HEcoPerMed

Health Economics for Personalised Medicine

Deliverable

4.2

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EXECUTIVE SUMMARY

The **HEcoPerMed**[1] project has the twofold **aim** of responding to the demand for health economic models that evaluate treatments made possible through innovations in personalised medicine (PM), as well as studying existing shortcomings in stimulating the adoption of personalised medicine in health care systems. In addition to funding and reimbursement mechanisms which are certainly an essential part of implementation and institutionalisation of personalised medicine, this report takes a complementary perspective in exploring challenges and drivers in the implementation of personalised medicine in health care from a wider angle. The current report aims at capturing a real-time perspective of citizens, patients and other stakeholders on the current challenges and drivers around anchoring personalised medicine approaches in health care systems. Hence, the tasks leading up to this report had process aims – identifying and approaching stakeholders and including them in a debate, as well as explorative aims in seeking to identify their perspectives on drivers and challenges.

HEcoPerMed is part of the "ICPerMed Family"[2] which comprises a number of related projects, initiatives and research infrastructures, funded by the European Commission in close cooperation with the International Consortium for Personalised Medicine (ICPerMed) European Research Area Network for Personalised Medicine (ERA PerMed).

The **methods** used for this report are explorative qualitative interviews carried out in January/February 2022, and focus groups, and small workshops in the period 2019/20.

The chapter on the **significance of personalised medicine for patients** captures jointly with patients and carers, patient organisations and NGOs in the context of health, the benefits and challenges as well as accessibilities of personalised medicine for the patients. Grey boxes give insights into personal experiences from patients that shall demonstrate on how the perception of people concerned by a disease may be in contrast to what outsiders might expect.

Institutional support means that **personalised medicine** is actively integrated at a larger scale in health care systems in terms of programmes, budgets, regulation, infrastructure or organisational processes. It refers to the whole innovation chain, starting from the identification of challenges in R&D and evidence generation, as well as challenges in innovation, i.e. the practical use and market implementation of technological novelties and evidence. Beyond the identification of challenges in the early phases, institutionalisation encompasses different forms of collaboration, identifying and organising education and training, setting up necessary infrastructure and a beneficial regulatory framework.

Concerning **health economic considerations in the implementation** of personalised medicine in public health care, there are two different perspectives across all countries, aligned with two basic sources of public financing for personalised medicine. One) health care budgets, and two) research and innovation budgets. Related to health care budgets, there is an evidence-based reimbursement logic: cost efficiency and budget impact are of vast importance, as decision makers on the basis of their budgets at hand have to allocate resources to the most cost-effective therapies. If personalised medicine compared to

[1] www.hecopermed.eu
[2] https://www.icpermed.eu/en/related-initiatives.php

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standard of care does not prove cost effective, it should not be implemented. Related to research and innovation budgets, there is an investment logic according to which personalised medicine has desirable functionalities, but is still in its early days, and still deeply in the research phase. It is expected to pay off in the future. Hence, for reasons of competitiveness and future benefits, it may be very important to stay at the edge of research and implementation.

These are two kinds of perspectives that exist in parallel across countries, and they are at the same time in conflict with each other. The conflict is that in evidence-based health care systems, the idea is to first have the evidence to implement some innovative service. But in order to generate the evidence, it has to be implemented first. Countries and regions where innovation funding and healthcare reimbursement mechanisms are organised more closely are likely to have an advantage in the transition from the research phase to the actual implementation in healthcare, they are more prone to overcome silo thinking, and link to other strategies, like smart specialisation strategies, to pull resources together.

Across all interviews it was evident that there are **no procedures or stage gates that uniformly function** as entry or transition channels from early applications of research to wider implementation. Instead, these are **individual negotiation processes, sometimes based on regulation.** Hence, what is already done across countries is to implement testbeds and pilot projects for experimentation. Often these are already protected spaces, in that they are exempt from the DRG system, but mostly based on individual negotiations. At the same time, there is an awareness across countries that these **testbeds and pilots** are to be implemented to generate data and learning, including also data important for health economic modelling, with evidence on costs and health impacts.

Countries use **different approaches to implement testbeds** and pilots

- Infrastructure- centred testbeds.
- Testbeds centred around stages of the disease
- Testbeds according to a catalogue of criteria
- Testbeds around particular promising technologies

For further implementation of personalised medicine in healthcare in a phase that is clearly still characterised by high research intensity, high uncertainties and low economies of scale, these **testbeds could be turned into innovation niches**. **Innovation niches are a concept aligned with the multi-level perspective of system transformation**. They are protected spaces where deviation from existing pathways is encouraged. Around these loci of experimentation there can be structures designed to continuously iterate and enhance experiments or parts thereof that are promising and abandon of the experiments that are not promising. Health economic modelling should be integrated from the beginning, also to define data needs. European structures for evidence generation and learning can support aggregate learning across Europe, so that mistakes are not repeated, but build on the past experiences. (see also section on Innovation Niches – Setting up Experiments and Learn from Them)

Collaborations between academia, mostly in the form of research hospitals, and firms mainly referred to licensing agreements, start-ups, collaborative research projects, infrastructure collaborations, and collaborations of a more explorative nature in the form of one or more academic organisation and several firms.

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For **education and training,** the vast importance of molecular tumor boards was stressed, as it is a stage for different disciplines to seamlessly work together, such as pathologists, oncologists, pharmacologists, molecular pathologists, geneticists, surgeons, radiologists, bioinformaticians and molecular biologists. Furthermore, the experimental nature was emphasised, the need of certain new competencies in the profile of established disciplines as pathologists and oncologists. Here, beside the molecular tumor board networks, also international research projects, i.e., in the form of European Union research framework projects are of importance for education and training.

Necessary **infrastructures** that are partly in the process of being built up, partly in their infancy, are organisational infrastructures like reference centres and networks thereof, technical infrastructure like laboratories and biobanks, as well as technical infrastructure like electronic health records and IT infrastructure.

Relevant **regulation** relates to data regulation, in vitro diagnostics regulation, the EU Pharmaceutical Strategy and the definition of “unmet medical need”. To date, unmet medical need is used in the context of access to new drugs in several member states and on the EU level. Specification of the definition unmet medical need is under discussion. Still, it has regulatory consequences as on the EU level it is a criterion for conditional marketing authorisation and accelerated assessment.

Scenarios offer parallel stories of what futures with personalised medicine might look like from a wider societal perspective. Scenarios are by no means predictions, but represent plausible alternatives that differ, however, because different aspects are dominant in them. The construction of our scenarios demonstrates future options for financing and reimbursement models for PM in the EU and provides incentives for the discussion of alternative health care models. The results for the qualitative outcome of the four scenarios can be sketched as follows:

- Scenario 1: Cooperation – Public Health at Center Stage
- Scenario 2: Privatization – Personalised Medicine between Liberalised Markets and Regulations
- Scenario 3: Scepticism – Personalised Medicine in a Niche
- Scenario 4: Technology-driven – Subscribing to Personalised Health

Despite health being a national agenda, interviewees see specific roles at the European level in the implementation and institutionalisation processes around personalised medicine. Specifically, they mentioned, the role of maintaining pace in agenda and priority setting, setting up European learning structures/platforms for sharing evidence and increasing patient cohorts, cross-border collaboration and treatments, education and training through international exchange, public procurement strategies, standardisation, and data regulation.

The annex provides an overview of diverse types of networks that are operative and have influence on institutionalisation and implementation of personalised medicine. A tentative Figure sketches of how networks enhance implementation and implementation of personalised medicine approaches through fulfilling crucial functions for health care innovation.

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1 INTRODUCTION

The HEcoPerMed[3] project has the twofold aim of responding to the demand for health economic models that evaluate treatments made possible through innovations in personalised medicine (PM), as well as studying existing shortcomings in stimulating the adoption of personalised medicine in health care systems. While HEcoPerMed provided an overview of and guidance on high quality methodological approaches for model-based economic evaluations (WP1) and applied these in three case studies (WP2), the project also sought to identify funding and reimbursement mechanisms that provide financial incentives for the rapid development and propose financial agreements that accelerate its diffusion in European health systems (WP3).

In addition to funding and reimbursement mechanisms which are certainly an essential part of implementation and institutionalisation of personalised medicine, WP4 takes a complementary perspective in exploring challenges and drivers in the implementation of personalised medicine in health care from a wider angle. In coordination with WP 3 this includes also aspects of innovation, education and training, regulation and collaboration for the further implementation of personalised medicine. D4.2 aims at capturing a real-time perspective of citizens, patients and other stakeholders on the current challenges and drivers around implementation and institutionalisation processes of personalised medicine in health care systems. Hence, the tasks leading up to this report had process aims – identifying and approaching stakeholders and including them in a debate, as well as explorative aims in seeking to identify their perspectives on drivers and challenges.

HEcoPerMed is part of the "ICPerMed Family"[4] which is a number of related projects, initiatives and research infrastructures, funded by the European Commission in close cooperation with the International Consortium for Personalised Medicine (ICPerMed) European Research Area Network for Personalised Medicine (ERA PerMed). ICPerMed and ERA PerMed have developed in the last decade and together have an important role in research on implementation of personalised medicine in Europe, but increasingly also in other world regions.

Overall, HEcoPerMed uses the definition of personalised medicine given in the European Council Conclusion on personalised medicine for patients (2015/C 421/03)1 which reads: "[…] that it is widely understood that personalised medicine refers to a medical model using characterisation 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."[5] However, interviewing a variety of stakeholders these often referred to personalised medicine being an umbrella term that covers a variety of healthcare services. Many experts rather understand it as precision medicine in the form of genomic plus medicine, others interpret personalisation as more granular data-based stratification. Throughout this report, we made reference to the distinction where appropriate.

Personalised medicine is a rapidly growing field and holds great promises and expectations on its impact in society. However, the novel and disruptive elements and particularities of

[3] www.hecopermed.eu
[4] https://www.icpermed.eu/en/related-initiatives.php
[5] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52015XG1217(01)&from=EN, last accessed 31/03/22

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personalised healthcare do not make it easy for European healthcare systems to smoothly integrate PM based services in their architectures. A fundamental difference in PM is the heavy reliance on large sets of data that in the end lead to very small patient cohorts or even single patients. Obviously, if the trial population goes down to one, this has implications on methodology of how to conduct and organise research in the area. A particularity of personalised medicine in general is the speed of new evidence emerging. This rapid scientific progress in many areas at the same time complicates monitoring by individual professionals or even hospitals.

Especially in oncology, patients already benefit from therapies that can now be better stratified and thus unnecessary burdensome interventions can be prevented, reduced and side effects better treated. As countries widely differ in their reimbursement practices, some countries make health economic modelling/HTAs a condition for approval and reimbursement. In other countries, personalised medicines therapies are reimbursed from the day the of EMA's approval, at least in a hospital setting. However, here further challenges come into play that are partly related to the above differences of personalised medicine compared to other approaches. Hence, this report builds on expert interviews to get a wider perspective on the current benefits and challenges of personalised medicine and its implementation in health care systems.

After this introduction (chapter 1), the report starts with detailing the methods used for this report (chapter 2), it then elaborates on the benefits and needs related to personalised medicine from a patients' perspective (chapter 3) and on challenges and aspects of institutional support for personalised medicine (chapter 4). It provides an overview of the scenarios, capturing drivers of change and future aspects of PM, developed also in WP 4 of this project (chapter 5) and offers insights into what interview partners mentioned as important aspects for policy and practice of personalised medicine (chapter 6). The Annex contains a chapter collecting - without any claim to completeness - networks enhancing personalised medicine for health benefits (annex 9) and the interview guidelines.

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2 METHODOLOGY

The overall aim of the project type Community Support Action (CSA) is to support the communities around personalised medicine, on how to make the best personalised medicine solutions available for the patient, including its benefits and challenges for the feasibility of the health systems.

Linked to this, the aim of this report is to get a real-time perspective of how the personalised medicine field has developed so far. A real-time perspective has explorative but also continual aspects, meaning it includes considerations that have been known in the area for some time as well as challenges and benefits that emerge newly in the process. In the first case, issues may have been known to stakeholders for years or even decades, however, if they are mentioned in the interviews frequently, they are apparently still an issue. In the latter case, challenges or benefits emerge newly in the process of developing and implementing personalised medicine further and hence are new at least to the majority of stakeholders. In total, it intends to give an overview of what is open and unsolved by combining diverse stakeholder perspectives engaged to some extent in implementing personalised medicine in health care.

Hence the overall methodology behind this report are explorative qualitative interviews carried out in January/February 2022, focus groups, and small workshops, especially the scenario workshops organised for this work package during 2020, a stakeholder workshop organised in WP5 of this project in October 2021, but also smaller project internal workshops from 2019.

2.1 Topics of the interviews

Personalised medicine needs to be institutionally anchored in the health policy context, in the financing of health care and in medical research and development. In this task, we target national ministries, health insurance companies, pharmaceutical companies and extent also hospitals to identify ideas and approaches that would pay attention to the benefits of PM, and to tackle new pathways that show options for integrating personalised medicine at larger scale in the medical sector. Institutionalisation means that personalised medicine is explicitly part of a programme, of an institution and/or of a budget. We conducted interviews with experts in health policy, health insurance, pharmaceutical companies, and hospitals to see how aspects of institutionalization link with economic considerations and health economic modelling. Our questions related to what needs to be done to better apply personalised medicine in health care. Knowledge and interpretation of personalised medicine and its opportunities for patients varies among citizens. It was part of this task to assess the benefits and challenges as well as financial accessibilities of personalised medicine for the patient together with patient organisations and NGOs from the health sector.

