERNs.

ERNs can be seen as pilots to integrate information on rare diseases into one single system. If we will manage to integrate information on RDs on a European wide level into a single system by using ERNs, we will be able to harmonize data integration for other sectors as well. Improving data integration will greatly improve the drug development process and consequently the access to drugs for rare conditions.

Conclusions

Emerging technologies such as Whole Genome Sequencing (WGS), Whole Exome Sequencing (WES) or Low-Coverage Sequencing (LCS) have proven that recent failures in stratified medicine show the need for better understanding of the molecular basis of rare diseases (RDs). The continuing advances in scientific knowledge will facilitate the move from the current stratified approach, which relies on static biomarkers of a RD, to a truly individualized treatment, which considers the combination of dynamic biomarkers, dynamic risk profiles,

RD heterogeneity in time and space, the ever changing environment, epigenomics and many other factors that modulate RD phenotype and response to treatment. For example, big data analytics (e.g. IBM Watson) has been identified as a tool for the management of RDs and solving the challenges in the monitoring of a RD of an individual patient over time and space, i.e. taking into account the dynamics of individual patient information.

Conclusions can be drawn, that, on the one hand, the field of RDs has stimulated and pushed discussions and solutions in other fields. On the other hand, the final 5 challenges for personalised medicine, which had been identified by the PerMed SRIA, apply to all diseases including RDs. Since the vision of PM implies that the idea of common diseases will be replaced by unique disease profiles, there are no specific research and policy needs for RDs. This result has enormous implications for European and national policymakers. Instead of asking for separate regulations for RDs, it asks for future regulations and infrastructures (e.g. ERNs), which apply to all diseases in the same way. Rare cancers had been identified as a best practice example and role model to prepare and guide EU Member States in that direction.

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CHAPTER 6

6

Innovation Literacy

Attitudes towards Personal Genomics and Sharing of Genetic Data among Older Swiss Adults: A Qualitative Study

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Abstract

Objective*:* To assess the willingness of older Swiss adults to share genetic data for research purposes and to investigate factors that might impact their willingness to share data. ***Methods:*** Semi-structured interviews were conducted among 40 participants (19 male and 21 female) aged between 67 and 92 years, between December 2013 and April 2014 attending the Seniorenuniversität Zürich, Switzerland. All interviews were audio-recorded, transcribed verbatim, and anonymized. For the analysis of the interviews, an initial coding scheme was developed, refined over time, and applied afterwards to all interviews. ***Results****:* The majority of participants were in favor of placing genetic data to research's disposal. Participant's motivations to share data were mainly driven by altruistic reasons and by contributing to the greater good. Furthermore, several factors which might impact the willingness to share data such as sharing data with private companies, generational differences, differences between sharing genetic data or health data, and sharing due to financial incentives were highlighted. Last, some participants indicated concerns regarding data sharing such as misuse of data, the fear of becoming a transparent citizen, and data safety. However, 20% of the participants express confidence in data protection. Even participants who were skeptical in the beginning of the interviews admitted the benefits of data sharing. ***Discussion:*** Overall, this study suggests older citizens are willing to share their data for research purposes. However, most of them will only contribute if their data is appropriately protected and if they trust the research institution to use the shared data responsibly. More transparency and detailed information regarding the data usage are urgently needed. There is a great need to increase the engagement of older adults in research since they present a large segment of our society – one which is often underexamined in research. ***Conclusion****:* Increased focus on general public engagement, especially of older adults, in scientific research activities known as "citizen science" is needed to further strengthen the uptake of personalized medicine.

Keywords

Altruism, Citizens science, Data protection. Data sharing, Direct-to-consumer personal genomics, Older adults, Personalized medicine, Privacy, Research participation

Introduction

Healthcare systems are in the process of being transformed by the emergence of "omics" technologies [1]. Genetic testing became one of the cornerstones in the development and implementation of personalized medicine (PM) [2]. PM "is a medical model using characteristics of individuals' phenotypes and genotypes (e.g., molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention" [3]. Additionally, developments in "omics" technologies have led to a more detailed understanding of the complexity of diseases, which allows a more accurate classification based on their molecular characteristics [4].

A major breakthrough with regard to the implementation and realization of PM was the first sequencing of the human genome in 2001 [5]. Since then, the costs for sequencing the human genome have steadily decreased from USD 100 million in 2001 to USD 1,000 per sequencing in 2016 [5–7]. Not only have technological developments led to immense reductions in costs, they have also enabled the sequencing of the human genome in less time [5]. Accordingly, commercial companies sensed the potential and have started to offer direct-to-consumer personal genomics (DTC-PG) [8, 9]. These companies are offering personal genetic risk profiles and genomic testing outside the traditional healthcare systems and clinical settings [8, 9]. Via their websites, saliva-based tests can be purchased and based on the returned samples, selected single nucleotide polymorphisms are scanned for a variety of different complex diseases [8, 10].

Proponents of DTC-PG argue that engaging with one's own genetic make-up and risk profiling will educate the consumers regarding genetics [11]. Citizens will become empowered to make informed decisions on health and treatment, to improve their health behavior with regard to diseases which were identified through the DTC-PG tests [8, 12]. Furthermore, they believe that DTC-PG tests will enhance the autonomy of citizens since the tests are providing the customer with valuable information [13]. However, in order to empower the customer, the clinical utility and validity need to be assured [14].

Next to the potential, the rise of DTC-PG companies over the last couple of years have provoked controversy. In general, opponents express three major concerns regarding DTC-PG tests.

First, they often criticize and question the analytical validity and clinical utility of the DTC-PG tests [10, 11, 15]. Clinical utility here is described by Grosse and Khoury [16] as "the ability of screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results." However, in the context of DTC-PG tests, it is argued that beside the discoveries enabled by genome-wide association studies and gene-environment interaction studies, there is still a lack of information regarding the genetic associations with certain common diseases and how this interaction shapes risks for diseases [17]. Due to this lack of evidence, in 2013 the US FDA stepped in and restricted one of the leading companies in the field, 23andMe, to limit their health risk information to a set of information with FDA-approved evidence. However, other companies are still unrestricted and uncontrolled in terms of delivering low-evidence-based information.

Second, related to the questionable clinical utility, it is criticized that DTC-PG tests are provided without the involvement of healthcare professionals. Discussions differ over whether DTC-PG risk information would improve health behavior and disease prevention or might result in psychological distress and will ultimately lead to increased healthcare consumption for clarifying tests. First results based on populations of early adopters indicate increased healthcare consumption [18], diverse findings in terms of behavior change and self-efficacy [19–21] and differing levels of understanding of genetic information, and increasing anxiety based on demographics, literacy, and education [22, 23]. Some argue, in order to help the customer and to minimize misunderstanding, the commercial companies should provide adequate information regarding genetic counseling and what it means. Furthermore, counseling needs to be available before as well as after test and needs to be done by trained healthcare professionals [24]. It is the companies' responsibility to provide a sufficient amount of information, provide genetic counseling, and not rely on healthcare systems to provide this information and counseling [24].

The third main concern regarding DTC-PG is related to storage and use of the customers' samples and genetic data [25]. Opponents are criticizing that companies do not clearly state on their webpages how the data will be handled and in how far the companies are applying anonymization procedures to protect the participants' privacy [10, 26]. Even though the companies are trying to be transparent with regard to their research, it is questionable whether the participants are fully aware of those activities and understand them [26]. Furthermore, the commercial companies are often using the genetic data obtained from their customers to conduct in-house research or to sell the data to third parties without informing the participants adequately. Often, the scope of research the company will conduct with the genetic data is not specifically described [26]. Previous studies investigating participants' attitudes and motivations indicated that participants are willing to share their genetic information, notwithstanding concerns regarding data protection, data safety, privacy issues, misuse, and governmental involvement [27, 28]. The main motivator of sharing data was the opportunity to participate in research [29]. Participants want to share their information to improve scientific knowledge and to help advance medical research [30, 31]. Furthermore, they are willing to actively participate in research to learn more about their genetics and their risks for developing certain diseases [29, 30]. In general, participants believe that genetic research will improve the understanding of the complexity of diseases and treatments [29]. Next to altruistic reasons, participants were motivated to donate their genetic data for research to receive financial compensation [29]. However, participants stated that they are only willing to participate in research when sharing data does not pose a threat to public trust [32]. Sharing sensitive data such as genomic information creates a tension in political discussions regarding advancing research and protecting the data and assuring privacy to the participants [33]. Therefore, it is important that regulations are in place, which protect the participants against misuse of their genetic data, but that research will not be hindered or slowed down due to overregulation [34].

Progress in the field of PM is highly dependent on access to genetic data and the willingness of people to share genetic and phenotypic data to advance research and fill the gaps of evidence on hypothesized associations between genes and diseases. To date, a number of studies have sought to understand attitudes of people to share their DTC-PG data and donate data for research purposes [35]. However, evidence is mainly based on early adopters,

experts, or healthcare professionals' attitudes regarding the potential and barriers to DTG-PG data sharing. To increase the power of the existing datasets, it is of great importance to assess the layperson's motivations and concerns regarding DTC-PG and their potential participation in genomic research [35]. Furthermore, while patterns emerge for the American population in the age range of 20–60 years [35], there is a need to conduct studies in the European context and to enlarge the age range – especially towards the increasing older segment of society [9].

Older adults present a segment in society which is increasing at tremendous speed due to medical advances and the aging baby boom generation [9]. To date, older adults have been underrecruited, and their potentially distinct motivations, attitudes and concerns towards DTC-PG and data sharing are missing in the discussion.

Following up on our initial quantitative investigation on attitudes towards personal genomics among older adults in Switzerland [9], this study aims to further fill the gap of knowledge with a focus on data sharing and research participation. Our previous survey was conducted among 151 older adults, (mean age 76 years, range 60–89 years) attending the Seniorenuniversität Zürich in Switzerland [9]. The results of the previous survey highlighted that one-third of the population was aware of PG and more than half expressed an interest to undergo PG. Underlying motivations included the interest in their own genetic make-up and the chance to participate in research. Concerns towards PG included the fear of worrisome results and questionable validity. Only a minority mentioned privacy-related reasons. Finally, participants preferred clinically based research and welcomed the opportunity to donate genomic data for research.

To further explore and understand the complexity of the factors which are influencing participants' high willingness to share their genomic data, qualitative semi-structured interviews were conducted. To advance the debate in the issues described above, the paper aims to provide a more systematic understanding of the following research questions:

1. Are older adults willing to share genomic data for research purposes, and what purpose do they attach to the practice of data sharing?
2. What is older adult's perception regarding the influence of sharing data with public

or private institutions, generational differences in data sharing, differences between health and genetic data, and the motivational role of incentives for data sharing?

3. What are the main concerns for older adults with regard to data protection and data sharing?

Methods

Sampling and Recruitment

Participants were recruited within the Seniorenuniversität Zürich, a wide-ranging continuing education program for seniors. During one of the lectures, the study was presented, and volunteers were invited to leave their contact details. According to the collected demographics, the participants can be characterized as seniors with an above average level of education and high levels of social participation and engagement in physical, cultural, and social activities. All participants were informed about the studies' aims and the voluntary and confidential basis of their participation. Written informed consent was signed by the participants.

Procedure

Approval for the study was obtained from the local ethical committee in Zurich. All older adults took part in a semi-structured interview at the Centre for Biomedical Ethics in Zurich. Each participant was reminded that their responses would be regarded as confidential and that they could terminate their participation in all or part of the study at any time. Interview guides were designed and pretested in a pilot, to address explorative and discovery oriented key topics, as well as structure the data collection process. The semi-structured interviews were conducted face to face and were held in German (Swiss German). The interviews lasted from 40 to 60 min. Participants were encouraged to express themselves within their own frame of reference. All interviews were audio-recorded, transcribed verbatim, and anonymized. The interviews were performed by applying a specifically designed interview guide. Questions intended to explore of attitudes, values, and concerns regarding the relationship between genomic testing, research participation and data sharing. The majority of respondents are unlikely to have had real experience in genomic testing and they were

asked to imagine the possibility of a personal genomic test and were asked for their hypothetical motives for sharing genetic data. Furthermore, demographic information was requested.

Analysis

First, two researchers (L.M. and S.S.g.H.) coded 20 interviews each, independently, and afterwards a cross-check was performed. Differences in codes and interpretations were discussed, refined and adjusted in order to agree on a final code set. The first coded interviews were reanalyzed after the authors agreed on the final set of codes. The final set of codes was assigned to three main parts including seven overall themes. The authors identified the following overall parts: Part 1, "Willingness and Purpose of Data Sharing," including the themes *willingness to share data with research, what purpose will shared data be used for*; Part 2, "Factors influencing willingness to share data," including the themes *differences in willingness to share data with public or private institutions, generational differences in willingness to share data, differences in willingness to share genetic data or general health data, beliefs and concerns regarding receiving financial incentive for sharing data*; and Part 3, "Concerns, Data Safety and Data Protection," including the theme *issues regarding data safety and concerns regarding data protection.* Furthermore, the authors decided to summarize and present the results in three main parts: Part 1, willingness to share data and purpose of data sharing; Part 2, influencing factors for data sharing; Part 3, concerns, safety, and protection.

For the purpose of this publication, the citations were translated by the authors from German into English language and then checked by a native speaker.

Results

A total of 40 participants agreed to conduct an interview. The mean age of the participants was 71 years ranging from 64 to 92 years. Twenty-one women (52.5%) and 19 men (47.5%) were interviewed between December 2013 and April 2014.

Part 1: Willingness to Share Data with Research and Purpose of Data Sharing

Data Sharing: The Majority Is in Favor of Sharing Data with Research and Anonymity is Important

The majority of participants were very much in favor of placing data to research's disposal. Descriptively, 22 out of 40 would explicitly share their data and trust in research. The focus of their argumentation was to contribute to scientific and societal development and progress. Participants explained that through the contribution of data to research they would hope to support science and society on a macro-level and thereby help others on a micro-level. When participants were asked about their willingness to share data with research, they responded, for instance, as follows:

Quote 1**:** *Yes, I would share my data, since that supports science. I mean, I do not need the data for myself, but if it helps society, it would be nice to be able to contribute something.* (No. 16, male, age 74)

They pointed out, that large volumes of data are important for reliable findings and expressed the importance that many people should contribute. Furthermore, they saw a long-term benefit for themselves in contributing data to science. On an emotional level, participants expressed pride towards contributing to the greater good of science. Interestingly, the comparison with organ donation was quite frequent and accompanied by the argument that contributing genetic data is a good alternative to donating organs, since, even though they are willing to donate their organs they might be too old, which is not the case with genetic data.

Quote 2: *Ah, I would share my data with science without any hesitation, if I were, younger I would even donate my organs to help others (..).* (No. 3, male, age 92)

Finally, one participant argued that a broad collection of genetic data might support in detecting crime.

The remaining approx. 45% participants did admit that sharing data would make sense, but did mention certain circumstances which should be fulfilled. Particularly for the 18 more

concerned participants, who believed it was important to remain anonymous and did not want third parties to access the data. Major concern was the fear of being monitored and controlled and being the "transparent citizen." "NSA" was frequently mentioned to illustrate the case of controlling society. It "depends where it goes and to whom" and overall the "internet" or "the boss" were very much mistrusted.

Quote 3**:** *Sharing data has two sides, on the one side it can improve healthcare and offer new solutions, on the other side private genetic information can be misused.* (No.28, male, age 70)

Finally, some mentioned that they did not yet fully understand the utility of genetic data and therefore are skeptical and cautious or acknowledged the difficulty of restricting science.