2.2 Selection of interview partners

Explorative qualitative interviews are the main source of information for the current report. Various types of stakeholders provided valuable information Implementation challenges, achievements, organisation structures and support in their contexts.

We started the selection of interview partners from the audiences of workshops organised for this project, but also external workshops. In a first round we identified potential interview

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partners representing policy, ministries, health care agencies, administrators, healthcare insurance, hospital managers etc. from different countries.

Relevant workshops relevant in the present context were:

- HEcoPerMed workshop on “Personalised Medicine specific Health Economic and Payment Modelling”, hybrid from Budapest, 5/6 October 2021
- ICPerMEd Family Meeting, 9/10 November 2021
- 1+Million Genomes on Financial Arrangements/ PPP Genetic Testing, 20 January 2022

Snowballing technique: At the end of the first round of interviews we asked interview partners to name a further expert who would have relevant insights on these questions, which then resulted in the second round of interviews.

Table 1: Countries represented in interviews, from 2019-2022.

Country	Number of interviews
AT	4
CH	1
CZ	1
DE	4
DK	1
ES	2
EU	6
FI	1
FR	1
IT	2
NL	1
NO	1
SE	1
UK	1

Legend: 25 interviewees in total, individually and in focus groups, two interviewees were affiliated in two countries, and respectively gave insights on both.

The qualitative interview programme had two phases: One phase was for the scenarios in 2019 and 2020, here focused scenario workshops and interviews were carried out. During the second phase from December 2021 to February 2022 16 stakeholders were interviewed:

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- 10 on institutionalisation and implementation
- 6 on the patient perspective

In total, 25 people from 2019-2022 were included in WP4 to explore perspectives on the future of personalised medicine, on financing, institutionalisation and the patient perspective.

Reference to interviewees is anonymised throughout the report.

2.3 Transcription and Qualitative content analysis

In order to facilitate desk research and to analyse the amount of qualitative information, we transcribed the interviews with the transcription software Trint and applied qualitative content analysis. The qualitative content analysis allows classifying relevant parts of textual data according to the categories and helps to identify the themes and patterns in the coded material. It also facilitates the extraction of specific information coded under each category. For the data analysis, we employed data analysis software Nvivo.

Overall, the content analysis in the current study will consist of the following steps:

- Firstly, we collected all the interviews to be used for the content analysis in the Nvivo database.
- Secondly, we developed the coding framework, which mainly corresponded to the operationalisation of guideline questions.
- The third step consisted of coding, i.e. categorising material by topic;
- During the fourth phase we analysed the coded information and description of the patterns, sub-structuring the content and making connections.

2.4 Triangulation

The interviews were triangulated with a focussed literature research and web research to provide background and wider information interviewees' statements and especially on good practice examples mentioned by interview partners.

Although it was not an explicit aim of this task to identify good practices, in their interviews stakeholders themselves referred to examples that they found a useful form of supporting implementation of personalised medicine in health care. We tried to provide a short overview of these potential good practice examples and marked this by presenting them in blue boxes, with their websites as sources of information. As a collection of potential good practices they may serve as input for further research on the matter of implementing PM in healthcare.

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3 THE SIGNIFICANCE OF PERSONALISED MEDICINE FOR PATIENTS AND CITIZENS

Knowledge and interpretation of personalised medicine and its opportunities for patients varies among citizens. This chapter is an attempt to capture together with patients and carers, patient organisations and NGOs from the health sector the benefits and challenges as well as accessibilities of personalised medicine for the patients.

3.1 Personalised Medicine: Expectations from Patients

Personalised medicine or targeted medicine raises expectations in all stakeholders. Many patients and professionals expect high benefits from precision medicine and have a positive attitude towards it but also perceive risks. Commonly perceived risks include: lack of evidence for accuracy of tests and efficacy of treatments; limited knowledge of patients, which makes informed consent more difficult; inaccessibility to precision medicine for underprivileged people and ethnic minorities; misuse of data by insurance companies and employers, potential of racial stigmatization due to genetic information; unwanted communication of incidental findings; changes in doctor-patient-relationship through focusing on data; and the problem that patients could feel under pressure to optimize their health (Erdmann et al., 2021). Some of these benefits and risks were confirmed by the interview partners and are summarised below.

Talking from experience

Before a certain type of patients who have a visual defect were only being treated via surgery, but now medicinal products are being developed for this group, because of the knowledge of the genetic defects. Treatments become available and are being investigated by companies or academia. For social interactions this is a big step, not only for the children born with these malformations, but also for their parents. (PP05)

Personalised Medicine – hopes from a patient's perspective. Recent advances in biomedical research and biotechnology offer new possibilities to tailor prevention, diagnostics and treatment to the specific needs of patients. By utilising information about the patients' genetic and molecular profile combined with their family history and clinical and environmental data, hopes are high that health care providers will be able to start interventions earlier and select therapies that are more precise, efficient and provide less side-effects – strategies broadly known as personalised medicine (Budin-Ljøsne and Harris, 2016). Some interview partners were more specific distinguishing between personalised medicine and targeted medicine, which is targeted at a group of patients rather than an individual. The awareness of interview partners, who were in some cases affected persons themselves or close relatives, was that patients thought of personalised medicine as being tailored to themselves. What the patient expects is that the treatment is individual, that one is not treated on the basis of statistical curves or simply as the cancer patient. Instead, patients with a very specific illness expect to be dealt with in a specific and individual way (PP02).

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Implications for everyday life. However, patients do not usually differentiate between all different classes of medicines, instead they want something that works for them, that has an effect on their disease and does not cause many side effect problems. From the patient perspective, relevant questions are 'How is this going to affect my condition? How is it going to help me in my everyday life? How is this going to fit in with the other treatments or the other activities that are important for me?' The expectation is that a medical approach, whether it is personalised medicine or not, will have an efficacy advantage and not result in side effects (PP06).

“With personalised medicine we can target therapy and diagnostics and interventions on the specifics and biology of the individual patient and tailor it to that, as the mechanisms of the disease and the mechanisms behind that are better understood. From a patient’s perspective this is desirable because they want timely diagnosis, the right treatment for the right patient at the right time, avoid overtreatment or undertreatment or ineffective treatment.“ (PP03).

Individual learning and acceptance. A patient, a person who is diagnosed with a certain condition, is at the very beginning of the route of accepting and managing their own condition. The expectation of patients toward personalised medicine is primarily that they are able to make necessary decisions without imposing unnecessary constraints or expectations on themselves or on their families. Personalised medicine is also described as a route towards finding out more about oneself, how is a person composed? What matters most to the individual? To what extent does the DNA, history of origin, family history of illness, everything that is somehow connected, play a role? And where can patients be treated individually? (PP01, PP02, PP04).

3.1.1 Benefits of Personalised Medicine for Patients

Superiority of a tailored approach. When asked about benefits of personalised medicine for patients the responses mostly refer to an increase in security, a high value attributed to getting a therapy that is tailored to the individual and which results in a better chance of being cured, increasing the quality of life or perhaps even prolonging life. (PP02).

Better self-management. Others saw the biggest benefit for the patient in the fact that they could manage their own condition better, have a broader choice, and a clear understanding about treatments. Patients really want to take control of their condition to have the opportunity for better treatment, to compare treatment and to decide themselves what is best for their condition (PP04).

Commitment. Patients perceive the commitment through allocating additional resources to their healing as a benefit. Benefits for the success of a research programme through patient engagement and empowerment were seen in much bigger commitment because a patient being approved for an expensive therapy and perhaps a very individualised therapy makes a difference to them (PP02). This has then also repercussions on the adherence to therapies.If patients are involved from early on in the planning process, how clinical development processes are designed, if patients and families are engaged, then (a) they are more likely to be successful, (b) it is likely to cost less because they will be able to recruit and retain patients and their families through the programme. Patients will comply with the programme more comprehensively and effectively. This in turn results in pharmaceutical companies being able to make informed decisions about quality, safety and efficacy (PP01). The advantage of involving the patient in developing and the personalising medicine is to increase the efficiency also of the clinical trials. (PP04)

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3.1.2 Challenges for personalised medicine

Increasing costs. High costs, that are involved with personalised medicine were named as one of the foremost challenges in personalised medicine. Budin- Ljøsne (2016) state that PM may be too expensive for many health care systems which are currently dealing with significant financial constraints. Thus, patient access to conventional treatment is increasingly restrained due to cost issues and new targeted drugs enter markets at prices that patients can hardly afford unless their cost is fully covered by insurance. These high costs may reinforce already existing health care disparities among social groups and cause inequitable access to Personalised Medicine. Therefore, it was seen important "that it is possible to explain to people who do not know the disease, why it is important to have a treatment which is often very expensive. Patients should ask industry to be more transparent about their pricing models." (PP05)

Transparency was requested, when differences between countries were visible regarding funding. If patients in one country are reimbursed and not in the other, it creates a tension. There is hope that a European access or European-level pricing negotiations can alleviate differences between countries. (PP05)

Accessibility in the form of availability. Accessibility has two dimensions, one is availability, the second comprehension in the form of patient literacy. The fact that PM may not be accessible for everyone was attributed to difficulties in access to specialists or specialised clinics, and furthermore a lack of time and thus commitment of patients to the numerous necessary tests and screenings: "A lot of tests, screenings, for example, biopsy and very complicated checks are necessary, but at the same time very different information is provided by health care professionals from the beginning. Very often patients are not able to dedicate the amount of time necessary because it is very time consuming, and it also depends on the condition of the patients." (PP04)

Patient literacy. Patient information and patient literacy were listed by interview partners and in publications as challenges for personalised medicine. Patients struggle with understanding medical information or have difficulties accepting that their disease does not have the genetic profile relevant for a certain medical treatment to work for them (PP06, Budin- Ljøsne, 2016). Also, a hype created by media regarding personalised medicine must be avoided. Furthermore, finding experts, healthcare professionals or an expert centre able to deal with specific mutations, expert in all latest developments and in providing and applying molecular diagnostics, plus on top of all this is also able to explain options and consequences in order to have shared decision making in personalised therapy is very challenging. (PP03, PP05)

Media hypes and disappointments. One of the major challenges with personalised medicine that makes it so different from other therapy types is that it inevitably leads to small patient populations. "Patients might read about a new development in the newspaper as being a breakthrough in treating lung cancer. However, that breakthrough might only apply to a very small number of patients, but that is never clearly explained in the mainstream media. Hence it can lead to a lot of disappointments from the patients' perspective. As the term personalised medicine has a lot of different meanings, that is becoming very confusing for the patients." (PP06).

Solitude. Targeting only small groups or single patients with personalised medicine also means that patients are more alone with their disease. This entails that they cannot share their experiences, and thus also have guidance from fellow patients on how to deal with side effects and symptoms. Patients then may perceive that they are increasing left alone.

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Talking from experience

10 years ago, when a new cancer treatment was launched, the standard of care was a drug called warfarin, which had a lot of side effects. Patients on warfarin have to go to clinics often, and have their blood checked to ensure they are on the right dose of warfarin. When new treatments come along these warfarin clinics were not needed anymore. It was expected to save the health care system a lot of money and that treatments were more convenient for patients. It turned out that patients liked coming to these clinics. They could see their friends at the clinic because they all had the same appointments on the same days. There was a lot of resistance from the patient community of abandoning the warfarin clinics. (PP06)

In total, benefits have to outweigh the disadvantages, which come along with more frequent testing, difficulties in finding experts or other patients with similar medical conditions to share of experiences.

Data collection & Data Security. Other challenges were seen in terms of data collection and sharing. Not only data exchange across borders, but also between specialists or clinics needs to be taken care of, as here data protection was named as issue as well. Collection of data must be carried out with moderation: “It is often that intersection: not where does the research stop but where does it definitely bring benefit to the patient and where is it only about collecting more data for the sake of it?” (PP02)

3.1.3 Perspective of relatives and caretakers

The impact of a chronic or acute disease on patients as well as their families must not be underestimated. Many interviewees stated that a small change in the health status of a patient can improve not only the quality of the patient’s life, but also the quality and the freedom of those who care to have a more normal life.

Impact on family life. Family members caring for relatives with various chronic diseases are impacted in similar ways in terms of physical, social and psychological wellbeing: “if it is their family members who are caring for the patient, then their lives are similarly constrained by the patient’s needs as the patient’s own life” (PP01). Some publications suggest the development of a generic family Quality of Life measure which offers acceptable practicality and flexibility both to the relatives and to researchers (Shah et al., 2021). For children, the burden of care usually falls mostly on parents and leads to a high level of stress exposing the entire family to a greater risk of psychological or functional problems. Depression and other consequences can also lead to negative effects on growth and the relationship with other children (Moretti et al., 2021). This was also emphasised by interview partners in terms of the societal costs of having a child with a severe disease. Often at least one of the parents works part time. Additionally, there are effects for the family and for the wider environment and the whole life. What makes lives difficult is the sum of a child’s illness, the therapies, care, disability levels and family allowance, or care needs and care facilities,. “Getting organised at home as a parent, kindergarten, school, allowances, subsidies, everything families need when they have a child with a disability or a chronic illness.” (PP02)

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Expertise of families and caretakers. At the same time parents and care givers have gained vast experiences and insight in the conditions of a disease. “Patients and families expect that attention is given to the sustainability of their knowledge for undertaking research into that particular condition” (PP01). Involvement of families and caretakers was therefore seen as beneficial at all stages of personalised medicine, from research development to regulatory issues. Special attention should be paid to the design of studies.

Ethical issues. Ethical issues have to be considered, especially in the design of a study with control groups, where a standard of care therapy is used that has proven not to be effective in the past. Involvement of patients or relatives in the design of a study will lead to a more beneficial outcome: “You do not participate in a trial to go in the control group. If you want the standard of care you take the standard of care, you do not go to trial. And if there is a potential benefit that research very concretely can deliver to people who have no other options, then it is necessary to learn from these experiences.” (IP09)

Talking from experience

There are always hurdles everywhere. If it is a particularly expensive therapy, then it can be difficult to get approval for the therapy costs by national health services and to find out how and if one can get it approved again. Especially for parents with children, and especially for single mothers, (“I deliberately say mothers because I think I know one single father and otherwise it was always the mothers.”) there is a vicious circle they get into: Not being able to go to work because of caring for a child. Not being able to find anyone who can adequately look after a child. School causes problems because the child cannot be included. And there are countries where there is no legal entitlement to kindergartens as an exception clause for children with disabilities for the compulsory kindergarten year. It says in a friendly way if it is not possible or if we do not have the staff for it, or if the care or medical care is too time-consuming, then the child may stay at home. But that only means that it is excluded and simply not included. (PP02)

3.1.4 Needs and additional requirements

Need for social integration. Today there is often a better understanding of the situation of what it means to live with a disease and what it means for a person to be prevented from participating in social life. Integration of children with diseases in all levels of education from kindergarten up to higher education systems so that also parents and care givers can be relieved and be able to work full-time is emphasised in many interviews. “I know that people need faces to go with the stories, because otherwise they do not understand. Nobody can imagine what our everyday life is like and what it means for a person not to be a member of society automatically. That is unimaginable for a healthy person.” (PP02)

Needs of patients, caretakers and relatives

Additional needs stated by the interview partners concerned relatives, patients and caretakers. Different circumstances and lifestyles have influence on the possibilities for patients. Needs might be very different depending on the stage or age, but also depending on the social status, the work environment, or single people versus people living in families. (PP03). How therapies can fit into daily life and routines must be considered, when designing

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studies as “we need to think about different ways how to cope with the fact that a lot of tests are time consuming and that not too much pressure is put on the patients” (PP04).

The integration of therapies and life outside clinics and hospitals has to be taken into account. Interview partners especially stressed the need for support of families with children who need medical treatments, when it concerns the possibilities of integration in the regular school system, and for adult patients after they are discharged from the hospital after a long stay to find out about where to exchange information, potentially find support or exchange groups or about access to different aids and assistance. ”Nobody in the hospital tells you that, at most the social worker, and they are constantly being cut back.” (PP02)

Need for mutual learning

Although many patients are convinced of the benefits of PM, their actual knowledge of its potential appears to be limited. Many professionals reported that patients have little or no awareness about the concept and potentials of PM and these professionals are sceptical about whether patients have the ability to understand PM (Erdman et al, 2021). Also, in the interviews in this project the interviewees stressed a need for information and learning, at the same time patients have diffuse yet very high expectations related to personalised medicine. “There is a big bridge of understanding that needs to be built about what is a personalised therapy, and why personalised therapies are so important.” (PP06). How the scientists and the doctors are talking about personalised treatments and how the general patient community sees these innovations talked about in the mainstream media or the web is largely unconnected. Information is necessary to make patients understand how personalised medicine works, how they could afford personalised medicine, and how actually the personalised medicine could have an effect on their quality of life and their treatment in general. (PP04)

At the same time, it is of importance for clinicians and industry to have more information on the burden of a disease for the patients and to accept patients as experts of their everyday life and requirements. Patient representatives can be of support here in translating and in thinking about how to better address what is the value of the treatments, also to make it more acceptable for society. “It needs an explanation for people who do not know the disease, why it is important to have a treatment which is often very expensive.” (PP05)

Overall, it will be necessary to avoid a hype of personalised medicine. The patient communities have to be careful of not over-hyping personalised medicine. They realise that evidence has to be generated to make sure that personalised medicine delivers on its promise. “Patients and patient groups are tired of the hope and hype cycle. Patients want to be told the full facts, the negatives as well as the positives, and all the unanswered questions.” (PP06).

Education and training for patients and for various other stakeholders were seen as the foremost action point and various organisations were named who already offer this service (e.g EUPATI[6]). Education is the first step that patients can really understand all kinds of aspects of research and development and involvement with different stakeholders. (PP04). The need for educational and training programs for both citizens and healthcare professionals and providers was confirmed in a survey taken by (Venne et al., 2020).

Need for communication

[6] https://www.eupati.eu/, last accessed 31/03/22.

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Not only information but also communication between stakeholders is needed to support the realisation of personalised medicine. Tthe “patient’s voice” is important and shall belistened to through the involvement of patient organisations. “On the other side there is a very limited understanding of what patients want because of the health system and health care responsibles often seem to assume they know best what is best for patients. They do not ask properly, and when they ask, then key opinion leaders and clinicians. Key opinion leaders and clinicians see the clinical sides in very short meetings with patients, and they see the biology and the clinical effect, but they do not see the whole context of what it means.” (PP03)

3.1.5 Modelling and Assessment of Personalised Medicine

Uncertainties about costs. Personalised medicine is on the one hand linked to high prices and costs, while others claim the potential of cost savings due to therapies being prescribed only to those likely to benefit and improve health outcomes, e.g due to dose adjustments in those at high risk of adverse events. Objective evaluation and assessment of effects and benefits are called for, especially as personalised medicine affects not only the patient, but also the industry and it is important to know about and assess these effects and benefits for both sides (PP04). Especially with personalised medicine, a number of uncertainties regarding the evaluations were mentioned in previous interviews in the project, such as in evaluation of effectiveness due to small study ample sizes or complex clinical pathways (Vellekoop et al., 2021).

Transparency in assessment criteria. Interview statements were aligned in that there is a need to be transparent and very clear about assessment criteria, the data and to create an awareness in patients what they are participating in and what the advantages and disadvantages of using this kind of medicine are. (PP04, PP05)

Assessment according to patients’ needs. However, it is perceived as problematic that industry is still focused on creating evidence to get regulatory approval with regulatory bodies, namely the FDA in America and the EMA in Europe, while not generating the kind of evidence to build an own narrative for assessment of personalised medicine and for potentially adapting existing assessment methods (PP06). For assessment it was considered essential to comprehend what patients want and to know the expectations in terms of effects on a disease, the effects of the treatment and the effects on everyday life. Here the perception of patients is that their priorities and needs are often neglected. The conception by interview partners was that it is assumed by the people in the health care system that they know best what is best for patients. For clinical measures, this suffices because it is possible to measure overall survival, but what is not measured is patient reported outcomes. Hence, the quality of life, their needs, functioning activities of daily living are often not taken in consideration. (PP03)

Patient reported outcomes. In assessing the patient reported outcomes creates a more comprehensive picture “than if clinicians are asked who maybe see the patients only once in a while” (PP01). For personalised or targeted medicine, which often includes rare diseases, it is more difficult to specify evaluation criteria, than it is in diseases like multiple sclerosis, with a number of validated quality of life measures that are condition- specific and that have been developed consulting with those who have the condition.

Assessment involving relatives. Interview partners stressed the importance to involve patients or patient representatives to think about how to better address what the value of the treatments is and to make it more feasible for society. As patient community indication must

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be given as to what should be measured and why it is of importance. (PP06) For some interview partners the assessment needs to include the societal costs of a disease, especially when considering the costs of having children with diseases as there are effects on families and caretakers that influence their possibilities to structure their life, e.g. parents only working part time.

Societal perspective in health economic modelling. Different kinds of data are necessary to assess personalised medicine and the standard of care from a wider societal perspective. It has to be defined where the data requirements are and how these data should be collected. Guiding questions should be: How much better are the citizens going to be? How much better is society going to work better because the citizens are in better health? (IP07, PP04, PP06)

Assessment steps. The definition of evaluation criteria is the first step, the next step is the actual technical realisation on "how you measure", and the evaluation of the relative importance and acceptability of those criteria, "which is something where patients can be of support ." (PP01)

Patients in Health Technology Assessment (HTA). Patient representatives often argue for specific patient reported outcome measures, which has disadvantages for the comparison of between different treatments to make resource allocation decisions. Hence, in HTAs standardised patient reported outcomes that work across disease areas are preferred as a benchmark. Patients feel there is a discrepancy between a standard that works across disease areas, and specific measures for one disease area, which is what patients would often prefer. As the connection between HTA and personalised medicine seems weak for some patients, they suggest this as an area to focus efforts for further developments. (PP04, PP06)

Patient-centred core impact sets. Patient centred core impact sets were seen as a possible way forward. France was mentioned as a possible model, where the health technology assessment body, took the model that was built by HTAi for patient involvement in health technology assessment and adapted from there. (PP06)

HTA frameworks for personalised medicine. Novel frameworks can help taking patients' views in HTA into account. Three roles that HTA stakeholders can play in innovation ("Developers," "Practitioners," and "Beneficiaries") have been defined, and a process on how the stakeholders innovate HTA methods is included. The framework visualises systematically which elements and stakeholders are important to the development and implementation of novel HTA methods. (Jiu et al, 2021[7]). (PP05)

Assessment and patient organisations. Involvement of patients in health technology assessment often takes place at the level of patient organisations. Patient organisations function as intermediaries finding patients for specific diseases within their data bases and mediating between patients and HTA agencies. In single cases, they may design apps for data collection that include the recording of additional data. This cooperation can change the conversation about where the value is for a particular treatment, from managing symptoms, to delaying a surgery, which for some subgroups of patients can be important and valuable (PP06).

[7] Jiu, L., et al. (2022). "Understanding innovation of health technology assessment methods: the IHTAM framework." International Journal of Technology Assessment in Health Care **38**(1): e16.

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3.2 Empowerment

3.2.1 Layers of Empowerment

Importantly, patients want to be involved at the design stage of a study, and not at the end of studies as reviewers. There are several tiers when it comes to the possibilities of patient and stakeholder involvement. Depending on the granularity, the different tiers must be integrated and consulted. “If high granularity is wanted, then they have to talk to the individuals. If an umbrella perspective is wanted, then it is better to engage with the advocacy group, the support group, and through that reach the patients.” (PP01). From patients and carers a subjective experience can be gained, while patient advocates give wider community insight (PP03).

Patients provide the first-hand experience to different stakeholders, on how to live with a certain condition. Close to them are the caregiver, who are sometimes relatives, spouses or partners, or parents. They also have this kind of first-hand observation how this condition affects the patient and the quality of life of the patients.

The **patient advocates**, **or patient representatives** are beyond personal experience with increased understanding of subgroups and patterns that concern the whole patient population. They see the whole diversity, which is essential for research. Often, but not necessarily, they started as patients themselves. They usually have in-depth knowledge, energy and understanding how to manage their own condition and at the same time, they are willing to help people who are going through the same experience. (PP03) They are often affiliated with patients’ organisations or institutions that are working with patients and they have an understanding about the condition from their work with patients. (PP04)

Furthermore, there are **patient experts** who have an increased understanding of the different research and development processes, and of how to interact with different stakeholders. These patients have technical training on, for example, drug protocols, patient reported outcome measures because they need to have some kind of technical knowledge to work with clinicians or researchers on eye level to understand the processes behind research (PP03). In HTA exercises, patient experts are often deliberately invited to meetings (PP06).

These patient groups or experts are expected to bring a broader view of what are the patients’ concerns or what are the expected benefits, while individual patients will be expected to bring their individual point of view. Patient groups would normally do surveys of their patient community as well as interviews. They are often consulted if they know patients who take a new treatment or have a relevant disease. (PP06)

A **third layer** is **patient organisation** representatives which are institutional representatives. They will provide the opinion of the organisation or their board, which for policy decisions might be important to weave into a political process. (PP03)

These different layers of patients, carers, patient advocates, patient organisation representatives, patient experts, can and should be involved, depending on the questions in research, treatment or policy development. (PP03) **Industry** involves patients, for example, for protocol reviews as well as for designing clinical trials. (PP04)

Additional Stakeholders. Not only the public-private partnerships but also different stakeholders like health care professionals, industry representatives and HTA bodies, are suggested to provide opportunities for engagement and cooperation which also needs awareness. “With the joint effort from all different stakeholders, we will get to the point where

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it is not going to be something extraordinary but something normal to have patients and other stakeholders collaborating during the course of developments." (PP04)

Formats. Most health care systems already work closely with patient groups in the patient community. They already work together on various projects and various forums with the patient communities. In different consultations the patient community is invited to take part in. (PP06) However, it depends on the disease area as well if there are any patient groups existing.