Quote 4: *No, I would not share my data. However, we should not prohibit science, otherwise it will all happen in the dark and the consequences might be even more lethal than if it would have been official.* (No. 13, male, age 71)

The Purpose of Data Sharing: Participants Want to Contribute to the Greater Good to Improve Society

When participants are asked to describe the utility behind sharing their data, the participants shared the overall opinion that they do something for the greater good. Twenty-five percent of the participants argued that sharing data will help to find new treatments and to improve diagnosis.

Quote 5: *…if you can improve treatment or…ehh.. you could detect problems early to prevent something or to reduce consequences or something like that. Yes, why not.* (No. 19, male, age 68)

Moreover, two participants believe that data can be used to show tendencies and can help to solve and indicate health problems from the beginning. It can help to detect certain risks for diseases and to improve prevention.

Quote 6: *I think it is especially valuable in case one can prevent it by acting early, that could even start in childhood, I regard this as very valuable.* (No. 20, male, age 73)

Another 25% of the participants share the opinion that, by contributing to science they can help others and that sharing data is important for scientific developments. They believe that sharing their data will help the next generations and will improve the public health of the population.

Quote 7: *If I place my data at disposal, I expect that insights will develop out of the data and that the obtained insights will serve everybody.* (No. 36, male, age 79)

A few of the participants are willing to share data with science but are not interested in what will happen to the data afterwards. One participant just highlighted that if his data makes a great contribution to science and helps towards a breakthrough in research, it would be nice for his self-confidence. Another argued:

Quote 8: *I would not want to know any further details. I would give it to research and they are free to use it and do more research, but that is not of my interest.* (No. 16, male, age 74)

One participant argued that genetic health information should already be collected from newborns (for example blood samples) to make predictions about their health. Furthermore, the participant argued that collecting blood samples from newborns and storing the samples in a big data bank could help in emergencies to determine the identity of persons in case no identification is available/exists.

Quote 9: *If you ask me, one should start with testing with newborns in the hospital and after testing, data should be saved in a database, just as we test blood group a or b.* (No. 21, male, age 72)

Part 2: Factors Influencing Willingness to Share Data

Difference in Willingness to Share Data with Public of Private Institutions: The Majority of Participants Clearly Oppose Data Sharing with Private Companies

Fear and distrust was expressed that the private companies only represent financial interests. Data sharing with universities or hospitals was perceived as safer, although there was a preference in sharing data with universities as compared to hospitals. Twenty percent of the participants, share the opinion that it does not matter as long as the data is anonymized.

Arguments related to the positive attitude of sharing data with universities include, that universities are serious, publically regulated institutions which are aiming towards the benefit of society. Hospitals are trustworthy and need data to improve quality, performance, and treatment. Private institutions in contrast are seen as uncontrolled, less serious and profit-oriented. Overall, money causes people's mistrust, they argue that privacy and data protection are not guaranteed, since the private institutions might sell or distribute data for financial gains.

Quote 10: *Personally, I would prefer the academic part of research, because with the others… I see the economic success of the company and… if there wouldn't be any potential, they would not do it.* (No. 13, male, age 71)

Finally, there was also a small proportion who did not express any concerns, as long as the data is anonymized or not available online. Three participants even explained that they do not have any concerns at all and that any kind of data sharing would help society to develop and progress.

Quote 11: *If it is anonymous, I mean, there is so much data around everywhere, I guess nothing worse can happen or circulate... that's why I do not really care. I mean, we are already pretty much transparent.* (No. 14, female, age 77)

Changing Attitudes Regarding Sharing with Age: A Small Majority of the Participants Agreed that There Is a Difference between Generations on the Attitude towards Data Sharing

When participants were asked whether they see or experience different attitudes towards data sharing, most participants agreed that there is a difference; however, the opinion about the direction of difference was mixed among the participants.

Quote 12: *When you are young you think different. Life is still ahead of you and you do not worry about tomorrow. You do not consider that you may drop dead tomorrow – it is a very different perspective and now, I am continuing on the life's journey and some things changes.* (No. 7, male, age 83)

Overall, people shared the opinion that younger people grew up in a technology-oriented generation and are therefore more open and used to sharing data (e.g., social media). Younger people's openness towards data sharing is motivated by returning benefit of data sharing. On the other side, participants argue, nativity might be at play, since they do not have the life experience of negative consequences. Furthermore, the data of young people is regarded as more valuable compared to data of older adults. Regarding older peoples' data sharing practices, the majority argued, that older people are more skeptical and careful regarding their data sharing practices.

Quote 13: *The older generation is just more critical regarding data transfer. The younger generation grew up with this and for them it is self-evident that you send data back and forth.* (No. 39, female, age 71)

However, there is also a proportion arguing towards the opposite direction: since young people are still facing a long future, they are more careful and cautious regarding data sharing as compared to older adults.

Quote 14: *Yes, I mean the younger generation could be more critical, since they still have all their lives ahead. Now we elderly, we think... we only have a couple of years left and it doesn't matter that much... but for the younger generation it could be a problem if they disclose too much.* (No. 31, female, age 80)

Or some argue that instead of age, personal preference or education might be more decisive factors.

Quote 15: *I think, no matter whether young or old, there are some like myself, who do not care, and there are, in both groups, people who do not want to share anything. And if you have to share something, then, for sure it has to stay top-secret.* (No. 15, female, age 71)

Furthermore, they argued that higher-educated people are more aware of the consequences and better informed on protection mechanisms, less educated people are more likely to fall into data sharing traps initiated by marketing initiatives. Finally, some argue that data sharing attitudes and data sharing practices might diverge and some reported an ambivalent behavior of data sharing in society.

Quote 16: *No, no, I am pretty liberal, I actually always wonder about the fact, that people are sit in the metro and scream all their personal information into their IPhones and are then surprised when everything is public. I don't have anything to hide. I don't have any constrains, no constrains at all.* (No. 18, male, age 68)

Differences in Willingness to Share Genetic Data or General Health Data: Half of the Participants Would Not Differentiate between Sharing Genetic Data or General Health Data

Regarding the question of whether participants would differentiate between sharing genetic data or general health data, the participants' opinions diverge. Fifty percent of the participants share the opinion that they would not differentiate between sharing genetic data or general health, since both types of information are important for research and contribute to the overall health state. However, both should be shared in a confidential manner, since they are both susceptible to misuse, and therefore anonymization is important for both kinds of data.

Quote 17: *No, not really – I think both are interesting – actually, I think both can contribute to science, therefore it doesn't make any difference to me.* (No. 2, female, age 81)

The remaining 50% of the participants argued that there is a difference between the two types of data. The underlying reasons for genetic data having even better protection is that

genetic data contains highly sensitive information about future health states and 12.5% of the participants believe that genetic data contains more private information.

Quote 18: *The genetic data, that is really my secret, because there could be any kind of information on diseases…genetic data that is really something very personal.* (No. 39, female, age 71)

A small proportion of participants share the opinion that genetic data is more difficult to understand for non-experts. Genetic information is difficult to define and too complex to interpret. Health information is instead described as facts easier to understand.

Quote 19: *Health data are real, in case I have something it is a fact, genetic data is still, still a little difficult to grasp and hard to define, for me as a non-expert. When I have a disease, I do have that disease, then I can look it up and read what it is… with genetic data, with data from the genes I receive and so on, that is very complex… that is less easy to understand for the average person.* (No. 18, male, age 68)

Beliefs and Concerns regarding Receiving Financial Incentives for Sharing Data: Financial Incentives Might Create False Incentives

Almost half of the participants hold the opinion that sharing data should not be financially reimbursed or incentivized. Twenty-five percent of the participants believe that data sharing should not be reimbursed since it benefits the general public and can help to improve the health of the public.

Quote 20: *…it has something to do with idealism. You donate something and science is supposed to make something out of it and in the end, everybody should benefit.* (No. 14, female age 77)

Twenty-five of the participants believe that financial incentives will create false incentives and as soon as money is involved, the integrity of the study becomes questionable. Rather than

being paid for sharing the data, 5 participants shared the opinion that it would be enough for the travel expenses to be covered or that food and snacks be provided.

Quote 21: *It would have the disadvantage, of financial interests becoming too prominent. If somebody lives somewhere in the mountains and needs to come all the way to Zurich, it would be appropriate to cover the travel expenses.* (No. 7, male, age 83)

Furthermore, 25% of the participants argued that no money should be paid for sharing data and compare it with the scenario of blood and organ donation, which are also not financially reimbursed.

Quote 22: *No, no, no, for donating blood you do not receive anything either. In this case it is even different... somebody will benefit and science will benefit, since they need the material. Where else should they get it from if not from us?* (No. 8, male, age 69)

Fifteen percent of the participants hold the opinion that financial reimbursement is acceptable if the person who wants to share data relies on the money.

Quote 23: *No, I am in the lucky position to not be dependent on the money. Others are selling their kidneys and… they have to make money somehow.* (No. 16, male, age 74)

Overall, 25% of the participants share the same critical opinion that money will increase the risk of misuse, and that people will become buyable and that financial incentives violate any ethical principles.

Quote 24: *It is a contribution to the overall wellbeing of society. Being healthy is already a gift, and there is no question in donating one's data. Reimbursement is not necessary.* (No. 13, male, age 71)

Part 3: Concerns, Data Safety, and Data Protection

Concerns: The Main Expressed Concern Is the Danger of Abuse

The majority of participants shared similar opinions regarding concerns that could emerge due to genetic testing and data sharing. The main concerns include, that their data could be abused and that strict data protection is necessary. They fear of becoming a "transparent citizen" which leads to the chance of misuse, selling data or leaking data to people or institutions that might gain unpredictable powers by it (health insurance, work employer etc.). In the context of genetic testing and family planning, the information might even enable us to "play god," by making decisions on the value of life or being socially pushed into questionable directions, as for example the question of abortion and the danger of designing artificial humans.

The main concerns the participants highlighted were related to misuse of data, discrimination because of genetics, access to data by unauthorized companies, and manipulation.

Some (12.5%) participants shared the opinion that they would only be willing to share their data if data protection and anonymization are provided.

Quote 25: *Mistrust, that the data will actually be used as discussed, anonymized and not accessible for other interest groups like medical... the pharmaceutical industry actually. There could be many more reasons, just general mistrust.* (No. 15, female, age 71)

Furthermore, participants highlighted that some people are afraid of science and therefore not willing to share data.

Quote 26: Y*es, one could say... ehh...one could mistrust the entire scientific community, the genetic science, just as it has been discussed to abolish gun-bullets...yes, there is the fear of science, that is true.* (No. 5, male, age 72)

Fourteen percent of the participants mentioned as a concern that people are afraid that unauthorized people will use the data. Furthermore, three participants are concerned that data will be used for manipulation of genes and that it will be used for military purposes to design the perfect human.

Quote 27: *So, my only concern is, it has once been talked about, that it could be used to create the perfect human... or... that everyone would have blue eyes or a standard type or for military purposes. Of course, that is a big topic. I would be absolutely against that.* (No. 11, female, age 69)

Fourteen percent of the participants are concerned that their genetic makeup will be used to discriminate against them, i.e. health insurance organizations will ask for higher premiums because of certain genetics.

Quote 28: *Or when the information is forwarded to the health insurance and the risk increases the premium will increase… yeah... that would be discrimination, because I did not chose my genes on purpose.* (No. 9, female, age 70)

Two participants are concerned that an employer will get access to the genetic data and that the employees could lose their job because of his/ her genetics.

Quote 29: *Yaa, the people who suffer from a disease, they want... they fear that it will become public, I think it is connected to their job, for example if they have an increased risk for diabetes, they might not get the job, since the employer might be worried that they will get sick, I guess that plays a role.* (No. 35, female, age 71)

Two of the participants are concerned that due to genetics the people will become "transparent citizens" and that all kind of personal information will become available and accessible.

One of the participants pointed out that we do not know at the moment what the negative side effects are since technologies are still developing and even if someone tries to do something about it to stop it, it will happen anyway.

Quote 30: *Yes… it probably does have its dark sides, but we do not know yet; however, I think it is something that will come for sure and that we cannot slow down. It will just happen, just as the computer just came, you cannot be against it.* (No. 31, female, age 80)

Two participants draw parallels to World War II. In detail, they argue that privacy protection is unable to guarantee safety and is too weak.

Quote 31: *It does need regulation... to prohibit that a single person can act populist and might receive dictatorial power and everybody will follow. In that case it would matter with what type of genes you were born with and in the case you were born with the wrong genes, you might be regarded as unworthy life. Actually, there should be a dialogue with ethical and philosophical experts. And even politicians. It has to be an interdisciplinary discussion.* (No. 9, female, age 70)

Data Safety and Data Protection: Confidence in Data Protection

Twenty percent of the participants express confidence in data protection. They feel the privacy discussion and the discussion on the doctor's confidentiality are exaggerated and that privacy regulations should be trusted. Especially in academia, data is saved under ethical standards, and surveillance and anonymity is guaranteed. A proportion among them even expressed that they have nothing to hide at all, arguing that they personally are not "interesting" and argue that privacy activists are anxious.

Quote 32: *The privacy advocate is active wherever he can be; however, we know that he is powerless and does not know what to do. We are unable to tackle the problem and these are all reasons for caution and this preoccupies people against seeing and enjoying the advantages of progress. As long as people do not have problems, they are against everything, however, as soon as they do have a problem, they want to benefit. But this comes at a cost. To act in a protected manner is very important; however, I think it is very important to continue along this path.* (No. 20, male, age 73)

Overall, 17.5% of the participants argue that more transparency and more detailed information on what is happening with the data are needed. On this basis, people would be more literate and able to better organize their data privacy. However, on a larger scale, they argue that data sharing is becoming an interdisciplinary question with the need for more

ethical surveillance and multiple points of control. Finally, they say that more laws are necessary to control and protect.

Quote 33: *I really do not have any problems with these databases and if the data of people is saved in such a database. However, lots of people are privacy apostles and want to keep everything secret, sometimes without any reason. There are many who are too afraid to share their data.* (No. 19, male, age 68)

Furthermore, in the course of the interviews, even previously skeptical participants admitted the benefit of sharing data and expressed their willingness to share data. However, certain requirements endured this change in attitude towards data sharing: under the guarantee of anonymity and privacy protection, people were very generous towards sharing data. Another requirement was the seriousness of the receiving institution and the information given on the data sharing practices, purpose, and aim. Furthermore, participants underlined the importance of the voluntary basis of data sharing practices, since it is everybody's own responsibility what data they want to share under what circumstances:

Quote 34: *… it has to be voluntary, because we have to respect different personal inhibition thresholds in terms of sharing data… you cannot force someone or share data behind someone's back. Out of respect.* (No. 18, male, age 74)

Finally, in many cases, the rater could sense a little insecurity in responses regarding circumstances of data sharing. People expressed that they are still too illiterate in the field of genomics to correctly estimate the risks or circumstances which might be necessary to safeguard data sharing practices.

Quote 35: *…I think it is still way too early. The topic has not reached peoples' awareness.* (No. 20, male, age 73)

Discussion

To realize the full potential, and strengthen the uptake of PM, genetic data is increasingly important [1]. This study has been conducted to gain insights into the prevailing assumptions and behaviors people exhibit when dealing with genetic data sharing. For the present article, results of 40 semi-structured interviews have been presented and discussed in three parts: (1) willingness and purpose of data sharing; (2) influencing factors in data sharing; and (3) data safety.