Initiation of patient engagement. Ideally the health care system should function as the initiator of patient involvement and also co-creation processes between patients and different stakeholders "as the health care system has the trust of the patient population already. Most health care systems already work quite closely with patient groups in the patient community on various projects. They have various forums and consultations where the patient community is invited to take part in these consultations." (PP06)

3.2.2 Benefits of Patient Involvement

Patient engagement or involvement is a form of commitment by healthcare professionals to include patients in discussions and decisions on individual care and on the development of plans for therapies and research. While empowerment is a wider, more complex concept that encompasses commitment and action by patients that are self-derived and self-driven and may occur outside the interactions with healthcare professionals. The European Patients' Forum (EPF [8]) defines empowerment as a 'multi-dimensional process that helps people gain control over their own lives and increases their capacity to act on issues that they themselves define as important'. However, it is also not easy to distinguish clearly between patient empowerment and patient engagement as they overlap, interact and strengthen each other. Also, in the interviews it was sometimes not clear if interview partners referred to empowerment or rather engagement, but all interview partners were strongly in favour of patient involvement to a higher degree.

Patients emphasise that bringing their context and insights into treatments and therapies is of highest relevance also for doctors, health economists, and HTA bodies.

Involvement at all stages. Patient involvement should already begin at the planning stage, if not before at the definition of research programmes and calls by funding agencies and should continue right through the process of research and clinical studies, to the ultimate delivery of treatment, leading further to regulation, legislation and ethical discussions. Patients should be involved at the time the research proposals are being written, where they can provide support in the formulation of research questions, the structure of the programs, definition of activities and work packages, hence spanning the bow from research design and conduct, over the evaluation and measurement, and interpretation of the research results. (PP03)

Commitment. Early involvement of patients will also ensure that therapies are better targeted at the needs of patients. Assessment categories have to be better adapted to evaluate what is relevant for patients' lives, while at the same time this engagement also ensures higher commitment of patients, families and care takers. Patient engagement may also result in reduced costs for recruitment and retainment of patients and families in a programme. Patients are important allies in engaging both with healthcare professionals and

[8] https://www.eu-patient.eu/policy/Policy/patient-empowerment/ last accessed 29/03/22

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with regulators, but also with policy makers to prepare the ground through advocacy and through campaigning for an appropriate licencing and regulatory decision and ultimately for HTA, pricing and reimbursement. (PP01)

Reporting outcomes. Especially valuable contribution was seen in the evaluation of the outcome of treatments on the (everyday) life of patients, their families and caregivers. What appears to be only a small change for clinicians may have a big effect on patients' life and thus may be considered of higher relevance. Patients' families can contribute insight into the nature of the condition, and they can report on changes that are brought about by the development programme, including things that were perhaps not thought about in defining the end points. "How to measure something is a technical question. How you evaluate the relative importance and acceptability is something which patients can help you with." (PP01) There is also sophisticated thinking from the patient community on what kinds of input should be captured in clinical trials. Here, patient centred core impact sets are seen as particularly promising. (PP06)

Talking from experience

One of the measures used as an end point was a mobility test using a six-minute walk test. For parents the point at which they transition to dependence on a wheelchair for mobility of their children marks a huge step in their perception of the progression of the disease. The longer they can delay the transition to a wheelchair from a parents' point of view, the happier they are. But talking to the patients themselves, for them actually transitioning to a wheelchair can be liberating because up to that point, their mobility is very limited as they dependent on crutches to support themselves. They cannot move around without spending a lot of energy, and they do not have a lot of energy because of the deterioration of their disease. And, what they would value more than delaying the transition to being a wheelchair user is the maintenance of their hand functions. Because with their hand functions, they can interact with the world at large through IT, through keyboards, through social media, which is more important to them. But there is not a sort of six-minute hand test like a six-minute walk test. "It is necessary to develop appropriate and reasonably well validated measures of quality of life that are to some extent disease specific, and which could pick up on the things that matter for the people concerned rather than the things that that can be simply counted and are understood by everybody." (PP01)

Insights on additional therapies. Patient engagement can also bring context and give insights to the needs of patients for additional therapies. Because of the close cooperation of patients with their clinicians, additional measures can be taken, that involve other professions, as physiotherapy. This can add to an improvement in patients' life circumstances. "The practicality, the applicability for the patient should be more in focus: what can this mean in a treatment or in a therapy, if certain data are collected? What are they good for? Will the data give insights to achieve a statistically relevant improvement in quality of life or prolongation of life?" (PP02)

Talking from experience

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Patients with speech impairments were offered speech therapy with logopaedics, which was a true add on to their therapy. “That meant something to the patients. Doctors do sometimes not realise what things are important for patients. Also the paramedical team can be involved in that, like physiotherapist or other people, health care professionals.” (PP05)

Benefits for industry. From the point of view of industry and the research institutes developing a drug or therapy patient engagement at an early stage is beneficial. “Industry, clinics and scientists put a lot of money into research, so they need to make sure that they are hitting the right target. And if they do not involve patients, they might end up with a study that is not able to recruit because patients do not like it.” (PP03)

Lobbying by patients. Still a lot of pressure comes from patients insisting on or lobbying for therapies, and reimbursement by health services, or for additional research (funding) in terms analysis of certain biomarkers. “Cancer groups are running campaigns like 'Know Your Biomarkers' and really advising patients to insist on having their tumor genetic profile. And the fact that the patient groups are having to do this, tells you that it is not routinely happening. “(PP06) “When Herceptin - came to the market, patient advocates were demanding it. They were wearing T-shirts and chanting that they want this medicine.” (IP05)

Organisation of data collection. Patient engagement can result in the collection of additional data. Increased patient involvement in studies also results in more willingness to report patient data provided the purpose is clear and beneficial for the patient’s life. Organising the data collection is a further challenge that can be more easily solved if patients are involved. Apps are a means to add additional data and collect them in a special data base. Patients report in the form of an individual logbook, that can also be used during doctors’ consultations or simply for their own reference. In an example mentioned, an app was designed in a co-creation process and is accessible through a patient registry. (PP05)

Raising community awareness and co-creation. Patients can help to engage others and make the patient community aware of the likely benefits of the novel intervention. It was generally perceived that patients who are more involved as partners in making decisions on their own therapy find that their quality of life is higher. In advocating for others and raising awareness in other patients they are important allies for different kinds of stakeholders, also industry, but also in co-creation processes of solutions serving different purposes. (PP06)

3.2.3 Negative Aspects of Patient Involvement

Frequent testing and scanxiety. Personalised medicine involves more testing, screening and scanning than regular therapies. Particularly in drug trials, but also in clinical practice, patients are followed up by scans frequently. Frequent imaging evaluations of new potentially long-duration treatments may be distressing for (cancer) patients, because they typically feel very anxious and uncertain in the weeks before medical check-ups or consultations, worrying about their medical status and the results (Custers et al., 2021). Apart from being time consuming these examinations may cause scan-associated distress in patients in the days and weeks leading up to the examination. There is already important research that provides evidence that many people will not benefit because increased monitoring leads to overdiagnosis and overtreatment, which causes very great harm (IP11). (Zimmermann et al., 2021) found for the Switzerland that there are two types of information seeking behaviour

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and that some individuals cope better with more information and are interested in disease interception, others better with less.

Time consuming. Further engagement beyond the treatment means also investment of time, energy and resources (PP03). It may be difficult to identify patients, who are able and willing to provide input to all kinds of processes involved with patient engagement, i.e., from planning and design of a study to discussions on regulatory issues. This is true especially in personalised medicine, where there are different diseases, different personalities of patients, different expectations, which play a role. (PP04)

Economic challenges were mentioned by interview partners as important. There are estimations that only a very small percentage (down to 1 per cent, see scenario workshops) will be able to benefit from different types of testing and precision medicine because they can afford these tests out of pocket and because they feel comfortable with information of genetic risks (see above scanxiety). Affluent people interested in disease interception are a group that will be consumers paying out-of pocket for testing and benefit from "multi-omic" testing (IP11). "Those with the most difficulties in accessing health care are most often in need of services. Those with the best access to health services, on the other hand, are at risk of buying services the do not really need." (Angus Clarke, University of Cardiff, cited in (Lipponen, 2021))

Even though these challenges are not to be neglected, involvement of patients was associated with more opportunities than risks "There is room for many improvements, but we are, let us say, in the middle of the road. With the joint effort from all different stakeholders, we will get to the point where it is not going to be something extraordinary, going to something normal to have patients and other stakeholders collaborating during the course of this." (PP04).

3.3 Financial accessibilities

Equal access to therapies. Access to therapies and even diagnostics to start with is depending on being financed by research programmes, health systems or through private funding. Differences between countries in funding of personalised medicine were criticised, with examples for Eastern Europa and other countries "In Eastern Europe, personalised medicine sometimes is a topic that is so much of out of scope and out of the radar for many health institutions and for health care professionals and it is still something that is not very well developed." (PP04) In contrast, in other countries medicines are often completely reimbursed within the health insurance package, without any co-payments. Then there are not many financial barriers for reimbursement of individual patients once a drug is approved. However, in order to get approval for reimbursements, there are still more barriers for personalised medicine (PP05).

Cross-border financing & ethical aspects. Cross-border financing of treatments, especially relevant for rare diseases or in border regions, is perceived as difficult when it comes to expensive treatments as is the case with most personalised medicine. Financing of personalised medicine is a very sensitive topic with a variety of ethical aspects to be considered. For patients it is difficult to understand why a treatment is approved in one country, while in another country access is refused or not available. (PP01).

Business models. As personalised medicine is very expensive in development of special drugs, treatments or because of numerous special tests, sustainable business models are of particular importance. Patients are well aware of the perspective of pharmaceutical companies where development costs associated with bringing a product from basic research

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to patient use will be disproportionate in terms of the cost per patient treated. This might emerge as sort of hierarchy of interests within a condition where companies reach a cut-off points and the sums below the cut-off point are too small to be economically viable. In that case clinical trials may not be started (PP01).

Conditional reimbursement. Some models for financing were mentioned in the interviews, that suggest conditional reimbursement, where an exit strategy is agreed upon between the patients, the HTA, the health insurance, the medical organisations, and the pharmaceutical company, based on a data communication strategy and plan. In case of negative results these have to be published and the medicine or treatment will no longer be reimbursed through national health services. However, it was also criticised that this remains a theoretical model, as in practice pharmaceutical companies do rarely deliver on the data they are supposed to collect after conditional approval. (IP10)

Health economy assessment. In most countries there are two steps of approval: at first, the regulator, in most cases the FDA in America and the EMA in Europe, will decide whether something is available to be marketed and then the HTA body will assess if the health care system pays and for whom, a certain group of patients or all patients. Patients are well aware that it is a challenge for the HTA and that models that work in one country cannot be translated to another country, ultimately leading to health inequalities across European countries (PP06).

Different aspects of assessment, when considering not only the price but the value of a treatment, will have to be integrated in the HTA. An attempt for this is patient centred core impact sets by the National Health Council[9], which is a patient-prioritized list of impacts a disease and/or its treatments have on a patient or their family and caregivers. Intentionally broad and inclusive, the term “impacts” includes short- and long-term health outcomes and any other related implications (e.g., caregiver/family stresses, economic burden, work and career loss, etc.). Since only patients can inform about what is important to them regarding their health and lives, development of such lists have to begin by engaging patients and their care partners and families to identify those impacts. (PP06)

3.4 Future

Transformative process of health care. Asked about their view of a future outlook for personalised medicine the interviewees stated that is will induce a system transformation, as personalised medicine will inevitably change the health care processes and system.

Particularly regarding rare and ultra-rare diseases, great scientific and medical progress has been made in the last few years. More patients with such diseases reach adulthood and this imposes challenges for treatments in the medical field, as it is difficult to find specialists who are familiar with these diseases.

Create evidence. How well personalised medicine will be implemented depends on evidence, on a recorded and clear benefit where personalised medicine shows a transformation in the outcomes of a disease. Then this will become the accelerator on various levels, be it research, funding or policy. However promising personalised medicine may seem, there is also a warning that the community has to be careful of not over-hyping personalised medicine. Evidence has to speak for itself. “And when personalised medicine delivers on its promise, then it is time to talk about hope.” (PP06)

[9] . https://nationalhealthcouncil.org/pc-cis-blueprint/ last access on 25.03.2022

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Fostering exchange of data and the establishment of biobanks to enable research, cooperation and exchange of information also across borders were named as important infrastructures that would benefit personalised medicine. Networks of clinicians of various member states should be able to consult across borders so that the patients themselves do not have to travel, but only their data travel. (PP04, PP05)

Patient centered care and developments, with recognising patients in a partnership of equals. ”Everybody has got expertise, but not everybody has got the same expertise.” (PP01). Early involvement in considering the patient’s perspective was named as the most desirable development, also for research and policy making. This can be achieved by involving patients as soon as possible in the development and implementation of personalised medicine because only they can provide very valuable feedback and insights into the effect and impact on their life. “What may be a small impact for somebody who is not affected might in reality - when you look at the impact on somebody who is affected - have a very significant impact.” (PP01, PP04).

Future outlook. For the future there was a desire that health care professionals and patients work together as a team, which is expected to provide more benefits for the personalised medicine implementation. There is a need to create a framework “whereby different expertise can be somehow melded together into a coherent home such that a rational decision is going to be made when it comes to assessment of benefits. There are already a lot of things happening that give hope for the future.“ (PP05)

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4 CHALLENGES AND INSTITUTIONAL SUPPORT FOR PERSONALISED MEDICINE

Institutional support means that **personalised medicine** is actively integrated at a larger scale in health care systems in terms of programmes, budgets, regulation, infrastructure or organisational processes. It refers to the whole innovation chain, starting from the identification of challenges in R&D and evidence generation, as well as challenges in innovation, i.e. the practical use and market implementation of technological novelties and evidence. Beyond the identification of challenges in the early phases, institutionalisation encompasses different forms of collaboration, identifying and organising education and training, setting up necessary infrastructure and a beneficial regulatory framework.

4.1 Evidence and R&D Challenges

R&D in the field of personalised medicine is to large extents clinical trials that test which approaches, drugs and devices are effective in patients in terms of risk reduction, toxicity or relapse. The quality of clinical trials is variable which is a general challenge in all medical areas, apart from that the following specific challenges were often mentioned.

Small Cohorts

Identifying patients to include them in clinical studies for R&D and evidence generation is a major challenge in personalised medicine due to patient stratification and leads to various forms of cooperation within and between countries. One example is the cooperation on the Nordic level between similar initiatives in Denmark, Norway, Finland and in Sweden, but sometime also Iceland and the Faroe Islands to build up joint cohorts in different areas.

Nordforsk

The added value of Nordic cooperation in the field of personalised medicine is obviously the cumulative population of the countries, which adds up to comparable numbers to a major European country. Furthermore, Nordic countries have a tradition of strong medical research, similar funding and health care systems.

Still, there are a number of barriers to be addressed, one is the coordination of registries and biobanks at the Nordic level.

Listed below is a selection of recent strategic initiatives related to personalised medicine on the Nordic level:

- Nordic Society for Human Genetics and Precision Medicine
- Nordic Health Research and Innovation Networks
- Nordic Alliance for Clinical Genomics
- Nordic Biobank Network
- Nordic Collaboration for Sensitive Data (Tryggve)

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- NORIA-net on Registries

Source: Nordic Council of Ministers, NordForsk (2019) NOS-M Report: Personalised Medicine in the Nordic Countries, http://norden.diva-portal.org/smash/record.jsf?pid=diva2%3A1347257&dswid=4915 ; last accessed 15/03/22

Administrative burden in(stead of) research

Some clinical researchers have a very strong feeling that they spend too much time on administrative documents to be compliant with GDPR or other demanding administrative requirements, instead of doing research that will benefit the patients. (IP01)

Apart from clinical research, personalised medicine needs progress in other areas in order to spread and be used in practice. Some stress cost-efficiency issues here (IP02), other stress issues of organisational structures and processes, service architectures in place, collaboration between actors (IP06)

Trial design

Personalised medicine and small cohorts challenge traditional trial designs in clinical research, with phase one, phase two, and pivotal phase three studies, including placebo patients. (IP07, IP09) Apart from the ethical implications of placebo patients, this kind of design is extremely difficult with personalised medicine and rare diseases of extremely low patient populations in Europe. Conditional approvals may be one way forward here, but in general it may need completely different approaches. An example for an ongoing project in support of ICPerMed seeking solutions and new trial design particularly for the area of personalised medicine is PERMIT.

PERMIT

PERMIT is a Coordinated Support Action funded under Horizon 2020 and aims at establishing standards for the design of randomised trials in personalised medicine through the involvement of multiple stakeholders including medicines agencies and HTAs. Thereby it addresses questions related to stratification in the context of new trial designs (umbrella, basket, platform, trials within cohort); the corresponding statistical analysis; the cost-effectiveness and socio-economic impact of personalised medicine; and the involvement of patients in trial design.

Source: https://permit-eu.org/about-permit , last accessed 15/03/22

Ethics of Control Groups

In some diseases, patients start with experimental medicine from day one. So there is a direct value of research to patients and their relatives who otherwise have no options. At the same time, these patients do not participate in a trial to be then part of the control group. If they choose to participate in a trial, they aim for the experimental therapy because they see

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no option otherwise. Several interviewees argued very emotionally and fiercely against the use of control (or placebo) groups in trials describing them as unethical.

4.2 Innovation Challenges

Equal access and justice

Equitable access to diagnostic services, especially genetic diagnostic services is a major challenge. Not even in well-developed countries, all citizens have access to, e.g. next generation sequencing, or even the access to the discovery of some biomarkers that are crucial in terms of granting patients access to certain treatments. For equal access, it is suggested to focus on a networked infrastructure of diagnostic equipment and also diagnostic services across countries/regions. (IP04, IP05)

Change in Complex Systems

To set up the whole area of personalised medicine, to enable wider implementation and diffusion is a form of systemic change or system transition. The effort to organise work processes differently and to adapt organisational structures must not to be underestimated. Complex organisational structures need processes of organisation on many levels /hospital, regional, national, etc). Additional loops of integration may be mutually beneficial in the longer run but also considerably slow down the current diffusion process and lead to a strain on resources in the short term. (Interview IP06)

“Personalised medicine challenges every structure, challenges the way we think about how we treat people, how we analyse, how we work together, how we generate data, how we think about evidence.” (IP09)

Service architecture – centre versus periphery

There is a basic tension of centres versus periphery in bringing new services of personalised medicine to people. Discussion arises whether to supply new PM-based services mainly in centres or trying to make it the mainstream in supplying them also by residential doctors on a daily basis in all places and day clinics. In case of big centres the question is if these should be organised mainly nationally or even internationally - the challenge becoming then to connect them with local patients in their home environments. In the case of broad diffusion, the challenge is continuous education and training, and quality assurance. (IP09, IP10)

Reimbursement is only one innovation barrier

In many EU countries, reimbursement is seen as a major barrier to the introduction of innovation in personalised medicine. However, decision makers do not seem to realise that there are also countries where innovation is not used, even though the costs are covered by public health insurance. This is crucial as it implies that after overcoming the first hurdle of reimbursement, there may me other hurdles. There is further research necessary of where hurdles are in the institutionalisation and implementation of personalised medicine in case cost coverage is not an issue (IP10).

Quality assurance

When complicated diagnostics and therapies are supplied in a wide variety in medical organisations, quality indicators have to be defined and observed to ensure up to date standards. This raises matters of defining indicators, monitoring them over a period of time, designing sanctions (a visit, or full publication of bad review in a non-anonymised form), and also dismissing a quality indicator once it has become a standard. (IP10).

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4.3 The Role of Markets for Personalised Medicine

The role of markets in the area of personalised medicine is a matter of disagreement. What are essentially public tasks and what are in turn private tasks in the area of healthcare is seen differently already across Europe. Below we tried to sketch focal points of the debate as they come out of the interviews.

"In Europe there is no market for biomarkers"

Here the line of argument is that investment in Europe is faltering, therefore – in contrast to the US - major discoveries in the field of biomarkers cannot become success stories. As there is no path for reimbursement, the market for precision medicine in Europe does not develop sufficiently. If there were private investors who would invest in precision medicine, that would lead to the implementation of precision medicine. The risk is that if this market does not develop, precision medicine remains a purely theoretical concept for Europe. (IP01, IP07)

In order to be competitive worldwide in the future, it cannot be expected that public platforms perform the sequencing. The question now is how AI, genomics, proteomics, RNS, special sequencing etc are integrated. These tasks are not going to be carried out by public hospitals. Instead, high levels of investment are needed in order to generate the evidence of clinical utility in patients and run the clinical trials. Investments here are expected to rise in the future because regulatory authorities in countries require more and more bioevidence for drug approval. These increasing needs for evidence require ever-increasing resources for the clinical trials. "It is not likely that governments put this money on the table." (IP01)

"We have to reduce costs for approval"

From a different angle, the solution is seen in reducing the size of necessary investment by reducing the cost burden. In this view, the main players in bringing personalised medicine to the patients are also the companies. Pharmaceutical companies are the ones who know to take a good research result from the clinic, comply to regulatory frameworks, bring it into networks, and provide them to patients where they are needed. In order to make this more easily achievable, regulatory needs in terms of proper data for the approval of treatments have to change by not being obliged to deliver large expensive clinical trials. This is even more necessary as the business model for pharmaceutical companies is different in personalised medicine due to increased patient stratification.

"Companies should not be doing what are essentially public tasks"

"Europe has a problem with private investment in the healthcare system." (IP01) "But it is not the companies, it should be the hospitals who do this." (IP07) There is a deep disagreement between different actors in the system about what are essentially public and what are private tasks. Hospitals are seen to have their strengths in the repurposing drugs and therapies. Although this is an important element, they are not the ones to develop drugs, which is essentially a task of companies. Hence, health care systems have to be set up to allow and preserve business cases or the basis for commercial activities for the companies. (IP07)

"*Business interests prevail*"

In contrast to the above, transparency of costs, transparency of investments by industry, reasonable profits were mentioned as challenges by many interviewees. There is little or no transparency as to how much pharmaceutical companies actually invest in the drugs, regardless of whether they are doing personalised medicine or not. And at the same time, of

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course, they also benefit from public funding, but also from universities and in the form of very well-trained scientists. Critique is raised that this is not reflected in the health care system, at least not for society. (IP11) “I have the impression that far too often we fall back on economic interests, in particular, Illumina itself probably introduced the bill on genome sequencing in our country.” (IP10)

4.4 Health Economic Considerations in the Implementation of PM

Across all countries, there are two basic sources of public financing for personalised medicine, one) health care budgets, and two) research and innovation budgets.

Aligned with these different sources of funding there are two different perspectives on cost efficiency of personalised medicine:

One) an evidence-based reimbursement logic: cost efficiency and budget impact are of vast importance, as decision makers on the basis of their budgets at hand have to allocate resources to the most cost-effective therapies. If personalised medicine compared to standard of care does not prove cost effective, it should not be implemented.

Two) an investment logic according to which personalised medicine has desirable functionalities, but is still in its early days, and still very much in the research phase. It is expected to pay off in the future. Hence, for reasons of competitiveness and future benefits, it may be very important to stay at the edge of research and implementation.

These are two kinds of perspectives that exist in parallel and are at the same time in conflict with each other. The conflict is that in evidence-based health care systems, the idea is to first have the evidence to implement some innovative service. But in order to generate the evidence, it has to be implemented first. (IP09) Some countries and regions, like Saxony in Germany, some regions in Italy and Spain, Sweden, Finland, Norway tend to implement personalised medicine more widely because they see it as the future. They do not seem to think that personalised medicine has to be cost-efficient already, and still pursue its implementation (IP03, IP04, IP05, IP06, IP08, IP09, IP10).

How implementation in public health care is approached

Across all interviews it was evident that there are no procedures or stage gates that uniformly function as entry or transition channels from early applications of research to wider implementation. Instead, these are individual negotiation processes, sometimes based on regulation. Particular regulation in Germany stipulates that if there is no prospect of a therapy and patients have run out of options in standard therapy, then the health insurance fund is obliged to pay for other [experimental] therapies, even arbitrary therapies. In Germany and in Austria, there is also particular regulation that in a hospital setting, medicines are reimbursed from the day they are approved on the European level. Hence, in hospitals approved testing will immediately get reimbursement. In other countries, e.g. Netherlands, the approach of financing off label therapies for patients out of options is framed as research and more likely to be covered by research budgets, but also negotiated individually with health care insurance. (Cambrosio et al., 2022) Several experts also emphasised that although in their countries reimbursement on the hospital level is aligned with the EMA approval, this does not necessarily mean that they are widely used by doctors. They conclude that there must be other barriers apart from reimbursement, reaching from the complexity and speed of knowledge creation and evidence in the area of personalised medicine to specific education and training needs or further regulation.

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From testbeds to innovation niches for system implementation

Hence, what is already done across countries is to implement testbeds and pilot projects for experimentation. Often these are already protected spaces, in that they are exempt from the DRG system, but based on individual negotiation.

At the same time, there is an awareness across countries that these testbeds and pilots are implemented to generate data and learning, including also data important for health economic modelling, with evidence on costs and health impacts.

Countries use different approaches to implement test beds and pilots (see also chapter 9, section on Innovation Niches – Setting up Experiments and Learn from Them)

- Infrastructure- centred testbeds.
- Testbeds centred around stages of the disease
- Testbeds according to a catalogue of criteria
- Testbeds around particular promising technologies

However, these testbeds can be valuable instruments to cross over from the early phases of high research intensity and high uncertainties and to phases of wider implementation and institutionalisation. Around these loci of experimentation there should be structures designed to continuously iterate and enhance experiments or promising parts thereof and abandon those parts that are not promising. Thus, they are apt to aggregate learning not only across countries, but also across Europe, so that others in other countries do not make the same mistakes but build on the past experiences. (See chapter 9, for concept of innovation niches in system transition)

Countries and regions where innovation funding and healthcare reimbursement mechanisms are organised more closely are likely to have an advantage in the transition from the research phase to the actual implementation in healthcare. They are more likely to overcome silo thinking. Combination with other regional strategies, e.g. the smart specialisation strategy, may then be even more apt to pull resources together (IP04, IP07). One way forward is seen in setting up experiments, forms of experimental medicine on the basis of personalised medicine approaches and use them to systematically learn from them. There will be many iterations necessary to try and fail, enhance what was working, abandon what was failing, providing the evidence in the form of empirical data and from early on define data needs for HE modelling and HTA.