Part 1: Willingness and Purpose of Data Sharing

Our findings revealed that the majority of participants were willing to share their genetic data, driven by altruistic motivations of wanting to contribute to the greater good and accelerating research to improve the health of society. Participants shared fairly similar views on the potential benefits of genomic data sharing, such as finding new treatments and improving diagnosis. Furthermore, they did not expect an immediate impact or beneficial return but ultimately wanted to help the next generation.

This is in line with the findings of our previous quantitative investigation [9]. In a review, Shabani et al. [28] identified five studies showing that accelerating advancements in research and maximizing the value of resources were underlying reasons that tipped the balance and motivated participants to share their data [28]. First, Kerath et al. [36] showed that participants had a generally positive view of genetic research and valued their personal participation positively. Second, in a focus group study by Trinidad et al. [33] participants valued the opportunity to share de-identified genotypic data and were motivated by the opportunity to improve the accessibility of data for researchers, promote scientific advancement, research efficiency and health benefits for others. Third, within a focus group study by McCarty et al. [37] participants were motivated to share data to help people with similar problems and contribute to the advancements in medicine to ultimately serve the greater good. Similar motivations were highlighted in the fourth study by Kaufman et al. [38] among 931 US veterans. The veterans shared the opinion that participation in a test would create a feeling of respect and involvement in the overall scientific development. Fifth, McGuire et al. [39] conducted focus groups with patients and controls from a genetic study

of epilepsy and concluded, based on the findings, that genomic information should not be publicly released without explicit consent from research participants. Furthermore, four quantitative investigations highlighted that the main motivations for participants to share genetic data were, first, based on altruistic reasons, to promote research and, second, the desire to learn more about ones' genetic make-up and their influence on one's personal health risks [9, 13, 29, 31].

Our data confirms the extensive investigations and findings that the moral duty of contributing to research is a major driver for people to undergo genetic testing. Generally, altruism as the antonym of egoism, is the principle and practice of acts which benefits others, rather than the actor him or herself. Apparently, being altruistically motivated to support scientific advancement is explicitly amongst older participants. Older participants generally expressed stronger trust in the research enterprise and greater interest in serving the common good, as compared to younger participants [33]. For genetic research, sharing data would be an altruistic act in the way that one contributes towards publicly accessible medical advancements which ultimately benefits society. This is potentially motivated by an increasing concern with age to care for the next generation which has previously been defined by Erikson et al. [40] as "generativity." Finally, having the chance of donating data for research is an opportunity for giving back to society and therefore adds purpose to the act of sharing data. Therefore, older participants indirectly benefit from participation through feelings of compassion, humanity and a sense of appreciation through having contributed personally to the common good and/or the next generation.

Part 2: Data Sharing

To receive a more detailed overview of the preferences in (genetic) data sharing practices, the following fields were investigated in more detail: (1) data sharing with public or private institutions; (2) differences among generations; (3) differences depending on characteristics; (4) difference between health and genetic data sharing; and (5) the perception towards receiving financial incentives for data sharing.

Data Sharing with Public or Private Institutions

Fear and mistrust regarding privacy and data protection was expressed towards private companies. They are perceived as uncontrolled, unserious, and profit oriented. Public institutions, in contrast, were described as serious and governmentally regulated institutions which are aiming towards the benefit of society.

Distrust accompanied by concerns of lacking federal oversight of private companies has previously been highlighted by Trinidad et al. [33, 41]. In contrast, trust in the institution was an important factor in participants' endorsement of data sharing [28], since trust often outweighs potential concerns [12]. Previous research considered trust as an antecedent, a consequence, a mediator or moderator to privacy concern and the intention to share data. For example, Critchley et al. [12] reported that participants trusted in the validity, after care, regulation, and privacy of a genetic test provided by a GP in contrast to tests provided by a DTC-PG company. The participants believed that private companies are less able to protect their privacy and to provide them with adequate counselling once the test has been performed. Furthermore, participants expressed reservations about sharing data with for profit-oriented organizations since this would conflict with their original altruistic motivations of research participation for the societal benefit [33, 41]. Private companies rely on financial returns which might be obtained through data transfer revenues. As previously described by Rogers [42], the reservations towards data sharing can evolve through an evaluation of risks, leading to protective behavior. In this study, perception of risks manifested as privacy concerns, validity concerns, lack of transparency, and risk of using data to target fiscal goals.

The explosion of DTC genomic companies raises pressing questions about whether commercial firms are gaining access to health data without the necessary accountability [31]. Many of the DTC genomics companies use the data they obtain from their users for their own research purposes or sell data to third parties which are willing to pay to access genetic data. As reported in Part 1, the idea of donating data to medical research is appealing, and notably many of the DTC-PG companies have presented the aspect of research participation as one of the attractive features of their services. However, opponents have already expressed concerns that these genetics companies are not adequately complying with informed consent

procedures [26]. For example, some companies use their website's Terms of Use as an equivalent to consent, while others use general consent which "fails to achieve (the) moral aim" of autonomous decision-making [43]. According to this line of criticism, companies fail to provide adequate information to consumers about the services they offer, while also providing limited information about the research uses of the data and the access given to third parties. A recent example presents the deal between the DTC-PG company 23andMe and the biotechnology company Genentech. Both companies seem to have agreed to cooperate to perform whole-genome sequencing by using DNA samples which were previously collected by 23andMe among people suffering from Parkinson. The plan to sequence the whole genome by using previously collected data generated further criticism of the company's consent procedures. 23andMe stated that they will ask the individuals for specific consent to use their data [25]. However, the information provided for users did not include appropriate reference to intellectual property strategies [25]. Criticism is increasing regarding the informed consent approaches 23andMe is using, and it indicates how a lack of open communication about commercial plans can damage trust of the participants [44].

Generation

A small majority of the participants agreed that there is a difference between older and younger generations in the attitude towards data sharing; however, direction of difference was mixed among the participants. Furthermore, level of education was regarded as significant determinant in data sharing practices. Finally, some argued that data sharing attitudes and data sharing practices frequently diverge, and an ambivalent behavior of data sharing in society was described.

Differences in privacy concerns according to age have been addressed in many studies, but results are contradictory [45]. For genetic research, Trinidad et al. [33] reported a more sophisticated understanding of the potential benefits of genomic research among younger participants. However, at the same time, this group was more concerned about privacy and had an increased desire for control of genomic data. With increasing age, participants were substantially less worried about privacy and confidentiality. These contradictory views can be seen alongside the "privacy paradox," i.e. the discrepancy between privacy concerns and the

lack of actual privacy safeguarding behavior. Due to the occurrence of social network sites (SNS), public self-disclosures have become prominent among young users, which illustrate the contradictory behavior or the potentially waning value attached to privacy in the age of connectivity and SNS [31]. Furthermore, empirical studies demonstrate the limited valuation of privacy with the exchange of access to personal information for very small monetary rewards or free access to services as, for example, in mobile smartphone application [46, 47].

Genetic versus Health Data Sharing

The difference between sharing genetic or health data was split: while one half of the participants would make no difference between the two, the second half described genetic data as more personal and sensitive due to its predictive power.

It seems understandable that part of the group perceives a difference between the two: although health and genetic data are sensitive, private and should be protected, many participants of the study, as well as previous investigations [48–50], described a difference between health data such as blood marker levels as compared to genomic test results. Aspects contributing to the perception that genomic information is of a special nature include the large quantity of information resulting from genetic tests, the predictive potential of genetic information, the rather frightening certainty about the connection to ancestors and relatives, and the conditional probability resulting in psychological distress or potential discrimination. All forms of privacy need to be protected, but some intimate aspects of our lives need special respect [50]. As a result, it might be reasonable to mandate special considerations in terms of privacy protection and regulation of access of genetic information and practice to a certain extent: “genetic exceptionalism” [48, 49]. As a result, clinicians and investigators dealing with genomic data ought to respect the special concerns of patients and participants regarding genomic data.

Financial Incentives

Almost half of the participants hold the opinion that sharing data should not be financially reimbursed or incentivized. Participants shared the belief that financial incentives will create false encouragements, and as soon as money is involved the integrity of the study becomes

questionable. The finding that older adults are more altruistically motivated than by financial incentives is in line with previous reports [29, 51, 52]. In detail, McCarty [51] reported that age was inversely related to the monetary influence on decision to participate in a large population-based genomic study. The same holds true for a study by Facio et al. [29] who reported that healthy volunteers perceived the financial compensation as an important motivator; however, again, age was inversely related to the importance of a monetary incentive.

Part 3: Data Safety

The main concerns participants highlighted were related to misuse of data, access to data by non-authorized companies or authorities' genetic discrimination and manipulation. Participants of the study were mainly concerned about abuse and argued that strict data protection is necessary. When talking about abuse, participants referred to the concepts of selling or leaking data to third parties and the fear that with access to this type of data they would receive increased power. In the long term, this knowledge might enable us to "play god," by making decisions on the value of life or, for example, the danger of designing artificial humans.

According to the literature, similar patterns evolved: First, the fear data would be used for unforeseen goals such as morally objectionable research purposes, non-research purposes, or even for-profit entities has been reported previously [28, 33, 53]. Second, the fear of utilizing data for discriminatory purposes by, for example, insurance organizations or employers has also been reported frequently [38, 39, 54, 55]. Interestingly, during this study, the World War II was frequently mentioned as a negative example for losing autonomy and abuse of information and tools for unintended purposes. Obviously, these experiences still shape people's attitudes and beliefs and seem to create and internal warning.

Nevertheless, collecting data on a large scale diminished the perceived risks of identifiability [33]. Oversight and governance of the data repository and/or biobanks was postulated to protect against the fear of losing autonomy and trust [28, 33]. A third factor which leads to insecurity in many of the investigated population is the lack of knowledge concerning

organizational privacy practices and policies in the process of sharing genomic data, also known as the degree of privacy awareness [28]. Further, the recognition of benefit often surmounted concerns about data sharing and outweighed the perceived associated risks including privacy [33, 54]. Regarding the question of research participation, the decision might be a compromise between the support of scientific advancement and taking the risk in the privacy and data protection realm [31].

Limitations

Due to certain limitations, the findings of this study should not be overgeneralized. First, participants tend to have a higher level of education and skills compared to the average population. The participants are enrolled in the Seniorenuniversität Zürich, which is a continuing education program for adults aged over 60. Therefore, the results presented and discussed in this paper represent a specific group of the elderly society. Attitudes and beliefs regarding personal genomics might differ between groups with higher and lower education and level of skills. Therefore, the participants of this study need to be taken into account while reading this paper.

Second, the participants were asked hypothetical questions regarding sharing genetic data for research purposes. Genetic tests were not executed in this study, and therefore the participants were asked to imagine the hypothetical scenario of being in the situation to share their genetic information for research purposes. Taking the limitations mentioned above, the presented study provides a qualitative approach to assess attitudes, motivations, and concerns of older Swiss adults regarding personal genomics and sharing data for research purposes. The studied participants present a fast-growing segment in our society which is not often included in research [9]. Since the European society is aging, it will be of great importance to strengthen the inclusion of older generations in research as a source of information to include in current political debates and policy making.

Outlook and Conclusion

Altruism is a major motivator for older adults to share genetic data for research purposes; in particular, in serving the greater good of society and the next generation without any expectation of reciprocity. Furthermore, academic research institutions are trusted, and the compromise between supporting scientific advancement while risking the protection of privacy is accepted amongst the older adults surveyed. As we move forward and strive to apply genetic advances to the benefit of individuals and patients, crowdsourcing genetic data in large networks and combining genomic and health data will be essential to realize the goal of PM. To benefit from this willingness to engage and share genetic data, and at the same time keep up with the commercialization of data collection via DTC-PG, increased focus on general public engagement in scientific research activities also known as “citizen science” is needed.

Commercial companies such as DTC provider 23andMe enable users to mobilize their own data for research and therefore undermine the scientific communities’ once unchallenged authority [31]. To keep up with the private sector which is gaining increasing access to genomic data and provide them with a trustworthy alternative, the academic science enterprise needs to tap into patient’s and citizen’s willingness to share and engage with their data. Academic research requires a paradigm shift: a new contract between all societal actors in order to address scientific challenges with a stronger focus on societal engagement and tailoring patient-centered advancements such as PM. Information and communication technology (ICT) will nurture open, efficient, and agile systems that help mobilize individual and collective engagement for the co-creation of sustainable science. The aim is to facilitate dialogue and raise awareness and transparency to benefit society – empowering patients to take action and learn about their health. Therefore, a framework for citizen science should be enforced in the context of genomics. Citizen science refers to the general public engagement in scientific research activities, where citizens actively contribute to science either with their intellectual effort or with their tools and resources. Collaborations between ICT, scientists, and volunteers have the potential to broaden the scope of research and enhance the ability to collect scientific data [56]. Therefore, citizen science has the potential to become an important part of research activities in the future, and research institutions need to prepare

for it. In a recent discussion, it was argued that citizen science should become a human right to science. This right enables the participation and contribution of everyone in the creation of valuable scientific knowledge [57]. It intends to respond to the "challenge […] to disconnect from traditional ways of conducting science and thinking about new opportunities for innovation and insights that lies at the interface of science and society and in the links between disciplines" [58]. If older generations are willing to participate in advancing PM for a better future, we must work towards this wish.

Statement of Ethics

Ethical standards were followed in the conduct of the study.

Disclosure Statement

All authors declare no conflict of interests. The entire study has been performed without external funding.

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CHAPTER 7

7

Enforce Laws

Clinical Trials, Data Protection and Patient Empowerment in the Era of the New EU Regulations

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Abstract

Cancer clinical trials and, in general, cancer clinical research by definition need a multi-modality approach. It is not enough to discover and register new drugs. To get cancer under control requires us to perform complex clinical studies that integrate drugs, companion diagnostics, new or improved surgical procedures and new radiotherapy approaches as well as, most importantly, to integrate all available information. This includes biological material and, of increasing importance, large amounts of data using big data technologies. To personalise treatment, genetic data are more and more frequently used. Therefore, the general approach is holistic. Legislators, on the other hand, work in a silo mentality; the needs of clinical research are poorly understood, and legislation focuses on either health care or the commercialisation of a product, and not on clinical research. In the last 2 years the EU has drafted several major regulations touching on clinical trials, in vitro diagnostics, medical devices and data protection, all of which will impact clinical research, although the silo mentality makes the overall framework inconsistent and potentially highly damaging to the EU's capacity to make rapid progress in the field of personalised medicine.

Keywords

Clinical Trial, Data Protection, Patient empowerment, EU regulations

Introduction

Back in 2012, the EU initiated several major legislative reforms that will shortly quite drastically modify the way clinical research is conducted in Europe. Those reforms are the Data Protection Regulation (proposal issued by the European Commission in January 2012), the Clinical Trial Regulation (proposal issued by the Commission in July 2012) and the medical device regulations (two proposals issued by the Commission in September 2012). These four major texts emanated from two different Directorates-General (DGs): DG Justice for data protection and DG SANCO, now SANTE, for other regulations. An additional difficulty is that the Data Protection Regulation is a general regulation and is not specific to research. These texts, though subject to transversal consultation mechanisms within the European Commission, have not been coordinated enough from the perspective of research and, more specifically, health research, even if they harmonise the situation in the EU to some extent insofar as each of them is concerned separately. Complemented by numerous international recommendations and guidelines, other EU directives that impact on research, additional member state legislations (consequent upon directives or not) and professional codes, they turn the health research framework into a nightmare for researchers and one of most tightly regulated areas. Figure 1 illustrates the current complexity of the EU research framework. In addition, all new reforms fail to take into account the changing clinical research landscape: clinical trials are more targeted; decisions on medication more and more rely on companion diagnostics co-developed alongside drug development, and studies incorporate technologies that exploit an ever-increasing understanding of the biology of diseases, thus creating important collections of bio-logical material and data that may serve health research for years, having the potential to rapidly provide answers to new questions as they arise and to explore research questions further before exposing individuals to any intervention, thus limiting the risks. Europe's clinical research ship seems more and more unfit to weather this storm. Last but not least, the EU struggles between its wish to increase transparency in all fields, including clinical re-search, and a strong call for singling out privacy as the key right, not caring enough about keeping a fair balance with other rights of individuals, such as the right to health care, which cannot be guaranteed without appropriate health research being performed.

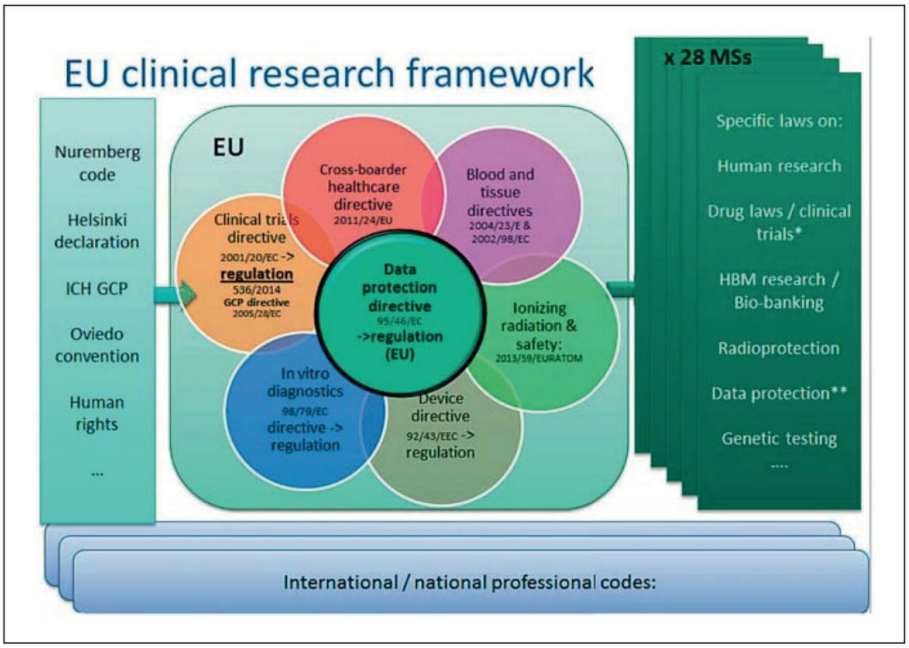

Figure 1. EU clinical research framework. ICH GCP = International Conference on Harmonisation Good Clinical Practice.* Will be largely abrogated after the implementation of regulation. ** Will be modified to provide scope for research after the implementation of regulation with no incentive for harmonisation.

New Types of Clinical Trials in the Era of Personalised Medicine

Moving towards personalised medicine is one of to-day's important objectives in the EU, as can be gathered from the website of DG Research and Innovation [1]: 'Today, many medicines do not work effectively for a large number of the patients they are supposed to treat. Personalised medicine aims to improve this situation by providing the right diagnosis leading to prevention or to treatment at the right dose to the right patient at the right time. Personalised medicine depends on the use of relevant biomarkers and the development of appropriate diagnostic methods, both in vivo and in vitro, for the stratification of patients into groups.'

Consequently, the number of tests aiming to measure relevant biomarkers is expected to increase. The FDA Table of Pharmacogenomic Biomarkers in Drug Labeling [2] and a McKinsey analysis [3] suggest that the number of biomarkers referenced in labels of FDA-approved drugs radically increased from 2010 to 2014 (with a compound annual growth rate of 21%). By 2018, the diagnostics of 50–70% of US lung cancer patients will be sup-ported by data resulting from the use of in vitro diagnostics (IVDs, such as next-generation sequencing). Therefore, though companion diagnostics indeed represent the minority of IVDs, their impact on the health of EU citizens in the very near future is likely to be great. This revolution is not only driven by commercial entities manufacturing and putting IVDs on the market, but also by academia and non-commercial organisations, since without their upfront research, which includes clinical studies, none of this progress would be possible. As with any research, not all of it will result in a product that can be put on the market.

Researchers use data and biological material to start looking for a new biomarker, frequently using already existing collections. As data and some biological material are timeless, today researchers can look into the DNA of patients treated decades ago. Back then, patients could have only been informed about future research in general terms, as no one could imagine what new technologies would appear. These precious data and materials are essential for new discoveries and are basic to the development of new biomarkers which will serve society and greatly increase the quality of public health. The current data protection reforms may very well render this research illegal or infeasible due to the amount of requirements. If additional hurdles are put in the way of this type of research, it will not be able to flourish in Europe as it should.

Once discovered in the laboratory, promising companion diagnostics will likely need to be tested in a prospective interventional study and may be tested at the same time as the drugs they go with. The newly approved clinical trials regulation puts a lot of emphasis on streamlining processes and reducing the administrative burden while guaran-teeing a high level of patient protection, and is believed to make Europe more attractive to clinical research (commercial or non-commercial). However, it only considers clinical trials from a drug perspective; it does not provide a comprehensive framework which embraces all aspects that can potentially represent a risk to trial participants. These other aspects are still regulated

separately. For example, in oncology, drugs are frequently used in combination with radiotherapy, which may also be part of an experimental intervention. Additional approval is needed to cover this aspect, and requirements and timelines are not harmonised among the member states.

With the IVD regulation, the EU had the opportunity to produce a more integrated framework for studies that would fall under both IVD and clinical trials regulations (see table 1) and to ensure these would not suffer from a duplication of the administrative burden. Indeed, the proposed IVD regulation imposes a formal approval process for interventional international trials. This process is similar to the one implemented by the clinical trials regulation, but not identical. For projects that will be part of both frameworks, substantial numbers of documents required for submission under both regulations are the same, and thus both reviews should ideally happen in a coordinated and integrated way.

Table 1: Studies likely to fall under both regulations

Trial title	Link to the public database
MINDACT (Microarray in Node-Negative Disease May Avoid Chemotherapy): a prospective randomised study comparing the 70-gene signature with the common clinicopathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0–3 positive nodes	https://clinicaltrials.gov/ct2/show/NCT00433589?term=mindact&rank=1
DAHANCA-29: a blinded randomised multicentre study of accelerated fractionated chemoradiotherapy with or without the hypoxic cell radiosensitiser nimorazole (Nimoral), using a 15-gene signature for hypoxia in the treatment of HPV/p16-negative squamous cell carcinoma of the head and neck	https://clinicaltrials.gov/ct2/show/NCT01880359?term=hypoxia+EORTC&rank=3
'Interleukin-12 and trastuzumab in treating patients with cancer that has high levels of HER2/Neu'	https://clinicaltrials.gov/ct2/show/NCT00004074?term=%E2%80%9CInterleukin-12+and+Trastuzumab+in+Treating+Patients+With+Cancer+That+Has+High+Levels+of+HER2%2FNeu%E2%80%9D&rank=1

The proposed text mentions the need for both systems to be 'interoperable' and 'linked'. However, the text does not specify what aspects shall be embraced by those links. Does interoperability also extend to the evaluation? Indeed, the aspects evaluated from the IVD perspective are not the same as those for the drug, but the global risk-benefit assessment, which is frequently led by ethics committees, will be performed on the trial globally; it does not make sense to receive 'drug comments' at one time and 'IVD amendments' later. The lack of clarity and will to further integrate frameworks might weigh heavily on these trials, which

are frequently run by non-commercial entities or small and medium-sized enterprises, and would ultimately make the EU less attractive regarding the development of companion diagnostics with a large proportion of research conducted abroad.

Clinical Trials Regulation and Transparency Instruments in the EU

The clinical trials regulation published in the official journal of the EU in May 2014 [4] and expected to be-come applicable in mid-2016 is a perfect example of how legal frameworks can rapidly be improved when legislators work hand in hand with all stakeholders supported by the results of several impact analyses. The decision to revise the framework came only 8 years after the implementation of the previous legislation, as the latter was held responsible for the 25% drop in the number of clinical trials in the EU. The new regulation was proposed and adopted in less than 2 years. It renders the clinical trial framework more efficient and better adapted to international trials; it reduces bureaucracy and, thus, unnecessary costs. It also consolidates patient safety by implementing a single submission portal with coordinated assessment that embraces all aspects of the trial including ethics and by introducing a risk-based approach to-wards trial management alongside centralised safety re-porting.

Most importantly, the new regulation has been applauded by many [5, 6] for having successfully addressed the urgent demand for increased transparency in clinical research, which was seen as an unmet need, allowing public scrutiny of results and offering the possibility for independent researchers to re-analyse data generated by the pharmaceutical industry. This success was further supported by the adoption of the policy on publication of clinical data for medicinal products for human use by the EMA [7].

Defenders of transparency, mostly patient organisations and the academic community, refer to a number of cases where a more transparent drug registration process could have saved lives, avoided serious health problems or disabilities, or saved large amounts of public money. However, industrial partners, although they have recognised the need for a more transparent process by issuing an international self-regulation [8], also cite the need to protect commercially confidential information in order to avoid the threat of unfair competition which could render the EU market less attractive. These arguments are supported by a recent

decision of the General Court of the EU [9] and by reference to the fact that requests for accessing data may come from competitors, including third-country market companies.

A critical re-analysis of clinical trial data is needed to ensure adequate public scrutiny, and frequently this is only made possible by having access to individual patient data (IPD). The use of fully anonymised data is usually not sufficient; coded data are used instead. Coded data are manipulated by a limited number of identified organisations using appropriately secured IT tools, and they are legally or contractually prohibited from trying to identify individuals; this ensures privacy. Open access to IPD was thoroughly debated and suggested by some. However, this would be inappropriate because it would clearly violate patients' privacy.

In clinical research, these three considerations, namely transparency, commercial confidentiality and participant privacy, constitute a delicate balance in which each component can potentially severely affect the other if it is not appropriately measured (fig. 2). The political debate about transparency and a strong call for the need to regulate this matter erupted in the public domain in November 2012, well after the release of the draft clinical trials regulation in June 2012 within the framework of requests for the EMA to have data released from the drug registration dossiers held by the agency [10]. Led by the author of the best-selling book *Bad Pharma* and the Cochrane association, this debate expanded from the scope of EMA dossiers to encompass the entire field of clinical trials and, in particular, the clinical trials regulation.

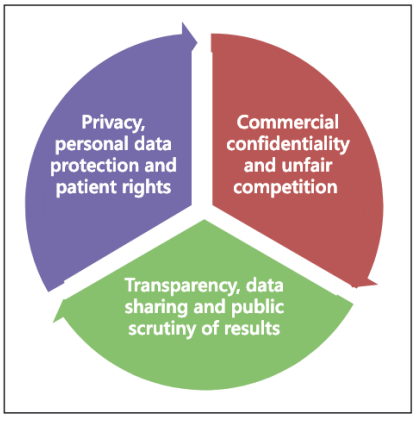

Figure 2. Key considerations to be balanced in clinical research.

Transparency and access to clinical trial data, specifically registration data, are not new within the EU. Over a decade ago, the EU enacted regulation 1049/2001 [11] on rules of public access to European Parliament, Council and Commission documents. The EMA began implementation of this regulation in May 2004 and adopted definitive rules at the end of 2006 after two revisions following consultation with the European Commission [12]. This regulation enables access to documents and information retained by the EMA upon justified and appropriate request. From 2005 to 2013, the number of requests for access to documents increased from 55 (in 2005) to 290 (in 2013) based on EMA annual reports [13]. The requests from industry represent 35.39% and those from academia only 11.68%. On the other hand, in terms of the number of pages released, industry represents 10.3% and academia 82.2%. The rate of acceptance or partial acceptance of requests is 49%.

However, this regulation seems to be poorly known, specifically within academia, and its application seems cumbersome. Therefore, it is very welcome that in the course of 2013 the EMA released its draft data sharing policy for public consultation, to which 169 organisations and individuals responded with over 1,000 comments, thus postponing the finalisation of this policy until autumn 2014. This policy was approved by the EMA management board [14] on October 2, 2014, and became applicable as of January 1, 2015. The policy focuses on trial results in the form of clinical study reports (CSRs), leaving the delicate issue of the sharing of IPD for a later stage.

In addition to the EMA policies, the release of limited amounts of information through the publication of summaries of trial results has been mandated by article 57(2) of regulation (EC) No. 726/2004 published on April 30, 2004. The IT tool that enables clinical trial sponsors to upload trial results was launched in mid-summer 2014. This instrument, however, does not provide access to the full CSRs. The clinical trials regulation [4], finalised just a bit earlier, guarantees access to CSRs (for trials with a registration aim) and makes public most of the information sub-mitted to the EU portal. It also mandates the Commission to explore IPD sharing possibilities in a separate guide-line, thus postponing this discussion to a later stage as well.

Regarding the priority given to trial results, the EU has four transparency instruments, two of which provide easy access to CSRs. Figure 3 summarises the dates of adoption of the EU transparency instruments and shows the progress that has been made in the EU within one decade. In-deed, from limited amounts of information being avail-able upon request, the EU has moved to directly making extensive documentation publicly available. It is, therefore, expected that, in the next 5–10 years, the public will mostly learn about trial results through EMA Policy 070 and EU regulation No. 726/2004, neither of which currently give access to IPD. By 2020, the clinical trials regulation will likely have become the key instrument, even if, currently, it does not provide access to IPD but only promises to consider it.

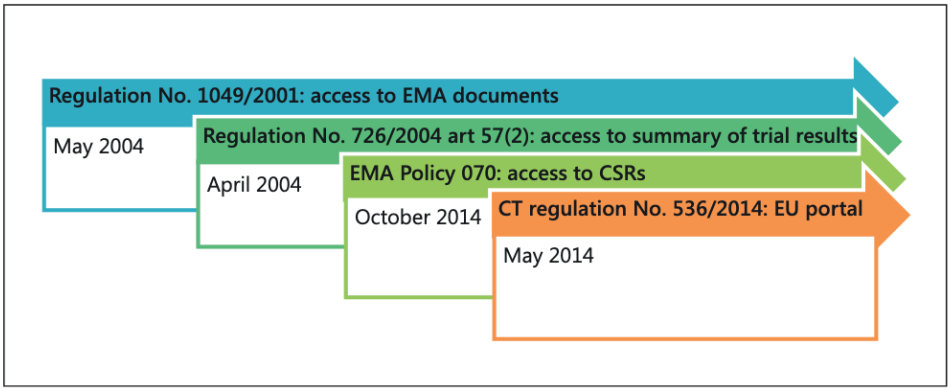

Figure 3. Summary of EU transparency instruments. CT = Clinical trial.

Moreover, even apart from considerations of confidentiality, CSRs are likely to be re-worked prior to making them public in order to delete any listings they usually include which are currently considered not in line with privacy rules. The EMA has the difficult task of pro-viding further guidance on the way listings shall be treated in the future in a way that allows sharing this information while respecting privacy rules. It is, therefore, quite likely that the scientific community will be rather disappointed by the level of information that will finally be made public.

It also becomes apparent that all recently developed transparency instruments delay the discussion about the sharing of IPD to a future, not-yet-defined date. Focusing on study results first and delaying IPD sharing is a way to avoid the dangerous triangle, since the debate focuses exclusively on the opposition between the need for public scrutiny and commercial

confidentiality. However, if this debate does not start now, when the data protection framework is still being finalised, the EU may find it impossible to share data in the future because of privacy laws.