Generating Evidence from Experimental Medicine, including data for HTAs

If patients decide on experimental medicine, this may have advantages for both sides. It may win time for the patients and generate data from research, and also for the health economic modelling side of research. However, many countries experience difficulties in drawing data from experimental research together and organise them in a way that learning on a more general level is possible and ineffective therapies are not duplicated. (IP09, IP10). One example to overcome frictions and organise processes for learning is ZPM in Germany.

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Germany: Centres for Personalised Medicine (ZPM)

Centres for Personalised Medicine in Germany cover a broad spectrum of diseases. A special focus is also on patients at the end of therapy options, i.e. off label use. A large panel study is being conducted for this purpose and evidence is collected for many kinds of tumors. These centres are financed with funds from the so-called Innovation Fund to learn which experimental therapies work.

The four Centres for Personalised Medicine (ZPM) at the University Hospitals of Freiburg, Heidelberg, Tübingen and Ulm in Baden-Württemberg have joined forces to make Personalised Medicine an everyday part of patient care. Common standards and coordinated diagnostic methods are the basis for optimised therapy decisions for all patients at ZPM.

Source: Interviews, and https://zpm-verbund.de/; last accessed 15/03/22.

In addition to the above there are also funds from e.g. the European Resilience and Recovery Facility to set up new centres for personalised medicine.

Funds from the European Resilience and Recovery Facility are being used to create a centre for precision medicine, e.g. at the MedUni Campus AKH in Vienna. The new research infrastructure creates modern framework conditions for digital and personalised medicine. In future, diagnoses, therapies and preventive measures adapted to individual factors will be developed here.

Taken from: https://www.meduniwien.ac.at/web/en/forschung/eric-kandel-institut-fuer-praezisionsmedizin/ , last accessed 25/01/22

The Facility allows the Commission to raise funds to help Member States implement reforms and investments that are in line with the EU's priorities and that address the challenges identified in country-specific recommendations under the European Semester framework of economic and social policy coordination.

Source: European Resilience and Recovery Facility https://ec.europa.eu/info/business-economy-euro/recovery-coronavirus/recovery-and-resilience-facility_en , last accessed 25/03/22

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4.5 Forms of Collaboration

4.5.1 Collaborations between academia and industry

In the following, academia mostly refers to research hospitals. For further forms of collaboration, see also the annex, on networks.

Licensing and patents

Particularly in the context of large research hospitals, academia develops solutions in personalised medicine which are subsequently protected by intellectual property and licensed to industrial firms. It is noteworthy that publications and other forms of early disclosure are also forms of intellectual property. Advantages may be that early disclosure and publication prevent standards that are in the process of developing from being monopolised by other companies through patents. If a company manages to file a patent for an area that is just becoming a standard, this can impose additional costs on an entire industry. In fast-moving areas this may cause frictions. It is also particularly controversial when the foundational research has been publicly financed. (IP11, IP04)

Start-ups

Academia develops solutions in personalised medicine which are subsequently protected by intellectual property and commercialised through starting up new firms. European start-ups in the area of personalised medicine suffer from strict regulations, particularly data regulations, administrative burdens and lack of financing (IP01, IP07).

Collaborative research projects

In a collaborative setting, researchers from academia and industry develop a device or drugs together, or in the opposite direction, where devices and drugs come from industry and are then used for clinical trials and research in clinics in a specific contract frame that is signed between the two types of organisations. Collaborative research between academia and industry is associated with vertical technology transfer. Vertical technology transfer generally refers to the transfer of knowhow or a technology from the research and development phase to the production and marketing phase, so from one phase of the innovation process to another. In vertical transfer, challenges are typically higher because people's languages are very different due to different organisations of origin, groups or functions. In personalised medicine up to phase two if not phase 3, most of the cost and most of the investment is carried by public funding. Then it is mainly from phase two to phase three of developing drugs where there is an investment by companies, in some occasions also with the aid of governments. Subsequent developments are also often supported by governments in the form of collaborative research grants etc. (IP04, IP10, IP11)

One incentive for these collaborative research projects is that without joining up with a clinical partner it is problematic for industry to find patients for their trials. Access to public healthcare data is denied for the industry, identification of patients and enrolment on their own is a slow process.

Infrastructure collaborations between hospitals and firms

These are bilateral longterm collaborations where companies deliver devices and analytical equipment that is then used by hospitals and research. Illumina is a main actor here as a provider of analysis and equipment (for gene sequencing), especially with its TSO 500 that is used by many hospitals and research in the area of next generation sequencing, thus

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enabling genomic profiling at the location of the hospitals. This is seen differently by interviewees, with some seeing it as a success story for themselves, fulfilling highest standards. Others view this critically emphasising the market dominance of Illumina.

Basket collaborations between one hospital and several firms

Pharmaceutical companies with drugs of potential interest for academia/research hospitals are drawn together in exploratory discussion settings (”basket”) for possible future collaboration. The basis are initial broad agreements with several pharmaceuticals. In such a setting, several competitors may sit around the table. Upon further interest, bilateral negotiations start and the collaborations enter from a precompetitive stage to a concrete contract phase. (IP06)

The precompetitive stage is characterised by exploratory discussions around joint possibilities. They can also include health care administrators and patient organisations. These are lengthy processes, finding a common understanding and a common language, understanding each other’s interests takes its time. Although there may not be very clear results soon, they are reported as being very good discussions with interesting partners engaged. However, working in explorative processes and setting, takes time to develop concrete innovations.

In the transition from the precompetitive phase to the contract phase, firm hierarchies, especially in large foreign-based firms are experienced as a challenge. “Some of them are global companies. And it is far away that the national directors can take decisions themselves. They have to go up through their hierarchies and discuss it. And it is not only the public systems that have bureaucracies, also these large firms have them. So it is an iterative and slow process with these kinds of firms as well.” (I0X)

4.5.2 Collaboration with patient organisations

There is a realisation that much would be gained in terms of efficiency, if processes of implementation were more centred around the patients. This has an intrinsic value as such in that personalised treatments work optimally for each individual and are not based just on averages in large groups. Major advantages are also to gain patient-specific information of various sorts, and to have a partnership with the patient around the treatment.

Hence, patient organisations are widely invited, but there are barriers of language and experience in the setting up of a professional working relationship. It is hard for patient organisations to be an equal partner to, for example, a regulatory agency with hundreds of medically trained people sitting on the other side of the table, to speak the same language. (IP06, IP08) Thus education and training for patient representatives and advocates was seen as foremost action point to enable eye-level discussions (PP04).

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4.5.3 Between collaboration and system governance

In some countries, collaboration is seen wider and includes a variety of stakeholders for multi-layered governance. To include not only partners from universities, university hospitals, industry, health care decision makers and patients. Finland and Switzerland provide very different examples of how to organise collaboration of diverse actors on a country level.

Swiss Personalized Health Network (SPHN)

Switzerland has developed a comprehensive approach of collaboration and inclusive governance. It encompasses the National Steering Board (NSB) as the highest body of SPHN. It includes representatives from key institutions in Switzerland (e.g. University Hospitals, Universities, ETH Domain, swissuniversities, FOPH, SNSF, patient organisations).

Additional Expert Advisory Groups and Boards are involved in the process of implementing personalised medicine in Swiss health care:

- ELSI Advisory Group (ELSIag)
- National Advisory Board (NAB)
- Hospital IT Strategy Alignment Group (HIT-STAG)
- International Advisory Board (IAB)
- Data Coordination Center (DCC)

SPHN intends to serve as a one-stop-shop for researchers and hence archives and makes accessible all SPHN relevant documents under https://sphn.ch/services/documents/.

Source: https://sphn.ch/organization/governance/, last accessed 14/03/22.

The Cancer Foundation Finland

The Cancer Foundation Finland is a charitable foundation in Finland. Through its grants, the Cancer Foundation Finland supports work benefiting cancer patients and their relatives, and cancer prevention.

The Cancer Foundation Finland is an important funding source for cancer research, in the form of the Finnish Cancer Registry and the Mass Screening Registry, and hence has had an important influence in developing cancer research and cancer control in the country.

The Cancer Society Finland joins forces with the Cancer Foundation Finland. They have a common strategy, share the same Secretary General and have joint boards meetings.

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The Cancer Foundation Finland also organises an annual symposium for experts on cancer research and cancer treatment. These national symposia bring together specialists in cancer types, cancer prevention, diagnostics, treatment, follow up and rehabilitation.

Source: https://www.cancersociety.fi/organisation/cancer-foundation-finland/, last accessed 14/03/22

4.6 Education and Training

4.6.1 Molecular Tumor Boards: Multidisciplinary Collaboration and Competencies

In the area of oncology and next generation sequencing it is essential that different kinds of specialists seamlessly work together, such as pathologists, molecular pathologists, geneticists, oncologists, pharmacologists, surgeons, radiologists, bioinformaticians and molecular biologists. (Russo et al., 2022)

Around molecular tumor boards a lot of multidisciplinary team collaboration takes place, on the level of hospitals, but also across hospitals and regions. In several countries (e.g. Norway, Italy) layered forms of molecular tumor boards have been established on top of existing organisational structures. From interviews, but also from the literature it seems that these molecular tumor boards, being rather influential in terms of deciding on patients' treatments and assigning or not patients to trials, are fluid in nature, blurred in membership and crucial in terms of forming competencies and increasing understanding across disciplines. (IP06, IP09, IP10) (Cambrosio et al., 2021; Russo et al., 2022)

Interdisciplinary tumor boards on the level of hospitals are rather common in most countries. However, some countries use molecular tumor boards as interlinked network structures on different spatial levels. So apart from the hospital tumor boards, there may be local or regional tumor boards as well as national tumor boards.

"We started just on a national level. And then very early we decided that it should be two meetings, a pre-tumor board and a tumor board. On the local levels there are additional filter meetings because here it is decided what cases are included in the tumor board meetings. The pre-tumor board meeting is actually the main event in terms of debate. This is a huge meeting for all the specialized providers of some kind of knowledge. Discussions are less standardised and hence more creative." (Interview)

Tumor board meetings have different functions, starting from an information exchange, they have 1) an educational and training function, 2) a networking function, and 3) an advocacy function for patients.

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4.6.2 Concentrating versus Distributing Education and Training Efforts

Education and training and certification for personalised medicine in general are seen as very important, however with extreme variation in strategic approaches between countries.

In Switzerland, the approach is to target medical professionals, doctors in general, including general practitioners in peripheral regions. “Education and training are a big issue and there is little understanding of those issues. So we are actually developing training for what we call frontliners of those who are in direct contact with patients to have the tools and the understanding to explain what it is about. We have now doctoral schools in genomic and digital medicine, and we have produced various kinds of MOOCs and other things so that basically knowledge can be made available to the practitioners and to the academic community for capacity building. But I think the most innovative form is really targeting the frontline healthcare professionals” (Interview)

Contrastingly, in many other countries, including Germany, Austria, Norway, the belief is that education and training in the areas of personlised medicine is no vehicle that easily spreads over centres as well as peripheries because of the multitude of specialised areas with highly frequent changes in evidence. To ensure a high level of quality and be up to date it would then be necessary to do trainings very frequently and in many areas as the evidence changes frequently as well. Considering doing further training every year for a number of different types of cancer seems hardly be feasible from the viewpoint of experts there.

Precision Medicine FRONTLINE

Precision Medicine Frontline is a multi-support learning platform on Precision Medicine for the daily practice of frontline care professionals.

Its vision is that primary care professionals delivering high-value precision medicine to their patients

To create a multi-support platform where updated information about Precision Medicine that is useful for the daily practice of primary care professionals is gathered the platform will offer basic and advanced training opportunities for primary care professionals, in addition to general up-to-date information

Example Switzerland. Taken from: https://health2030.ch/project/precision-medicine-frontline-a-multi-support-learning-platform-on-precision-medicine-for-the-daily-practice-of-frontline-care-professionals/, last accessed 31/03/22.

Also training and education for citizens, referring to patients and their care takers, was confirmed as a need in a survey taken by (Venne et al., 2020) and by interviews of patient organisation representatives (see chapter 4).

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4.6.3 New competencies within existing professional specialties

Some professional specialties have existed for a long time but with personalised medicine now they need certain new competencies in their profile. Pathologists and oncologists by their very nature are of strategic importance in the area of cancer treatment through PM. But there is a need for pathologists who are more than the average interested in asking new questions and start new trajectories. “In our hospital, if I should point out the one person that actually is really the hub for all these processes, she is what we call an experimental pathologist. She is the actual leader, although formally she is just the leader of one type of meetings.” (IP06)

Hence, it is also new skills and competencies and knowledge in the old professions, established specialities like the pathologists that are of crucial importance. This may even lead to tensions within these specialties and within hospital departments. “And it is a kind of tension between the old and the new, both in the case of oncologists as well as pathologists. In the weeks or months before we started to take the personalised medicine initiative, we almost drowned in the tensions between these different camps of beliefs, especially amongst oncologists and pathologists. We had to organise additional strategic meetings to get them to cooperate and see the possibilities. Some followed the argument that personalised medicine is very exciting and has a lot of potential, the others within the same profession still do not believe in this precision medicine development because there will be too few patients that benefit from it in too short a period of time compared with the money that directly and indirectly has to be used. In the end we resolved the tensions in restructuring the departments according to the lines of the frontier.” (IP06)

How do experimental pathologists and oncologists get their training?