The European Commission, European Parliament and member states will look carefully at the data protection regulation from the perspective of transparency and IPD sharing within the scope of the clinical trials regulation. As it stands, the draft data protection regulation would make this re-use of data impossible in many in-stances for the same reasons it would hamper transparency. Researchers would simply not be given access to these data, even if their research was ethically approved. Such a situation would be unethical in itself, as it would result in unnecessary exposure of individuals to prospective interventions – and the risks that go with them – even though the information could have been obtained using already existing data without any risk to patient safety. If one-time consent is not allowed by the frame-work, or if requirements are too divergent between member states, with some countries still requiring very narrow and specific consent, IPD sharing will never take place.

Data Protection and the Needs of Health Research

Researchers claim anonymised data are frequently of little use for health research. On the other hand, using sufficiently pseudo-anonymised data in a secure way for ethically approved research projects can rapidly advance medical and health research without violating patient privacy and data confidentiality. This capacity to collect and store data long term is essential for health research.

Going beyond the previously published study results, new knowledge can be gained by analysing these vast re-sources of data, including those from patients seen years ago and analysed from a new angle or in combination with data from other sources such as registries. This is what is called secondary use of data, and it is essential for achieving progress in health care. The questions we ask today could not even have been conceived 50, or even just 5–10, years ago, because we now have acquired addition-al knowledge and new technologies such as big data – big with regard to volume, velocity and variety. Secondary use of data is also essential to ensure the necessary transparency of research. It allows public scrutiny of data

sup-porting drug registration, and the clinical trials regulation invites sponsors to share data obtained from their trials. However, the data protection regulation in its current form is likely to prevent such data sharing.

Combining data from different sources is justified by the need for long-term follow-up of patients to gain a better understanding of treatment effects such as late toxicity. These data are routinely collected within the frame-work of medical follow-up, and their analysis improves the quality of health care and increases the knowledge of existing treatments and procedures. An inability to perform such research would decrease the quality of health care and thereby violate one of the fundamental rights of EU citizens.

The question, then, is whether it is justified to spend time and money on gathering new data and seeking the specific consent of patients even in situations where these patients have already given their consent for use of their data in future research in general (‘one-time consent’). It is also a question of whether the political will really exists to stimulate controlled data sharing between different stakeholders, thus maximising the available knowledge and carefully scrutinising clinical practice-changing results before they are adopted and potentially affect mil-lions of individuals, or whether the choice is made to strengthen data privacy rules to the point where they prohibit any use of the data.

The European Parliament defended its amendments on the basis of article 8 of the Charter of Fundamental Rights of the European Union, which guarantees the adequate protection of personal data to all EU citizens. However, fundamental rights are not limited to a single right. Article 13 states that scientific research shall be free of constraint, and article 35 guarantees access to health care (fig. 4).

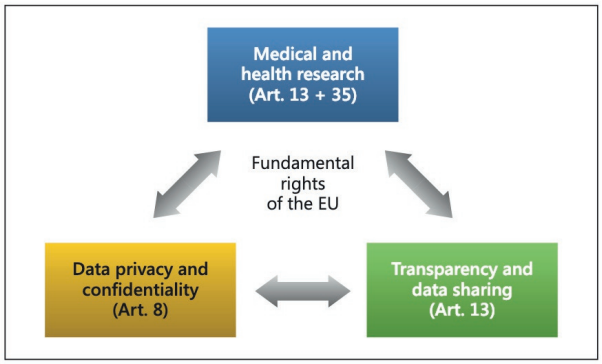

Figure 4. Fundamental rights of the EU

The European Alliance for Personalised Medicine (EAPM) believes that the current text, as applied to health research, violates articles 13 and 35 because it would cause serious constraints on scientific research and pre-vent or significantly hinder health research and innovation to such an extent that Europe would no longer be able to guarantee the quality of the health care to which its citizens are entitled. Patients and the general public regularly send messages to the research community as many of them have no access to satisfactory care. There is an urgent need to sup-port research, because any delay results in loss of lives every day. Many patient communities have come together to help researchers gather the data they need to pursue their research [15, 16]. The expectation is that existing databases are used, rather than letting the data lie fallow or, worse, deleting them [17].

Patients state that they want to share their data for the sake of research: 'We, as patients, are increasingly aware of the value and importance of sharing our data. From the patients' perspective, use of health and genetic data is vital to advancing health research' (European Patients' Forum statement on data protection [18]).

As health care improves, Europe faces new societal challenges. Treatments can have long-term effects, many of which are not well documented, though they have the potential to significantly impact EU health care costs in the long run as well as the quality of life and productivity of EU citizens [19]. Cancer care is a perfect example of these new needs and societal challenges. Cancer survival rates have increased over the past decades, and society

needs to ensure that former cancer patients are not only cured but have active lives and can contribute to the growth of European society. These new challenges can only be appropriately tackled if underpinned by evidence from real-life data.

Protection of privacy is a serious matter. However, in health research, straightening and narrowing a participant's consent or limiting the time data may be stored is unlikely to increase the level of protection. On the other hand, such measures jeopardise health research, hinder the progress of medical science and violate the rights to adequate health care and freedom of research.

Information Overload

Patients are typically seen only as passive recipients of care. The more desirable model of personalised medicine better enables patients to be participants and guides in their own health care. Patient participation in treatment decision-making is increasingly being advocated as a desirable model, especially when patients have serious ill-nesses, when there are different treatment options and when the benefits of treatment have to be weighed against possible adverse effects [20]. Also, involving patients in treatment-related decision-making is in line with the increasingly acknowledged right of patients to autonomy and self-determination [21].

Such an approach adopts a biopsychosocial dimension rather than, or in addition to, a biomedical one. This starts with the attitude that the patient is a person, and not merely a body with an attached illness, and it supports the sharing of power and of responsibility between doctor and patient [21, 22].

Health literacy is closely associated with empowerment, because it involves people's knowledge, motivation and competence in accessing, understanding, appraising and applying the health information needed to make judgements and in taking decisions in everyday life concerning health care, disease prevention and health promotion [21, 23]. However, the process of involving patients in their care decisions implies not only health-liter-ate patients but also a 'health literacy-friendly system' that provides transparent and credible information

about the chances of benefit and the risks of harm from distinct medical diagnostic and therapeutic interventions and that decreases the information and power asymmetry between doctors and patients (i.e. the doctor knows every-thing, the patient nothing) [21].

This means increasing patients' medical information via a language that is matched with their educational level and allowing patients to effectively state their own preferences and concerns. The information exchange needs to be two-way: the health professional provides in-formation to help explain the clinical situation and sub-sequent decisions, and the patient provides information on his/her values, preferences, lifestyle, beliefs and previous knowledge about the illness and its treatment [21, 24].

The first type of information flow ensures that all the relevant treatment options are on the table; the second ensures that these can be evaluated by both the health care professional and the patient within the context of the patient's specific needs. When this happens, the health professional can create the shared knowledge necessary to consolidate the patient's engagement and to successfully execute the shared decision-making process. There is some evidence that a good information exchange within a good health care professional-patient relationship could be considered as a therapeutic intervention [25], because it helps in preserving or improving the patient's ability to deal with his/her illness and even in maintaining a good quality of life. This is particularly relevant in the chronic phase of any disease, as it helps to increase the patient's vitality and social functioning and to reduce the incidence of depression and anxiety [21].

A limited level of health literacy, i.e. a reduced under-standing of medical information, may hinder the whole process. Limited health literacy is not only an issue for vulnerable groups such as elderly people or people with low education. A recent study revealed that 47% of the general population faced difficulties in accessing, under-standing, judging and applying information to make decisions regarding their health [21, 26]. Also, several studies focusing on the assessment of the most common conceptualisation of cancer found that most people know very little about it. Downs et al. [27] found that, on the surface, many interviewees seemed relatively well in-formed, talking about risk factors, eating habits and treatments, for instance using words like 'remission'. How-ever, further probing showed that many knew the

terms but not the underlying concepts; their mental models were typically incomplete, inconsistent and error laden [21, 27].

When individuals are diagnosed with a serious condition, they have to absorb a series of new details about their illness. To make sense of the new information, and to understand the details, patients have to integrate the new information with their existing beliefs, which determine what data and what perspectives are examined, acting as a sort of filter through which they can look at the situation.

Several difficulties may arise both when patients have misleading existing beliefs or 'knowledge', or none at all about their illness. In the former situation, contrasting and inconsistent beliefs lead to the construction of a fragmented and confusing overall picture, making people feel overwhelmed. Thus, patients may retain disparate beliefs, loosely organised around whatever overall mental model of their illness they happen to have [21, 27]. In the latter case, it is known that patients with low health literacy tend to have a poorer health status, tend to be less likely to adhere to prescribed treatments or to comply with self-care plans, and are likely to experience more drug and treatment errors. Thus, comprehension of medical terms is fundamental to patient engagement, and achieving a greater ability to understand medical terms in the population is integral to improving the health of disadvantaged populations [21, 28].

For instance, between 40 and 60% of the medical in-formation provided by health practitioners is forgotten in the few minutes after it has been received, and these rates increase in old age; furthermore, not all the information 'remembered' is correctly recalled [29]. Knowledge also confers confidence: patients are more likely to trust their capacity to make decisions when efficiently informed [30]. Hence, limited health literacy is a public health challenge which should be taken into account by health professionals and decision-makers when improving patient empowerment [21].

Role of Health Professionals in Informing and Engaging Patients within a Personalised Medicine Context

The role and degree of patients' preferred involvement in care decisions, as well as the volume of information desired, depend upon the psychological, cognitive, social and cultural characteristics of each patient as well as upon the characteristics of the health care professional-patient relationship [31]. This observation explains why empowering patients is not easy. In order to incorporate a patient's preferences into clinical decisions, and considering that communication styles vary from patient to patient (influencing their physician's behaviour), the physician should: (1) recognise the patient's health literacy; (2) monitor and facilitate the patient's understanding of the diagnosis and the therapeutic strategies; (3) provide in-formation about different treatment options, the possible benefits and risks and the rationale for diagnostics and pre-emptive testing; (4) assess the patient's decision-making needs (e.g. decisional conflicts, values, willing-ness to participate/not participate in the decision-making process, family/social support and resources), and (5) monitor and facilitate the patient's ability to communicate his/her preferences, values and lifestyle. These are complex talents, which allow the health care professional to ascertain whether the patient is sufficiently knowledgeable and confident about constructing informed preferences.

What can health professionals do to improve health literacy and the capability of patients to understand their disease? Given that it is the responsibility of health professionals to speak to patients in an easily understandable language, several strategies have been proven to be effective in improving the comprehension of medical terms [32], such as well-designed written information used as an adjunct to professional consultation [33], websites [34] and targeted mass media campaigns [35].

Adequately informing patients, as explained above, is key, but it is a delicate and sensitive process that needs to be adapted to each patient's health literacy. The regulator, on the other hand, sees the need to inform patients from a more legalistic perspective. Different regulations accumulate what patients need to be informed about; consent via separate documents may sometimes be asked for (e.g. separate data protection or genetic testing

documents), bringing the amount of information patients have to di-gest up to several dozens of pages. This approach does not help them to make an informed decision, as it may dilute the key questions patients need to focus on by the amount of administrative and legalistic details mandatory by law [21].

Conclusions

Research and innovation, and specifically health research, continue to be part of what Europe has a reputation for and what makes it a better place to live in. Research and innovation play important roles in increasing Europe's growth and competitiveness. Several EU member states, such as Luxembourg, clearly place research and innovation as two of their key priorities, as they generate an important part of their income and create jobs. In 2014 the EU launched Horizon 2020, the biggest EU research and innovation programme ever, with a budget of around EUR 79 billion over 7 years. While increasing its investments in research and innovation, the EU regularly de-bates the affordability of care and the sustainability of the health care systems. Researchers have warned regulators and the general public about dramatic increases in the costs of clinical research and their impact on health care expenditure, partly due to the cumbersome nature of the regulations in place [36].

At a time when all stakeholders are trying to improve their processes to increase the efficiency of research – making it quicker, more straightforward and cheaper while delivering high-quality results – regulators still underestimate the value of health research for society and little understand its modern complexity. A very pragmatic way to decrease the costs of research is to try to answer as many research questions as possible within the same project. This also decreases exposure to risks for patients as fewer individuals are likely to be exposed to those risks. However, such comprehensive research projects suffer from legislation in a silo mentality, where each regulation only considers a few elements, with a lot of regulations not specific to research and requirements as applied to trials piling up, creating barriers to research rather than serving patients. Patients indeed need to be protected, but killing research or making it unaffordably expensive does not help patients – or society for that matter.

Moreover, research does not recognise borders, especially within the EU, where the research community more and more tries to behave like one. Thus, having such a cumbersome legal framework, without sufficient consideration of how all its bits and pieces come together within one single pan-European project, makes all efforts at efficiency useless and clearly discourages the young generation from getting involved. As stated in the report from the conference 'Innovation in Healthcare: From Research to Market' [37]: 'stop treating tomorrow's needs with yesterday's models'.

Disclosure Statement

The authors declare no conflicts of interest

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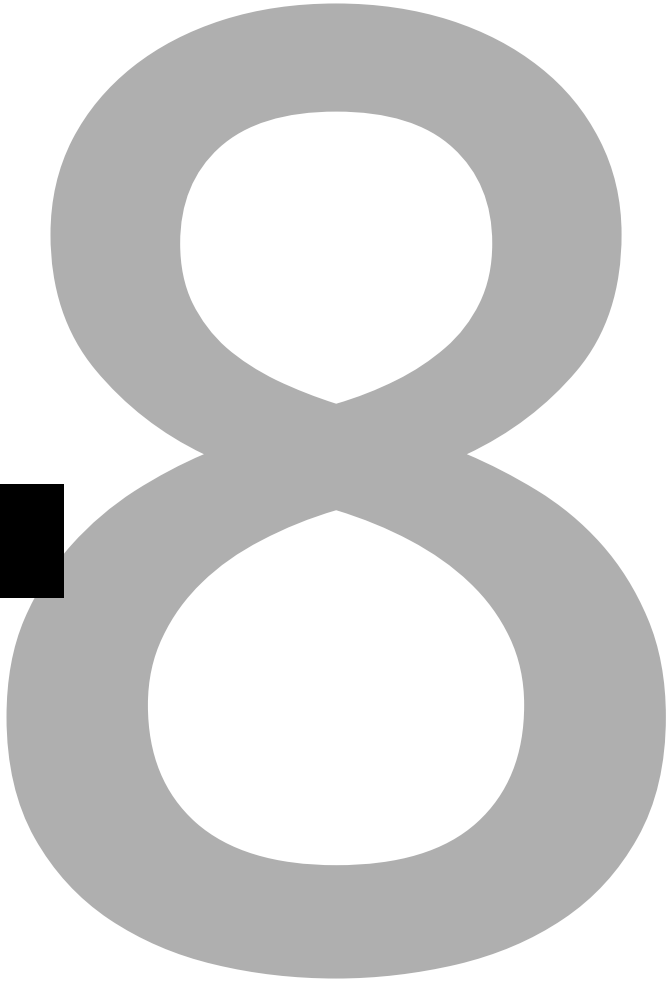
CHAPTER 8



General Discussion

Research has been conducted to describe the innovation process in more detail and to analyse the current landscape of innovation in Europe using the example of Personalised Medicine. The aim of the dissertation was to analyse the current status of the implementation and uptake of PM in Europe. This was done by applying the innXchange innovation wheel, which is explained in more detail in the Introduction and Chapter 2. The framework provides specific guidance on the essential parts and principles of innovation creation and innovation management. PM was chosen as an example since this innovative healthcare approach has great potential to address many of the healthcare challenges we are facing. Several parts of the innovation wheel have been analysed to identify factors which are either hindering or facilitating the uptake of this innovative healthcare approach. In addition, several solutions to address the current challenges regarding the adaptation and implementation of PM in Europe were introduced and discussed. In this thesis the following parts of the innXchange innovation wheel have been analysed in more detail: *Evaluation, Research, Systems Management, Develop Policies, Innovation Literacy and Enforce Laws*.

The main findings of my research have been summarized below and have then been put into the wider context of innovation and in particular, healthcare innovation using the example of PM.

Part 1: Current landscape of innovation

In the first part of the dissertation (Chapter 2 and 3), the current innovation landscape was analysed, and gaps and needs were identified. The findings indicated that besides its great potential, innovation is often hampered due to a lack of systematic stakeholder collaboration and engagement throughout the whole innovation process. The findings also highlighted the importance of the innovation ecosystem which largely determines the success of the innovation process. In such an innovation ecosystem a variety of different actors such as large and small enterprises, policy makers, academics and the civil society participate and collaborate from local level up to international level. Moreover, infrastructure, education, a skilled workforce, regulation and legislation and innovation funding schemes are all important pillars of the ecosystems. In addition, creativity, societal norms and values and attitudes towards innovation are of equal importance for the success of the innovation process. The

research findings indicated that many of those factors are often lacking in the innovation ecosystems in Europe limiting innovation capacity.

The studies revealed the importance of open, frugal mindsets for successful innovation and that the landscape of innovation has drastically changed over the last few years. Being a top innovator is no longer necessarily linear associated with R&D spending's. New emerging low-cost innovation approaches such as frugal innovation are currently challenging mature markets and have great potential to address the many challenges the world is facing. Several examples of frugal innovation and how they impact the lives of millions of people are described in more detail in Chapter 3 [1]. Moreover, the results of the studies highlighted that due to the complexity of innovation and the many different aspects of which are influencing the innovation process, that there is no one-size fits all innovation approach.

Part 2: Application of the innXchange innovation wheel to analyse the uptake and implementation of Personalised Medicine in Europe

In the second part of this dissertation (Chapter 4-7), the innXchange innovation wheel was applied to assess the current situation of the adaptation and implementation of the innovative healthcare approach of PM in more detail. Applying the innXchange innovation wheel allowed to investigate whether we are currently doing the right things right with regard to the implementation and adaptation of PM in Europe or whether our actions actually have negative impact and are instead of facilitating, hindering the uptake of PM.

Systems management (Chapter 4)

In Chapter 4, the European healthcare system readiness to shift from 'one size-fits all' to PM was assessed [2]. The research was conducted based on the "Conceptual model for considering the determinants of diffusion, dissemination, and implementation of innovations in health service delivery and organizations" developed by Greenhalgh et al. [3]. Originally, the model was developed to describe under what conditions innovations are more likely to be implemented within healthcare organisation. For the purpose of the research, a more holistic approach was chosen, and parts of model were applied instead to healthcare organizations to healthcare systems. In this study the 'system readiness' part of Greenhalgh's

model was applied to assess the readiness of European healthcare systems to shift towards personalised medicine. According to Greenhalgh et al. 'system readiness' consists of six components of which the following three were applied to evaluate the healthcare systems readiness: tension for change; innovation-system fit; and assessment of implications [3]. According to Greenhalgh et al. tension for change occurs "if staff perceive that the current situation is intolerable" [3]. Furthermore, innovations are more likely to be adapted (innovation-system fit) when the innovation "fits the organization's existing values norms, strategies, goals, skill mix, supporting technologies and ways of working" [3]. In addition, according to Greenhalgh et al. it is more likely that innovations will be adapted when "the implications of the innovations (including their subsequent effects) are fully assessed and anticipated" [3].

The results indicated that there is a clear tension for change. The current applied 'one-size fits all' healthcare approaches are no longer working due to the new understanding of diseases and the large varieties in drug responses among patients because of their unique molecular characteristics. There is a clear need to shift towards new innovative healthcare approaches to make healthcare systems more effective and efficient. In addition, the results highlighted that there is still room for improvement regarding the uptake and diffusion of PM among European healthcare systems. PM is challenging current ways of working and several obstacles need to be addressed to make full use of the potentials of PM. Challenges that need to be addressed include the integration of big data, regulations that do not address the new healthcare approach adequately, and outdated curricula. Furthermore, financing and reimbursement issues need to be addressed and updated to fit PM, as well as health literacy needs to be promoted to further strengthen the uptake of PM. Since PM is a relatively new healthcare approach, there is currently no harmonization in defining PM, which makes it difficult to develop tools and methodologies to assess the implications of PM.

Develop Policies (Chapter 5)

In Europe, diseases have always been classified either as common diseases (CDs) or as rare diseases (RDs). The emergence of 'omics-technologies' which allowed the sequencing of the whole human genome, however, has led to a new understanding of diseases. Omics-technologies have proven that each patient has unique molecular characteristics and that

each patient reacts differently to treatments. This new understanding allows a more precise classification of diseases based on their genetic characteristics. In addition, the new understanding no longer differentiates between CDs and RDs. Therefore, the vision of PM implies that every common disease will become a rare disease. Against this background, research has been performed in Chapter 5 to assess the impact the new understanding of diseases will have on healthcare polices [4]. Since the approach of PM is based on the understanding that every disease will become a rare disease, there are no longer specific research and policy needs for RDs. This vision of PM will have great implications for all policy makers both national and European since it calls for regulations and infrastructures that can be applied to all diseases in the same way and does not differentiate between CDs and RDs anymore. The research results highlighted that in order to strengthen the uptake and implementation of PM, current policy tools need to adapt faster to the new understanding of diseases to bring the benefits of PM to the patients. Moreover, the research highlighted that together with emerging technologies such as big data analytics, the new understanding of diseases applied by PM, has the potential to make healthcare systems more effective and efficient and treatments for patients safer.

Innovation Literacy (Chapter 6)

Since the economic value of health data is increasing rapidly, security and data protection have become major issues. In particular, the rising number of commercial companies offering direct-to-consumer personal genomics (DTC-PG) is often critically discussed. Against this background, research has been conducted in Chapter 6 to assess the attitudes towards personal genomics and the sharing of genetic data among older adults [5]. Older adults have been chosen as the study population since this segment is often not included in research even though this part of the society is rapidly increasing due to the aging of the baby boomer generation and medical advances. The results of the study highlighted that majority of the research participants were in favour of participating and sharing their genetic data. Their motivation for sharing sensitive data was mainly driven by altruistic reasons. Participants believed that by providing genetic data for research purposes they would contribute to the greater good. However, the participants also highlighted that they were only willing to share data if adequate data protection and data safety mechanisms were in place ensuring that their data would not be misused or end up in the hands of third parties. The participants

were hesitant sharing data with commercial companies and would rather share data with academic research institutes. Overall, participants were in favour of sharing genetic data to improve science. To further strengthen the uptake and implementation of PM in the years ahead, crowdsourcing genetic data in large networks and combining the large variety of data collected through different sources will be essential to realize the vision of PM. To achieve that, engagement of the society in scientific research, also known as 'citizens science', will be essential. To achieve this, a paradigm shift will be needed and engagement of the society in research needs to become a major pillar of research. Only if all parts of the society are equally included in research, will the benefits of PM reach the patients in need and make healthcare systems more effective and efficient.

Enforce Laws (Chapter 7)

Legislation plays an important role in the innovation process and is a major pillar of the innovation ecosystem, especially, with regard to PM. Legislation can either hinder the uptake of PM or facilitate it. The quickly changing landscape of health technologies and the emergence of new approaches such as PM means that national and European legislations do not adequately address those new approaches and are thus described as outdated and not fit for purposes. Research conducted is described in Chapter 7, providing an overview of the current legislation landscape with regard to PM and analysing the impact legislation currently has on the uptake and implementation of PM [6]. Even though PM has become a major objective in the EU and the benefits of PM have been well described in several reports by the European Commission and European Parliament, current legislations are often hindering the uptake and further implementation of PM. The results highlighted that the current national and European legislative frameworks suffer from silo mentality and fail to take into account the changing landscape of clinical research in the era of PM. As long as the silo mentality is dominating European legislation, the uptake of PM will drastically slow down. Cancer clinical research has been identified as an example in this research to highlight the need of a multi-modality approach. Since PM has highlighted the failures of the current one-size fits all approach in oncology, it becomes clear that it is no longer enough to only discover and register new pharmaceuticals. To address the increasing cancer pandemic, it will be of great importance that all available data and technologies is used to improve diagnosis, develop effective and safe personalised treatments and prevent diseases. Therefore, legislations

related to clinical research need to be updated, harmonized and need to adequately address the new understanding of the complexity of diseases.

Are we doing the right things right?

In the following part of the discussion the research findings focus on innovation in healthcare by using the example of PM. This is important because the results of this dissertation will be compared with published scientific research and policy reports and similarities as well as differences will be highlighted.

The research performed in this dissertation revealed that Europe is facing several challenges regarding the creation and management of innovations. Even though the potential innovations may have to address the many economic, environmental and societal challenges Europe and the rest of the world are facing, the benefits of innovations often do not reach the society [7]. Therefore, the following question remains: **Are we doing the right things right?**

First it is discussed how far our actions are fit-for-purpose to enable the creation and to support the management of innovation. The current landscape of PM is then taken as example to assess whether our current approaches are supporting the uptake of PM or hindering the implementation. To do so the concept of 'fitness-for-purpose' is applied to answer the question "Are we doing the right things right?" Fitness-for-purpose is a concept of quality, which has become a widely used concept to assess the quality of higher education [8,9]. According to Woodhouse (1999) 'fitness for purpose' is a concept of quality that "allows institutions to define their purpose in their mission and objectives, so "quality" is demonstrated by achieving this" [8]. For the purpose of the discussion, a heuristic approach is applied. Both, innovation and personalised medicine are main objectives of the EU. Therefore, our actions should fit the purpose in achieving those objectives. In the following part of the discussion, the quality of our actions regarding strengthening innovation and the uptake of PM will be analyzed and discussed, assessing whether our actions are fit-for-purpose to achieve the objectives of innovation and personalised medicine. According to the

concept, if the set objectives are not achieved, quality is not demonstrated, and actions are not fit-for-purpose.

Innovation – Are we doing the right things right?

Europe has always been a top innovator and innovation is a main objective of the EU [10]. However, Europe is struggling to keep up with the leading innovators such as the US and Japan and is increasingly being challenged by rapidly growing and emerging markets [11,12]. Looking at the R&D to GDP ratio, it becomes clear that Europe is lagging behind. Countries such as South Korea, Singapore and China are quickly catching up with the EU [11], and China even overtook Europe and is now, behind the US and Japan, the country with the third highest R&D expenditure [12]. In addition, , none of the 15 largest digital firms, is from Europe, which indicates that there is still room for improvement in Europe in attracting global companies [12]. When looking at the Innovation Union Scoreboard (IUS), which was developed by the European Commission as a tool to assess the innovation capacities of countries [13], Europe scored lower in almost all indicators compared to the US in 2015 [11]. However, the recently published European Innovation Scoreboard 2019 Report, highlights that Europe has improved its innovation performance and has even overtaken the US. Even though Europe has improved its innovation performance, it is still lagging behind South Korea, Canada, Australia and Japan [14]. The improved innovation performance indicates that Europe is doing several things right with regard to innovation but to keep up with the leading countries several challenges need to be overcome.

As highlighted in the first part of the dissertation, the innovation ecosystem plays an important role to successfully innovate. However, it can be argued that the innovation ecosystem in Europe is often hindering innovation rather than facilitating it. The Joint Research Centre of the European Commission published a report “Current challenges in fostering the European innovation ecosystem” in 2017, highlighting factors impacting the innovation process [15]. The following challenges have been identified “need for an improved innovation performance to boost EU productivity growth; need to increase knowledge-intensive industrial activities linked to global value chains; access to finance: the need to make financial markets more responsive to high-growth opportunities in highly innovative

activities; Universities and skills: the need for higher education institutions to strengthen their role in local innovation ecosystems; the governance of research and innovation systems: the need for long-term planning, removal of administrative barriers and increased flexibility; social sciences and humanities (SSH) research: the need for greater contribution to shaping research and innovation policies" (page 3)[15]. All those challenges are in line with the findings of the research performed in Chapter 2 and 3.

However, the research in Chapter 2 and 3, highlighted additional factors that are currently lacking in the European innovation ecosystem and which to a large extent determine the success of the innovation process, namely creativity, trust in institutions and openness towards innovation. Those factors have been identified as important pillars of the innovation ecosystem which are often not taken into consideration. Only if the complexity of the innovation ecosystem is adequately addressed, actions will be fit-for-purpose to make Europe a global player again, but as long as certain parts are left out of the discussions, Europe will struggle to regain its position as top innovator.

The importance of start-up companies as catalysers for innovation is widely recognized in the scientific literature [16-18]. However, too many new companies are not passing the start-up phase in Europe. The few companies that survive the critical first years, often leave Europe [12]. A reason why many start-ups fail is because they are facing financial challenges after the basic research/ discovery phase, which limits their capacity to innovate and to successfully develop their discovery and bring it to the market. The funding gap is often referred to as the 'valley of death' in the innovation process, which occurs between the discovery or basic research and the commercialization of the innovation [7,19,20]. Public and federal funding is often exclusively dedicated to early stage basic research. As a consequence, innovators are facing funding shortages and roadblocks in the intermediate phase between basic research and the commercialization where the discovery is developed into a marketable product [7]. Therefore, it can be concluded that the current approach of focusing federal funding exclusively on basic research, does not fit-the-purpose, since innovations/ discoveries do not reach the citizens.

Another reason why some innovations fail is due to a lack of coordination, collaboration and engagement of all stakeholders involved in the innovation process [20]. However, little research has been conducted to assesses the impact stakeholder engagement has on the innovation process and its argued that more research is needed on this topic [21]. The research performed in Chapter 2 and 3 addresses this need for more evidence and provides new insights into the importance of systematic early dialogue among stakeholders to successfully bring a discovery to the market [1].

Other important factors for innovation, which were identified in the first part of the dissertation, are creativity and open/frugal mindsets. As described in Chapter 2, most innovations in Europe mainly appear in a highly regulated and R&D intensive predefined setting. Moreover, top-down innovation approaches often leave out the great majority of the European society. This might also explain why Europe is struggling to keep up with emerging economies. New innovation approaches such as frugal innovation are continuously disrupting the innovation processes in Europe and other mature markets [22]. Those emerging innovation approaches focus on inclusiveness and are designed to address daily problems at low cost. This allows lower socioeconomic groups to access those innovations [22]. However, to keep up with emerging economies, changes in mind-sets will be needed. Being a top R&D investor no longer a guarantees being a top innovator [11].The widely applied understanding of investing more in R&D to become a top innovator is no longer fit-for-purpose. Europe needs to adapt faster to the changing landscape of innovation to ensure it does not lose market segments to emerging economies. To achieve this Europe and other western countries need to be open to learn from other countries/continents and move away from the belief that they can teach the rest of the world how to innovate [23].

Based on the above described trends and the findings of the research, it can be concluded that we are currently not always doing the right things right and that several of our actions do not fit-the-purpose of being a top innovator. The challenges identified in this dissertation need to be addressed in order to ensure that Europe remains a top innovator and regains a leading position.