First, through international research projects, the European Union framework research programme is a major pillar here. These kinds of international projects offer training opportunities in cooperation also with the basic scientific community that can be found in Cancer Research Institutes, which is cooperating with the basic scientific community at another university hospital. The partners there have international connexions and mostly have themselves gone abroad on international scholarships.

Second, through regular molecular tumour board meetings. These may serve as an excellent training stage, depending on the number of people participating, also via virtual participation. “These meetings are a tremendous learning opportunity, probably the most important.” (IP06) Furthermore it was pointed out that there are more discussions on revising the cancer strategy for hospitals as a result of these collaborations and exchange meetings. An awareness was created also for the needs for trainings and education for the upcoming generation of oncologists as well as other specialists, which include knowledge of handling these processes, procedures and thinking.

4.6.4 Young Professional Specialties and Interfaces

Some professional specialties are missing or have only been recently developed. Specifically, the bioinformatics and biostatistics, as well as even molecular biology have been comparably recently developed, they now experience difficulties in interacting with established professions and specialties like pathologists and oncologists. Here the issues seem to establish a clear professional profile vice versa established professions, and hence having a clear position and role vice versa different kinds of established specialists like the clinicians and pathologists. Furthermore, in order to be clearly visible contributors, the rather novel specialties need arenas for interactions with the clinicians and a common language.

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They also need to share their results and learn from each other. There seem to be major obstacles in everyday practice of personalised medicine. (IP06, IP09) “If I talked to clinicians, they often do not understand the molecular biology side of things, and vice versa, so the ones who do the test do not understand that medicine thinking and the other way round. “I talked to colleges who were really upset about the recommendations - have you ever seen them in the patient?” Or: This has already been tested everyone knows, this is not working.” According to several interviewees, circulating results outside specialists’ own communities is missing hence feedback and mutual learning is missing. (IP06, IP09)

Setting up interdisciplinary trainings

There are many examples for disciplinary trainings of personalised/precision medicine matters. The European Society for Medical Oncology organises trainings, there is HTAs training on personalised medicine, regulators training on personalised medicine, pharmacists’ training, etc. What is missing is trainings across disciplines, across different specialties. “Everyone does training in their own little corner, and that is why it is not working.” (IP09). Also (Venne et al, 2020) suggest reinforcement of education of health professionals and medical training around PM in favour of interdisciplinarity an essential next step.

4.6.5 The timeline of education and training

In the interviews it was stated that it may be too early now to introduce special content for future personalised medicine in the general training of all doctors because the number of patients is still small. But at some point, this will be an important part of education health care. “So maybe around 2026, you need to start doing it. The timing problem is interesting because if it will have to take place some time before treatments are provided on a more regular basis. We think maybe 2030 or 2035 there would be thousands of patients. It is a timing problem 'when' to scale up? Now there are so few products coming to market, so it is not a big problem now, yet challenging. But once there will be tens or like 50 to 100 gene therapies per year coming to market, then that would be a big issue to manage them.” (IP08) Recommendations from (Venne, et at 2020) also stress the need for large-scale education and training programs both for citizens and for the healthcare professionals and providers.

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4.7 Relevant Infrastructure

4.7.1 Organisational infrastructure: Research hospitals

One form of key organisational infrastructure for innovation and system transition in personalised medicine are university or research hospitals. Apart from being major providers of health care services, they are at the same time performing cutting edge research and using and adopting new technologies. As leading centres in their regions, they have privileged access to patients for clinical trials. Furthermore, they are an integral part of the education systems in educating and training health care practitioners of the future. Often, they are also at the core of infrastructure innovations and new organisational processes on a system level. For an overview of the crucial role of research hospitals for medical innovation in the adoption, reproduction, and generation of medical knowledge, see (Gulbrandsen et al., 2016; Thune and Mina, 2016). For personalised medicine, they are certainly also of crucial importance in combining health care provision and research, systemic synergies that are a starting point for further developments in the area in many cases (IP03, IP06, IP07, IP09) They constitute huge hospital systems, with large numbers of people, laboratories and organisation sub-structures that commit their resources to approach a problem. As such they are well suited to carry developments along and serve as a bandwagon (Fujimura, 1988).

4.7.2 Organisational infrastructure: Reference Centres

Due to increased patient stratification, Reference Centres, as already in place for Rare Diseases, were frequently mentioned as potential models for personalised medicine as well. Via reference centres exchange between medical experts, but also across disciplines, is institutionalised which seems a major advantage. (IP02, IP04, IP06, IP07)

New PM based health care services largely require specialised knowledge and most experts estimate that it cannot be offered well across the board. With increasing specialisation, there is an urgent need for concentration due to volume-outcome relationships. Although the relationships are not necessarily causal, higher volumes of care in a specialised field yield better outcomes. There are also proven volume-outcome relationships, for a variety of surgeries but also in cancer therapy. (IP02, IP04, IP06, IP10)

However, there can also be difficulties in establishing centralised structures in order to concentrate resources. If doctors or small hospital feel passed over, they boycott the large centres. This can be solved in that only the samples are sent to the centre which do the diagnostics on the sample and then give therapy recommendations to the hospital of origin. Thus, specialised knowledge can reach the periphery with speed, plus the sample are analysed at the highest quality. The next level would then be multi-stage treatment schemes. (IP10)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

European Reference Networks (ERNs)

European Reference Networks (ERNs) are virtual networks that involve healthcare providers across Europe. The aim of ERNs is to tackle complex or rare diseases and conditions that necessitate highly specialised treatment, knowledge and resources. The ERNs program intends to improve health care quality, to reduce access inequalities, and to increase overall medical experience and knowledge (Wijnen et al. 2017).

These networks are relatively new and were launched in March 2017. Upon their launch it was quite uncertain how they would be put into operation, due to lack of previous experiences. European networks in the past had not been funded in the context of care (Heon-Klin 2017).

The legal basis for ERNs was the directive 2011/24/EU [1] of the European Parliament and of the Council on the application of patients' rights in cross-border healthcare (cross-border directive).

Source: (Frezza et al., 2019; Héon-Klin, 2017; Wijnen et al., 2017)

Patients and the Last Mile – the "Hub-and-Spoke" Model

However, with centralised infrastructure as is the case with Reference Centres there are concerns about equitable access to these centres. With centralised structures, often especially in acute phases, patients have to move close highly specialised health care services. This is normally accepted by the patients, in general patients understand that the quality of the treatments increases with centralisation of highly specialised competencies. However, it may become problematic when the patients return to their home region after a surgery or other therapy. In such a case, the process should be seamless for the patient, but can currently be problematic especially in advanced therapies.

Digitalisation is of course seen a solution to many problems around finding the right level for supplying health care services health care services, however, problems/difficulties may still arise if physical samples or physical persons need to travel. These problems include a seamless continuation of treatments in their home environment, i.e. "the problem of the last mile". Hence after the acute phase, there need to be networks established, e.g. a mobile system by which equitable access to aftercare services is granted. Hence, it is much more in focus on how to distribute those services even with parts of personalised medicine based health care centralised. Digital technologies are an obvious candidate for a solution here, but more analysis and discussion is required regarding such technologies. (IP04, IP08)

(Frezza et al., 2019) speak here of the "hub-and-spoke" model that connects collaborating centres ("spokes") to the expertise of reference centres ("hubs"). A "spoke" works in close connection with a hub but offers a limited range of health care services. Its main goal is to ensure geographical coverage. "The "hub-and-spoke" model maximises efficiency and effectiveness in those settings marked by a medium-low number of cases and a need for highly specialised expertise and access to innovation." (p16).

The "hub-and-spoke" model was stablished in rare cancers due to patient stratification. To overcome the limitation of broadly available professional expertise and the necessity of

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multidisciplinarity in a narrow field, “hubs are designed to concentrate the best expertise available and ensure an accurate clinical, pathological, and biological assessment of the disease, as well as an expert clinical decision provided by a dedicated multidisciplinary team. In addition, in rare cancers hubs have the task of promoting research on new treatments, setting up clinical registries and biobanks and referring patients to open clinical studies.” (ibid. p17) “Spokes” are located as close as possible to the patient's home thereby providing a limited array of high-quality services, e.g. medical treatments as well as surveillance. It is hereby rather crucial to determine the required number of spokes across a country thereby balancing patients’ quality of life and at the same time limiting efforts and costs due to migration and diagnostic delays. (Frezza et al., 2019)

4.7.3 Technical infrastructure: Laboratories

Although laboratories are seen as a crucial infrastructure for personalised medicine to spread in the system, they do not seem to be viewed as a bottleneck by the people interviewed for this project. The overall attitude seems to be that there is a need for the right kind of labs to do kind of the right diagnostics. But there do not seem worries that these kinds of facilities, will be in place. It is of course acknowledged that testing is very advanced and that quality assurance across laboratories is an issue to be tackled with interlaboratory comparison.

4.7.4 Technical infrastructure: Biobanks

The debate around biobanks as a crucial infrastructure for personalised medicine revolves around two focal points, one the implementing of biobanks and platforms, two, secondary use of bio samples (IP04, IP07, IP08, IP 09)

There are high hopes around being able to use liquid biopsies like blood and which are routinely collected in primary care, for research and early screenings in central laboratories. Hence, being able to use the same biobanks for regular health care as much as for research, and not duplicate the efforts of two different utilisations of biobanks is seen to lie some time in the future but will be of high potential to increase the health care level in the longer run. (IP03, IP08)

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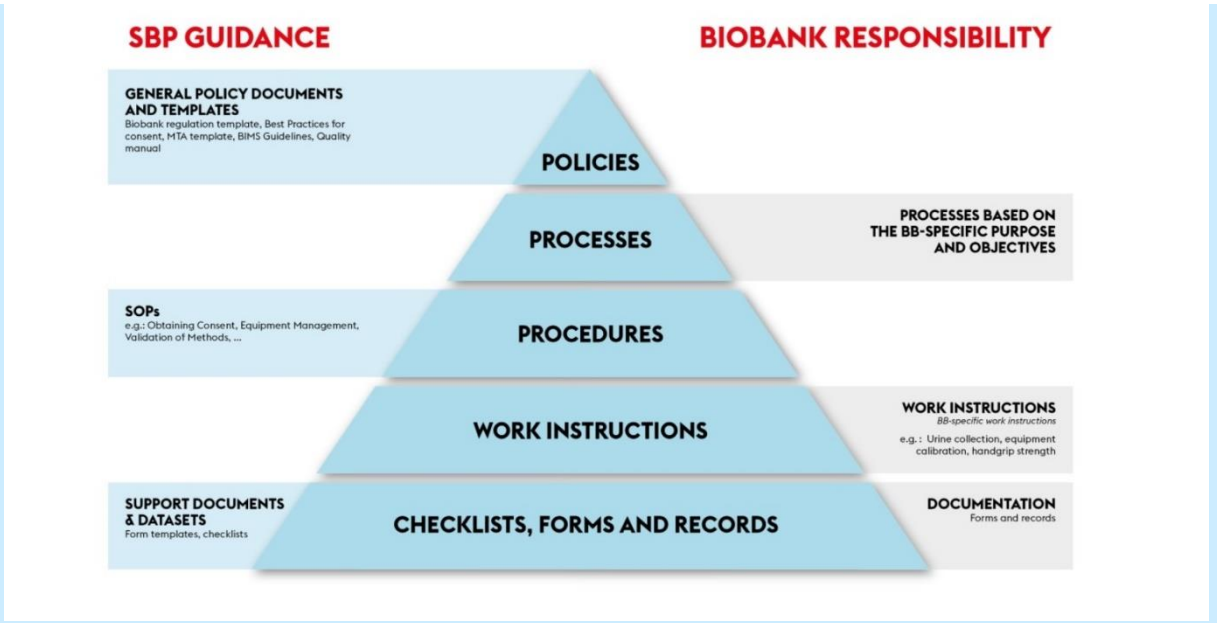
Swiss Biobanking Platform

In terms of setting up biobanks, a good practice example is the Swiss bio banking platform, a national structure of bio samples which supports the definition of standards, protocols, how to share data, how to annotate samples so that metadata can be used to decide whether it is appropriate for research.

On its website it states that “Swiss Biobanking Platform (SBP) is the national coordination platform for human and non-human biobanks. It aims to respond to the increasing requests from biomedical researchers regarding quality and the interconnectedness of biobanks for research purposes. SBP was initiated by the Swiss National Science Foundation (SNSF), and the association was created in 2016.”

Figure 1: Swiss Biobanking Platform and Services



Source: https://swissbiobanking.ch/unique-set-of-services/, last accessed 16/03/22

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Basque Biobank, Spain

The Basque Biobank is open for external use and has a network structure and organisation made up of nodes located at main healthcare centres, both public and private, in the Basque Country. Part of this network is a DNA Unit, as well as a Tissue Unit (tumors and brains). The Basque Biobank was created by the Basque Foundation for Health Innovation and Research, as an instrument for advanced biomedicine and biotechnology research in the Basque country, by managing classified biological samples and associated data. All kinds of samples, mainly oncological and neurological tissues and biological blood samples are collected from diagnostic excess, or requested for research purposes to obtain different products such as serum, plasma, DNA, RNA, cells, etc. Other sample types such as urine, saliva, etc., are also processed.