The momentum is right for innovation

The importance of innovation is recognized and highlighted in many reports of the United Nations, European institutions and other key stakeholders [10,24,25].

As highlighted by the United Nations innovation can play an important role to achieve the UN Sustainable Development Goals (SDGs) and improve the well-being of millions of people. In 2015, the United Nations General Assembly adopted 17 SDGs to address the many global challenges and to move towards a more sustainable future. The SDGs are "No poverty; Zero hunger; Good health and well-being; Quality education; Gender equality; Clean water and sanitation; Affordable and clean energy; Decent work and economic growth; Industry, innovation and infrastructure; Reduced inequalities; Sustainable cities and communities; Responsible production and consumption; Climate action; Life below water; Life on land; Peace, justice and strong institutions; Partnerships for the goals" [26]. New technologies and innovation will play a pivotal role in achieving those ambitious goals [25,27]. Emerging innovation approaches such as frugal innovations have great potential to address the many challenges, we are facing by promoting inclusiveness of all parts of society and offering low-cost solutions to address major needs.

The potential impact innovation has to move towards a more sustainable future is widely discussed in the scientific literature and reports of key stakeholders. Many of the challenges that are currently slowing down innovation are identified and potential solutions to overcome those are presented. To achieve the SDGs and improve the well-being of millions of people, those solutions need to be translated into concrete actions and implemented. It is not enough to only recognize those challenges on paper. To be fit-for-purpose, it is now time to translate those recommendations into clear actions to meet the SDGs.

Personalised Medicine – Are we doing the right things right?

Over the last decade, the European Commission has been the leading driver for the expansion of PM throughout the EU. The EC has recognized the potential PM has to improve current healthcare approaches and to make healthcare systems safer and more effective. The impact

PM could have is discussed in several reports and studies [28]. During its previous funding programme, the 7th Framework Programme (2007-2013), the EC has committed to than €1.3 billion of the total €50 billion budget to support scientific research related to PM and has funded more than 200 research projects focusing on PM. The EC has continued its commitment and has invested in the first three years of the current funding programme, Horizon 2020, already close to €900 million into research projects related to PM [28,29]. The EC aims with its funding to simulate collaborations on national and European level between relevant stakeholder such as academics, policymakers, industry and the society.

However, as the results of the research performed in this dissertation highlighted, providing funding and investing in R&D will be not enough to strengthen the uptake of PM. Funding is only one pillar of the innovation ecosystem and only if all pillars are addressing the new approach of PM adequately, the uptake and implementation can be improved. In addition, as highlighted before many innovations end in the Death Valley of innovation because federal funding is mainly focused on basic research and as a consequence many innovators are struggling to be able to further develop their discovery to a marketable product. Therefore, it can be concluded that the EU needs to adjusts its funding approach. In order to be fit-for-purpose, the EU needs to pay equal attention to support basic research and also the intermediate phase to support innovators to successfully develop and commercialize their innovations.

Furthermore, silo mentality in legislation is currently hindering clinical research and slowing down the implementation of PM and therefore it can be concluded that the legislative framework is currently not fit-for-purpose [2,6]. The findings of this dissertation highlighted that instead of more legislation and regulation, smarter legislations and regulation will be needed [2]. In addition, legislations need to adapt faster to emerging technologies. It will be of great importance that legislation will on the one hand protect the patients/citizens and on the other hand support research [2]. The EC aims to make the EU 'a stronger global actor' [30] but as long as innovators are challenged by legislation which are not fit-for-purpose, the EU will continue to struggle to keep up with emerging markets and other continents and will lose its reputation of being a top global innovator.

The EC has recognized this need and has initiated the regulatory fitness and performance programme (REFIT) in 2015. The main aim of the REFIT programme is "to ensure that EU legislation delivers results for citizens and businesses effectively, efficiently and at minimum costs" [31]. With this initiative the EC hopes to make the legislative system simpler by removing unnecessary burdens and to align the legislation more with policy objectives [31]. This is a promising step forward, to ensure that regulation supports innovation instead of hindering it and that innovation is embedded in regulation [10]. REFIT has the potential to strengthen the uptake of PM by reducing current regulatory barriers and breaking down the silo-mentality in the regulatory process.

In addition, as highlighted in this dissertation, openness towards innovation and PM will be of great importance to increase acceptance among the stakeholders and the society. For example, PM utilizes an immense amount of data as highlighted in Chapter 6, and concerns regarding data protection are increasing among the society [5]. To be fit-for-purpose, EU legislations needs to find a balance between protecting the privacy of the citizens and patients and supporting responsible data sharing to further strengthen the implementation of PM in healthcare practice [32].

Even though PM is already successfully applied in many different medical areas, PM is not yet truly individualized. One problem is that definitions of PM vary greatly and that terms such as personalised medicine, precision medicine and stratified medicine are used interchangeably. Too many studies are still focusing on patient stratification, which means that patients are grouped into subpopulations according to their likelihood of responding to a certain therapy [33]. The focus is not on the individual but rather on a group of individuals with similar characteristics. To bring PM to the next phase, it is important to move away from stratifying patients in subpopulations instead of focusing exclusively on the individual. To make PM truly individualized, patients/ individuals need to be actively involved in their treatment decisions [33]. PM is not only based on the genetic characteristics of the individual but also on their beliefs and preferences. To make PM truly individualized, patients have to take an active role in the treatment decision process.

In summary, several of our current approaches with regard to PM are not fit-for-purpose and in order to move towards truly individualized healthcare, a shift in our understanding of PM is needed.

Several challenges impacting the uptake of PM have been highlighted throughout the research performed in this dissertation and the discussion. To overcome those challenges disruptive solutions that are fit-for-purpose are needed to strengthen the implementation of PM in Europe. In the discussion that follows, several solutions are presented which have the potential to improve the uptake and implementation of PM.

Systematic early dialogue

As highlighted throughout the dissertation, systematic and early stakeholder engagement and collaboration is often lacking. To further strengthen the uptake of PM, it is of great importance that all relevant stakeholders are collaborating from the beginning. The 'innXchange innovation wheel', which is discussed in more detail in Chapter 2, provides a tool to incorporate 'systematic early dialogue' as a key pillar in the innovation process. Only if all stakeholders, including policy makers, industry and citizens stop working in silos and start collaborating on local, national and international level from the beginning, will the benefits of PM reach the patients and healthcare systems. The EU's actions need to be fit-for-purpose to make Europe a leading innovator and to further strengthen the uptake of PM [34].

Health data cooperatives

The integration of big data analytics and the integration of ICT solutions will be important to strengthen the uptake of PM [2,4]. New technologies allow the collection of immense amounts of data through a large variety of sources. The integration of different data including biological, environmental and lifestyle data has led to a new understating of the complexity of diseases. However, healthcare systems and healthcare professionals cannot make full use of the potentials of big data mainly because data is often collected through different sources and stored in various silos, making it inaccessible. This inaccessibility is causing increased healthcare expenditures and ineffectiveness of healthcare systems [35]. Inaccessible data

restricts patients/citizens to be in control of their medical information and to actively engage in the decision-making process regarding their own health [35]. Patient empowerment is a crucial aspect of PM and as long as patients cannot access their health data, the uptake of PM will be challenging, and PM will not be truly individualized. The challenges that we are facing with regard to big data integration and patient empowerment indicate that current approaches are not fit-for-purpose.

As highlighted in scientific literature, 'Health Data Cooperatives' (HDC) could play an important role in overcoming those challenges to strengthen the uptake of PM [35-37]. HDCs are conjoint data systems which aim to improve access to data and to improve interoperability of data collected through a variety of different sources. HDCs are seen as a solution to addressing the problem of inaccessible data and patient empowerment [36]. The core underlying concept of HDCs is that those data systems are controlled and owned by its members (citizens / patients) and are based on an adherent trust structure. This disruptive solution allows the citizens to be in control of their sensitive data and addresses the challenge of data protection and data safety [35]. Patients can decide for which research purpose their data will be utilized and which company or research institution will receive access to the data system. The general idea is that HDC will remain non-profit and that revenues will be directly invested into the data systems and/ or used to fund research projects to address an unmet medical need [36]. The main characteristics of HDCs are transparency and collectiveness. Data will be shared in a transparent way and decisions regarding who will receive the data will be made collectively by its members [37]. In addition, patients/ citizens will become more empowered and health literate by being more involved in research and actively participating in the decision-making process regarding their treatment. In summary, HDCs are fit-for-purpose to address the need for more integrated and accessible data and to empower patient/ citizens.

N=1 Trials & Virtual Twins

New approaches such as 'N=1' trials are fit-for-purpose to further strengthen the uptake of PM. N=1trials are based on the understanding that each patient will be his or her own reference point/control. N=1 trials rely on frequent (daily, weekly) collection of all kinds of

data from one person over years [38]. The design of N=1 trials is based on the understanding that patient health data and genetic information are dynamic and changing over time [39]. Current statistical safeguards and standard designs can also be employed in N=1 trials. The response of patients to a certain drug can be done by applying statistical analysis similar to the analysis used in classic clinical trials. Not only have N=1 trials the potential to make treatments safer and healthcare systems more effective, N=1 trials are also fit-for-purpose to empower patients and include them in their treatment decision-making [38].

Computer models such as 'virtual twins' can be applied to improve treatment decisions and predict treatment response By using the available data of each patient, including genomic characteristics, lifestyle data and environmental data, patients can be modelled on the computer and treated virtually with a certain medication or a combination of drugs. This modelling allows an optimal treatment based on the individual characteristics of the patient to be found [40]. Computer models can find the right treatment in an easy, safe and cheap way instead of testing drugs and certain combinations of drugs on real patients which often causes health threats and adverse reactions, greatly impacting their quality of life. Computer models such as 'virtual twins' will not only achieve better treatment outcomes for patients, but are also fit-for-purpose to decrease the great financial burden on healthcare systems caused by ineffective treatments and related health consequences [40].

Flexible market authorization methods

Due to the new understanding of the complexity of diseases, large phase III clinical trials are no longer applicable and new ways of marketing authorizations are needed to further strengthen the implementation of PM. One promising disruptive approach is the adaptive pathways pilot that was launched in 2014 by the European Medicine Agency (EMA) paving the way for flexible marketing authorization for PM drugs [41]. MAPPs are defined as "flexible development and access pathways within the current regulatory framework that balance early patient access, public health and societal benefits" [42]. If safety and efficacy have been proven in a well-defined target population, early market authorization will be granted. Some stakeholders concerns regarding MAPPs include that pharmaceutical companies will try to acquire orphan drug status for their pharmaceuticals and consequently drastically increase

the prices of their drugs.[43]. However, the EMA's MAPPs approach is a pilot and there are still aspects which can be improved, and weaknesses identified in pilots will lead to improvements and further developments.

The momentum for PM is right

As described in this dissertation, the emergence of new technologies has led to a new understanding of the complexity of diseases and has shown that the current 'one-size fits all' healthcare approach is no longer fit-for-purpose. Thus, the momentum for PM is right to make healthcare systems more effective and efficient and improve the quality of life of millions of patients.

Over the last years several milestones have been achieved in strengthening the uptake of PM in the EU. One was the initiation of the Coordination & Support Action (CSR) PerMed, which was funded within the 7th Framework Programme. The aim of CSR PerMed was to increase collaboration among key stakeholders across the EU, to further strengthen the implementation of PM and to bring the benefits of PM to the patients and society. As part of the project, the 27 consortium partners, formulated the 'Strategic Research and Innovation Agenda' (SRIA) [34]. The SRIA was generated to provide a clear roadmap to further strengthen the implementation of PM. The PerMed consortium highlighted five key challenges with regard to the implementation of PM including: Developing of Awareness and Empowerment, Integration of Big Data and ICT Solutions, Translating Basic to Clinical Research and Beyond and Shaping Sustainable Healthcare. In addition, the SRIA includes 35 recommendations to address the five challenges [34]. The results of the research performed as part of this research are in line with the challenges highlighted by PerMed. The recommendations identified in the SRIA together with the best practice guidelines described in Chapter 2, can help to address the many challenges we are currently facing and to strengthen the uptake and implementation of PM in Europe and beyond.

Another key achievement in the last years was the launch of the International Consortium Personalised Medicine (IC PerMed). The consortium is built by more than 40 European and international high-level partners including several national ministries and the EC. The main

aim of IC PerMed is to support and strengthen research to further develop and implement PM. The work of this voluntary collaboration, which is led by European Member States, is based on the five challenges identified in the PerMed SRIA. The launch of IC PerMed is seen as an important step towards a stronger uptake of PM [28,44].

Not only is the EC supporting and promoting healthcare research, it also aims to strengthen the role of the healthcare industry to improve the implementation and adaption of PM. A flagship of the EU is the 'Innovative Medicine Initiative' (IMI). IMI is the largest public-private partnership (PPP) for health and care in Europe between the EC and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI aims to "boost the development of new medicine across Europe by implementing new collaborative endeavours between large pharmaceutical companies and other key actors in the health-care ecosystem" [45]. The mission of IMI is completely aligned with the vision of IC PerMed and both will be crucial to further strengthen the development of PM approaches [46]. In addition, PPP such as IMI can play an important role in supporting innovators to successfully bridge the Death Valley of innovation and to allow them to further develop their discoveries into marketable products.

Limitations

In this section I elaborate upon broader limitations regarding the innXchange innovation wheel and the scope of the thesis.

The innXchange wheel has been developed as part of the innXchange project among experts in healthcare and ICT in two European countries (Germany and the Netherlands) and two African countries (Kenya and South Africa). It is important to highlight that those countries are ranked high on the global innovation index. Germany and the Netherlands are ranked in the top 10 most innovative countries in the worlds, and South Africa and Kenya are the highest ranked Sub-Saharan African countries. The results might have been different if other countries would have been investigated which are less innovative. However, the research results of the dissertation have been compared with published scientific literature and reports and are in line with other research which addressed the whole of the EU and Africa.

The wheel has been developed by applying mostly qualitative research methods. To further validate the wheel and to generalize the results, quantitative validation will be needed. Moreover, more expert studies will be needed to further validate the innXchange innovation wheel. Therefore, larger study cohorts will be needed with experts outside of the healthcare and ICT sectors and in countries that score lower on the global innovation index.

However, even though the generalizability might be questionable, many of the findings of the research performed are in accordance with the findings of reports and publications of key stakeholders such as the United Nations and OECD.

In summary, the study design used in this dissertation has both pro's and con's. However, for this thesis an explorative research approach has been applied to shed light on the creation and management of innovation and to further study the importance of stakeholder participation and collaboration in the innovation process.
The explorative research performed in this dissertation provides new insights into the innovation process and the uptake and implementation of PM. However, more research is needed to fully understand the factors which are hindering or slowing down the innovation process.

Future outlook and concluding remarks

As highlighted throughout the dissertation, innovation in healthcare will be essential to address the many economic, environmental and societal challenges, which we are currently facing. However, the creation and management of innovations is often hindered by actions which are not fit-for-purpose to make Europe a stronger global player and to further strengthen the uptake and implementation of PM. As a consequence, we are often not doing the right things rights.

To overcome the identified challenges and to strengthen innovation and PM, systematic early dialogue between all stakeholders involved in the innovation process is needed. This includes policy makers, industry, researchers and the citizens/ patients, who need to start

collaborating from the beginning to ensure the that breakthrough discoveries or technologies can be developed into marketable products.

In addition, well organized innovation ecosystems, which address the whole complexity of innovation, will be of great importance to support innovators in the creation and management of their innovation. Legislations need to be revised and need to adjust quicker to emerging technologies and healthcare approaches such as PM, in order to be fit-for-purpose. Funding programmes need to ensure that there is a balance between funding supporting basic research and funding of the intermediate phase, to prevent innovators from ending in the Death Valley of innovation. In addition, changes in mindsets will be needed. Emerging innovation approaches are challenging mature markets and in order to keep up with emerging economies, Europe needs to be open and to learn from other countries and continents. Those emerging innovation approaches highlight that innovation is no longer linearly associated with R&D investments. Co-development and early dialogue will help Europe to regain its position as global leader.

The innXchange innovation wheel was developed in the context of healthcare and ICT and has been applied in this dissertation to assess the current uptake and implementation of PM in Europe. However, the innXchange innovation wheel also has the potential to be applied to other sectors. Many of the challenges identified in this dissertation regarding innovation are not only related to PM and healthcare but also to other areas. Therefore, the innXchange innovation wheel can be applied as a tool to strengthen the innovation process in many different sectors and can help to ensure that we are doing the right things right.

As highlighted in this dissertation, there are several issues i.e. early stakeholder collaboration, attitudes towards innovation, innovation ecosystems, that we are currently not doing right, and which greatly impact Europe's innovation performance. However, if those challenges are adequately addressed in the years ahead and we ensure that our actions are fit-for-purpose, Europe will again become a global leader and will be in the forefront of PM.

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VALORISATION

Valorisation

Personalised medicine is no longer an abstract healthcare approach. However, to become truly individualized, a final step is needed. The advances in genetics and healthcare over the last two decades have changed the landscape of healthcare and have led to a new understanding of diseases. In the coming years/decade further advances will enable the discovery and developments of truly personalised medicines and treatments. The analysis performed in this dissertation identified several hurdles and barriers that are currently slowing down the innovation process and the implementation and uptake of PM among European healthcare systems. Those insights will contribute to further strengthen the uptake of PM by addressing those challenges.

In the following paragraphs it is described what impact the research performed in this dissertation is likely to have for different stakeholders. In general, the results of this dissertation might be of interest for several stakeholders including policy makers, citizens, healthcare professionals and innovators. However, the relevance of the findings is not limited to the beforehand mentioned stakeholders, the result might also be of interest for other stakeholders.

Impact for innovators

The first target groups are the innovators. The innXchange innovation wheel, described in Chapter 2, is designed to help innovators to address the identified barriers as well as allow them to successfully create and manage innovations such as PM. The innXchange innovation wheel is not only providing guidance for innovators, it also emphasizes the inclusion of all stakeholders involved in the innovation process. The underlying concept of the wheel, systematic early dialogue, can be a crucial enabler for innovation and PM. The innXchange wheel and the guidelines are in accordance with the PerMed SRIA and are complementing it. In addition, applying the innXchange innovation wheel in this dissertation allowed to provide new insights with regard to barriers that are currently slowing down the uptake and implementation of PM. This new knowledge can help the PerMed consortium to further strengthen the implementation of PM in Europe.

The findings of the research performed in Chapter 2 and 3 have the potential to help innovators to improve their innovation capacities by addressing common challenges and

hurdles in the innovation process from the early beginning. The importance of systematic early dialogue has also been recognized by International Consortium for Personalised Medicine (PM). The consortium can play a crucial role in further validating the innXchange innovation wheel and to support its implementation and dissemination among key stakeholders.

In addition, the innovation wheel has been presented and discussed during two high-level workshops in Pretoria, South Africa in September 2017 and in Brussels, Belgium in October 2017. Invited participants of the workshops were high-level experts from the pharmaceutical industry, governmental institutions such as the representatives of the Ministry of Health of South Africa, research institutions such as the Netherlands Organisation for Health Research and Development (ZonMw) and the German Forschungszentrum Jülich, health technology assessment experts and private entrepreneurs. The framework was well recognized by the different stakeholders and more expert studies are now needed to further validate the wheel.

Impact for policy makers

The second target group are policy makers. The main findings showed that the innovation-ecosystem is of prime importance for the innovation process. Relying in the findings presented in this dissertation may improve the innovation process, since policy makers will understand the changing landscape of innovation better, which will allow them to modify their action to ensure that they are fit-for-purpose. As described in Chapter 2 and 3, innovation is no longer associated with R&D spending's. In addition, supporting the involvement and inclusion of all parts of society could be the key to improve the innovation process and to enable further developments in PM. Top-down approaches will be no longer applicable. New innovation approaches such as frugal innovation are currently challenging traditional approaches and have the potential to address many challenges that we are currently facing. If policy makers do not recognize those changes, Europe will fall further behind.

Approaches such as 'citizens science' and 'innovation / health literacy', which are described in Chapter 4,5 and 6, have to potential to strengthen the innovation capacities of Europe and the Member States. Citizens (the third target group) need to become actively involved in the

innovation process as well as in their treatment decision-making process. Health data cooperatives, described in more detail in Chapter 4,5,6 and 8, can be a crucial enabler for more involvement of citizens in science. However, it is important to mention that it is not exclusively the responsibility of policy makers to enable the involvement of citizens, it will also be the responsibility of the citizens themselves to become more active in the innovation process and as well as in the healthcare process.

In addition, policy makers will need to adapt regulation faster in order to ensure that new technologies are appropriately addressed. As highlighted, regulations and legislations need to support innovation and not hinder it. The results of the thesis highlight several regulations and legislations which are currently slowing down the innovation process and the uptake of PM. Policy makers can profit from the performed analyses. Throughout the dissertation disruptive solutions are presented will allow policy makers to address the current challenges appropriately. Disruptive solutions such as HDC and N=1 trials will ensure that our actions are fit-for-purpose to make Europe a global innovator and to further strengthen PM.

Impact for healthcare professionals

Furthermore, healthcare professionals, the fourth target group, can also benefit from the new insights. It will be of great importance that they understand the changing landscape of innovation and the potentials new technologies have. Therefore, healthcare professionals need to be more open for new technologies and medical approaches to provide patients with the best possible treatment. Especially, older generations of healthcare professionals are often reluctant to change and innovation and prefer traditional ways of working. The results dissertation highlight, that the traditional understanding of diseases is no longer working and in order to provide patients with the best treatment, they have to adapt their practice. The presented findings might help to introduce new approaches to healthcare professionals and to increase awareness of new technologies and healthcare approaches such as PM. Furthermore, healthcare professionals will have to include the patient as active participant in the treatment process instead of as passive recipient to further strengthen the role of PM.

I am aware that the research I performed is very explorative and that more research is needed to further validate the findings. However, key barriers that are currently slowing down the

innovation process and the uptake and implementation of PM have been highlighted and several disruptive solutions such as systematic early dialogue, health data cooperatives, N=1 trials and virtual twins are presented and which could help stakeholders to address the current challenges. Addressing the highlighted challenges, first on a small scale i.e. on local or regional level, can lead to bigger changes on national and even international level. The time is right for innovations in general and personalised medicine however we have to make our actions fit-for-purpose to achieve our objectives in the future and to make Europe a global innovator and to make Europe a pioneer in PM.

As it is with all scientific work, it can never cover the whole complexity of a topic in a limited number of pages. However, I believe that the findings of my research performed as part of this dissertation are innovative and contribute to the ongoing scholarly discussions as well as highlight / introduce new, until now rarely discussed topics, which need more attention in the next years to further improve the innovation capacities and the uptake of PM.

SUMMARY

Summary

To leapfrog into a future of sustainable growth, there is a pressing need to find new sources of growth to address the many economic, environmental and societal challenges Europe and the rest of the world are currently facing. Innovation will play an important role in addressing those challenges and is therefore receiving increasing attention on local, national and international levels from different stakeholders such as policy makers, researchers, industry, non-governmental organisations and the civil society.

Innovation policies not only matter for economic growth, but also for healthcare, the environment and many other areas. However, even though the benefits of innovation are well known and widely described in literature, these benefits do not always reach the society because many innovations end in the Death Valley of innovation during the process. Therefore, it is important to ask the question: **are we doing the right things right?**

In the past, the relation between innovation and economic growth has been studied in more detail compared to other policy areas such as healthcare. Against this background, research has been conducted to describe the innovation process and the current landscape of innovation in Europe in more detail. The focus of the thesis is on innovations in healthcare and the impact innovations can have on healthcare systems and the well-being of the citizens. The approach of Personalised Medicine (PM) was discussed in more detail as one current example of innovation in healthcare. Research was conducted to analyse the current status of the implementation and uptake of PM in Europe. This was done by applying the innXchange innovation wheel, which is explained in more detail in Chapter 2. The framework provides guidance on the essential parts and principles of innovation creation and innovation management. PM was chosen as an example since this innovative healthcare approach has great potential to address many of the healthcare challenges we are facing. Several parts of the innovation wheel have been analysed to identify factors which are either hindering or facilitating the uptake of this innovative healthcare approach.

Part 1: Current landscape of innovation

In the first part of the dissertation (Chapter 2 and 3), the current innovation landscape was analysed, and gaps and needs were identified. The findings indicated that besides its great

potential, innovation is often hampered due to a lack of systematic stakeholder collaboration and engagement throughout the whole innovation process. In addition, the importance of the innovation ecosystem which largely determines the success of the innovation process was highlighted. In such an innovation ecosystem a variety of different actors such as large and small enterprises, policy makers, academics and the civil society participate and collaborate from local level up to international level. Moreover, infrastructure, education, a skilled workforce, regulation and legislation and innovation funding schemes are all important pillars of the ecosystems. In addition, creativity, societal norms and values and attitudes towards innovation are of equal importance for the success of the innovation process. The research findings indicated that many of those factors are often lacking in the innovation ecosystems in Europe limiting innovation capacity.

The studies revealed the importance of open, frugal mindsets for successful innovation and that the landscape of innovation has drastically changed over the last few years. Being a top innovator is no longer necessarily linear associated with R&D spending's. New emerging low-cost innovation approaches such as frugal innovation are currently challenging mature markets and have great potential to address the many challenges the world is facing. Several examples of frugal innovation and how they impact the lives of millions of people are described in more detail in Chapter 3. Moreover, the results of the studies highlighted that due to the complexity of innovation and the many different aspects of which are influencing the innovation process, that there is no one-size fits all innovation approach.

Part 2: Application of the innXchange innovation wheel to analyse the uptake and implementation of Personalised Medicine in Europe

Over the last years, PM has become a reality and is successfully applied in various medical fields and therefore is no longer an abstract healthcare approach. Although there are success stories of implementing PM, several challenges need to be addressed to further implement and make full use of the potential of PM. By applying, the theoretical framework of the thesis, the innXchange innovation wheel, the current situation of the adaption and implementation of PM in Europe is analysed in more detail. Factors that are currently hindering or facilitating the uptake of PM are described and highlighted in Chapter 4-7. Analysing parts of the

innXchange innovation wheel in more detail provided insights into whether we are currently doing the right things right or whether some of our actions have negative impact on the uptake of personalized medicine in Europe.

Several challenges impacting the uptake of PM have been highlighted throughout the research performed in this dissertation and the discussion i.e. funding approaches which focus almost exclusively on basic research; silo mentality; outdated regulation and legislation; PM is not yet truly individualized.

To overcome the identified barriers that are currently slowing down the innovation process and the uptake and implementation, the importance of systematic early dialogue is emphasized in this dissertation. It will be of great importance that all relevant stakeholders are collaborating from the early beginning in order to further strengthen the uptake of PM. The innXchange innovation wheel provides a tool to incorporate systematic early dialogue as key pillar into the innovation process.

Only if all stakeholders start collaborating in the innovation process on local, national and international level from the early beginning, the benefits of PM will reach the patients and healthcare systems and our actions will be fit-for-purpose to make Europe a leading innovator and to further strengthen the uptake of PM. In addition, health data cooperatives; virtual twins; N=1trials and flexible market authorization models are disruptive solutions and will improve the uptake and implementation of PM.

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I was not on top of my game. Thank you, Laura! I wish you all the best for your upcoming adventures and I cannot wait to cook a recipe from your cookbook.

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The next people I would like to thank are my “Maastricht boys” and my best friends. Dear Kevin, thank you for your support. You were the first person I met from our EPH bachelor program and of course we met at the bar. Since this day in August 2011 you have been one of my best friends and the best roommate I could have wished for. And yes, I think you are pretty.

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Cheers to all of you!

CURRICULUM VITAE

Curriculum Vitae

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Everyone has a right to health. I dedicate my ideas and strength to achieve this goal. I have a motivated, committed and problem-solving nature to apply my thorough theoretical knowledge to real life scenarios.

PROFESSIONAL EXPERIENCES

2018 - Present **Catalyze-Group, Amsterdam, The Netherlands**

Life Science Consultant

- Supporting project proposals, business plans, and grant applications for our clients in the life science sector, biotechnology and pharmaceutical development (SME's, academic research groups, large companies
- Market research on commercialization strategy of new medical products & medical devices, price setting of new medical products, league analyses, etc
- Building consortia by bringing different parties with innovative technologies and complementary expertise
- Function as contact person with each client and between consortium partners
- Taking care of complete proposal process up to project start including the project concept design, budget drafting and negotiation, involving end user organizations (professionals and patients)

2015 – 2018 **United Nations University – Maastricht Economic and Social Research Institute, Maastricht University,**
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Project Manager, Junior Researcher

- Project Manager of the EU FP7 project "innXchange", a project funded with 300,000 Euros within the ERA-net ERAfrica
  - Managing the projects agenda; project budget and meeting deadlines
  - Coordinating and managing the project communication (internally and externally),
  - Liaised with European and African policy makers, pharmaceutical industry and other relevant stakeholders
  - Conducting research focusing on social and technological innovation in healthcare systems in Europe and beyond.

2016 – 2018 **Department of International Health, Maastricht University, Maastricht, The Netherlands**

Teaching Assistant

- Tutoring and Lecturing of student groups in Bachelor and Master European Public Health;

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Policy Officer (internship, 4 months)

- Involved in organising the annual conference 2015 "Smaller Member States and Regions Together" (SMART)
- Contributed to the lobbying strategy and proactively engaged with policymakers (European Commission and Members of the European Parliament) and other high-level stakeholders
- Responsible for Social Media (Twitter, LinkedIn)

EDUCATION

2014 – 2015 **Maastricht University, Faculty of Health, Medicine and Life Sciences, Maastricht, The Netherlands**

***Master European Public Health* (1 year, 60 ECTS)**

Master Thesis: "*Does the European Union need more or better regulation to ensure equal access to Personalised Medicine?"*

2013 – 2013 **Malmö University, Malmö, Sweden**

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Participated in classes focusing on Physical Education and Sport Psychology and the impact on Health

2011 – 2014 **Maastricht University, Faculty of Health, Medicine and Life Sciences, Maastricht, The Netherlands**

***Bachelor European Public Health (*3 years, 180 ECTS)**

Bachelor Thesis: *"Is the health gap between Western and Eastern European countries still increasing 25 years after the fall of the iron curtain? Myth or reality?"*

LEADERSHIP & PERSONAL INTERESTS

2016	**Awarded Young Forum Gastein Scholarship**, European Health Forum Gastein, Austria
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SKILLS

Languages:

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Advanced working knowledge of MS Office
Endnote
Basic web page design skills

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Publications

Schee genannt Halfmann S, Evangelatos N, Kweyu E, DeVilliers C, Steinhausen K, van der Merwe A, Brand A: The Creation and Management of Innovations in Healthcare and ICT: The European and African Experience. Public Health Genomics 2019;21:197-206.

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