Source: https://www.science.eus/en/infrastructure/basque-biobank-0, last accessed 16/03/22.

Auria Biobank, Finland

Auria Biobank is a clinical biobank and part of the Turku University Hospital. It was founded in 2012 by the University of Turku and three hospital districts and registered as a biobank by the National Supervisory Authority for Welfare and Health in 2014. All biobanks in Finland have to undergo a registration process as defined in the 2013 Biobank Act (§688/2012).

In 2019, it was one of the eight biobanks in Finland. It actively supplies its data to outside research institutions and pursues collaborations and commercial activity. According to a case study by Lehtimäki et al. 2019, “Auria is engaged with dozens of research projects with universities, pharmaceutical companies, and diagnostics and information and communication technology (ICT) enterprises. Collaborators include pharmaceutical firms Bayer, Roche, and Novartis. Some 40% of Auria’s projects are with private companies.” (p6)

It is essential for the success of biobank-related research that Finish people are willing to donate their tissue samples and personal data to the biobank. As such trust of patients and citizens is a crucial factor for building up the collection of samples for the depository.

Source: https://www.auria.fi/biopankki/en/, last accessed 16/03/22; (Lehtimäki et al., 2019)

4.7.5 Technical infrastructure: Electronic Health Records

A further infrastructure of high relevance and disputed interests is the electronic health records. In many countries for the moment, the law does not envision these to be connected to other infrastructure and research data relevant for the area of personalised medicine. One interview partner was optimistic that within the next five years the law might evolve so that patient data can be made available under certain conditions of consent for research. Several interview partners express that this would be very desirable and an important step forward but seem sceptical about its realisation. Including patient-related data more widely would allow the identification of small cohorts of patients for clinical trials. This is seen as a major

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challenge connected to infrastructures and legal access to networks of data and knowledge between the different hospitals. (IP03, IP05, IP07, IP08, IP09) “I am not worried about setting up technical infrastructure, I am more worried about setting up the whole regulatory framework that is needed to put it to work. This leads us to politicians and the legislation in order to make sure that we kind of have these frameworks so that we can use data both from a research perspective, but also from a treatment perspective towards the individual patient.” (IP07)

However, some countries still lag behind in setting up their electronic health records as their patient data are still extremely local, attached to one hospital which is then the only hospital to have access to these data. A wider inclusion of patient-related data would have the advantage to also account for risk factors and lifestyles in personalised medicine approaches. (IP07)

4.7.6 Technical infrastructure: IT Infrastructure

Setting up interoperable IT systems is a further major challenge for personalised medicine. These have to serve as research infrastructures (platforms) for multi-disciplinary purposes and involve clinical and science/engineering expertise. Mostly they have to build on pre-existing infrastructures and data sets and should encompass clinical as well as analytical data (e.g., multi-omics. (IP03, IP08) (Russo et al., 2022) emphasise the significance of these also for molecular tumor boards. The smaller the patient cohorts, the more interwoven the organisational structures, not only within a region, but also between regions and countries, the less likely that specialists meet face-to-face. Hence, complete and real-time facilities of sharing different kinds of data and information, including patient records, molecular data and imaging must be workable.

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4.8 Relevant Regulation

At the present stage, by many stakeholders the most critical part is seen in the legal infrastructure for handling information. The problem that researchers and doctors, different regions and different hospitals cannot share information slows down many processes. Different laws govern the information flow in clinical trials and in regular care. There is an urgent need for adapting the legal framework for sharing information in these settings. “It is a timing problem of when to scale up what kind of infrastructure. The first part of the infrastructure is the legal and then the technical side of it and then you need to start working on scaling up the competencies. And at some point, we will also need to have the right institutions in place to evaluate the cost effectiveness of these treatments, but that comes later as now is very early days.” (IP08)

4.8.1 Data regulation

4.8.1.1 Secondary use

Secondary use of health data can be defined as “non-direct care use of personal health information”. (Safran et al., 2007) Four broad categories of secondary use of health and clinical data were identified: 1) research and analysis, 2) quality/safety measurement, 3) informing financial management, and 4) education (Robertson et al., 2016). Some studies indicate that patients and healthcare consumers are generally supportive of using health data for research, particularly if the data is de-identified or anonymised. (Hutchings et al., 2021) However, many countries struggle with the remaining risks for patient self-determination and privacy e.g. through unauthorised reidentification (Jungkunz et al., 2021) and with different interpretations of what is actually permitted and forbidden by the existing laws (Aula, 2019).

Finland succeeded in implementing big and open data inspired policies in a Secondary Health Data Initiative. (Aula, 2019) argue that a necessary precondition for the success of this was that the regulatory and infrastructural elements of the regulatory reforms were adapted simultaneously. Thereby tensions that otherwise would have prevented the reforms from happening could be solved.

4.8.1.2 Consent: specific, general, dynamic

Citizen consent to data use is an important topic concerning the use of health-related data. There has been an evolution over the last years to move away from specific consent, which is consent to a specific study that ends when the study ends. A more general consent for research and for making patient data available for research is favoured and often citizens or patients agree on this. (IP03, IP06) “We are moving now to what we call dynamic consent. Dynamic consent intends to get patients to play a more dynamic and active role in deciding how their data or their samples can be used for research. Currently, our hospital is launching a website that communicates in a non-technical way with patients about the ongoing studies. The idea is to make them want to participate, but also get information. The lines are fuzzy between this and participatory science, citizen science, different ways to engage citizens, not only just by handing over a part of them, data or samples, but also to be part of designing studies or running studies, because we believe that this is an important way to really get societal acceptance and more participation in research.” (IP03)

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“In our hospital, we are also working on the general consent for all cancer patients that is open and total, comprehensive and accepting to be included in any study, and we are implementing that. And probably that will also then solve admissions into these studies for our patients.” (IP06)

4.8.1.3 Access of in situ data

Secondary use of the data may mean that the data is not moved, but can be requested without having to move it, and queried in a way that is not privacy endangering. In this respect, sharing data is then actually a misguiding notion. The future lies in generating insights from large data sets without actually drawing them together in one data base or data lake and without directly working with the raw personal data. (IP03, IP09, IP10)

“We have the Stone Age people who think they have to own the data, and they want to make a fence around it. Then we have the Bronze Age, those are the ones who want data lakes, they want to put everything together, and then put a fence around it. And then they realise that any lake is already a security problem by design because at some point, something will leak. The most advanced generation are the ones who have understood you have to set a rate, it is not going to be very elegant. You have to be pragmatic. You can only ask questions, you cannot have it all and you cannot do whatever you like.” (IP09)

4.8.1.4 How GDPR is instrumentalised in practice

GDPR was the one topic that was mentioned by every single interviewee, mostly in an emotional way. “I think everything we do to safeguard the privacy of citizens should not endanger the research that is done on a mass level. Because we have so many promises from algorithms and mass data and biobanks. This has been labelled a revolution in our area, so the regulations should be in place that allow scientific activity.” (IP05)

“GDPR is not just a barrier, it is the death of research.” (IP01)

“But there is the problem of GDPR in our country, huge discussions, and I would even say quarrels between juridical specialists, how we are going to interpret and then implement them. And that also has consequences, even hurdles. The Research Council, together with a couple of other social scientists and professor in juridical sciences, they are the most important supporters of a liberal interpretation of the GDPR. But we have the National Data Security Authority who are very strict and they question everything. We are able to settle this in national projects. But, for example, when going into international cooperation, that raises a lot of questions that we have not solved. Lots of people think that a minority wants to impose restrictions and use GDPR as a kind of legal tool for having relatively restricted practise there.” (IP06)

“I think that the revision of the GDPR is going to be a good thing. I mean, people use it to prevent access to their data sets, especially hospitals, for example. It is not really from the legislation itself. And the different interpretations at country level do not help. I think that we will have a harmonisation in the interpretation of the GDPR.” (IP09)

4.8.1.5 How to collect standardised data

Implementing apps has been suggested to collect data fit for the purposes of health research and health economic modelling. Often these kinds of novel applications are still funded by innovation funds, not health care funds. With the support of apps, data can be collected by the doctors and combined with the patient reported outcomes. Patients can enter their data

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via the app, which is connected to network centres and the data from the health insurance company. “This could be a way forward to collect reasonable data sets, but it also needs a proper collection of genetic data. There are different standards for what is determined in the network, and they depend on which reference genome data set a centre uses and how they define a mutation. This means that a lot of work is still needed on standardisation.” (IP10)

4.8.2 In vitro diagnostics regulation (IVDR)

As of May 26th 2022, not only the new regulation on medical devices (MDR) that was introduced two years ago, but also the new regulation on in vitro diagnostics (IVDR) will be fully effective and replace other regulations that had been in place for around two decades. There has been a transition period, three years for the MDR and five years for the IVDR to allow all manufacturers, notified bodies and regulatory authorities to prepare for the changes. However, it is expected to be very challenging. Because in practice it means that all IVDs that had been self-assessed by manufacturers previously have now to be CE-marked according to the IVDR by May 26th, 2022. (Ritzhaupt et al., 2020) Companion diagnostics (CDx) are categorised under the second highest risk classification (class C). This means that they will have to meet stricter performance requirements, including clinical evidence. (Colombage and Lee, 2018)

In the EAPM Autumn Presidency Conference Paper the fear is expressed that the IVDR and its deadline in May 2022 pose serious risks to disrupt the supply of current diagnostics and endangers the development of new testing techniques, which includes the manifold opportunities of genomics. (EAPM Autumn Presidency Conference Paper, 2021)[10]

“Of course, we need to adjust to change, and here I think the MDR and IVDR have been positive, at least from a system view in terms of creating trust. Maybe we have to re-think some of the role of notified bodies therein, especially in terms of the approval of medical devices and diagnostics. And perhaps the CE mark approval in some locations is not sufficiently fast to obtain. But in general, in terms of personalised medicine, I am quite convinced that the regulatory authorities at the national level and obviously at the European level, are agencies that create more trust.” (IP04)

4.8.3 EU Pharmaceutical Strategy and Unmet medical need

Adopted on 25 November 2020, the Pharmaceutical Strategy for Europe aims at creating a future proof regulatory framework and at supporting industry in promoting research and technologies that actually reaches patients in order to fulfil their therapeutic needs while addressing market failures. It will also take into account the weaknesses exposed by the coronavirus pandemic and take appropriate actions to strengthen the system.

It will be based on 4 pillars, which include legislative and non-legislative action:

- ensuring access to affordable medicines for patients, and addressing unmet medical needs (in the areas of antimicrobial resistance and rare diseases, for example)
- supporting competitiveness, innovation and sustainability of the EU’s pharmaceutical industry and the development of high quality, safe, effective and greener medicines

[10] https://euapm.eu/past-events,92.html, last accessed 17/03/22.

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- enhancing crisis preparedness and response mechanisms, diversified and secure supply chains, address medicines shortages
- ensuring a strong EU voice in the world, by promoting a high level of quality, efficacy and safety standards

Source: https://ec.europa.eu/health/medicinal-products/pharmaceutical-strategy-europe_en, last accessed 17/03/22.

Unmet medical need was also mentioned in several interviews in the form of “options for people out of options” or “hopeless situations” and the “off label use” of drugs and therapies. Unmet medical need is a concept that origins in orphan medical products and plays a role in a regulatory context, but without a harmonised definition.

According to (Vreman et al., 2019), there are three groups of existing definitions:

- one) definitions referring to the absence of available treatments or the low number of available treatments,
- two) definitions including one) plus referring to the disease severity or disease burden, and
- three) definitions including one) and two) plus referring to the small size of the patient population.

To date, unmet medical need is used in the context of access to new drugs in several member states and on the EU level. Specification of the definition unmet medical need is under discussion. Still, it has already regulatory consequences.

On the European level, unmet medical need is a criterion for conditional marketing authorisation and accelerated assessment. Furthermore, it is the basis for prioritisation of eligible products for EMA’s Priority Medicine scheme (PRIME) (Vreman et al., 2019). “PRIME is a scheme launched by the European Medicines Agency (EMA) to enhance support for the development of medicines that target an unmet medical need. This voluntary scheme is based on enhanced interaction and early dialogue with developers of promising medicines, to optimise development plans and speed up evaluation so these medicines can reach patients earlier.” https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines, last accessed 17/03/22.

“I think our problem is more with drug approval. Unmet medical need already plays a role there, and then the approval goes faster because there is very little evidence necessary. One would like to see this combined with a conditional, if the evidence is not yet there, then this must be used in a knowledge-generating way, so that we really do get this knowledge. Because the need for additional evidence in these conditional approvals is never fulfilled by industry.” (IP10)

Regulation in Germany according to the Social Code is that if there is no prospect of a therapy and there is no remote indication of a benefit of a standard therapy, then the health insurance fund must pay for other therapies. This can then lead to very arbitrary therapies. However, at the same time there have to be organisational structures in place to generate knowledge from experiences and not repeat therapies that did not have the desired effects. “One example here is a project in paediatric oncology, which is financed by the German

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Research Foundation. In these hopeless cases, all centers for paediatric oncology send their tumor samples to one centre, the DKFZ (Deutsches Krebsforschungszentrum), where the samples are examined using very modern methods that most of the others are not able to use. The point is that these tumors are rare. The results are then collected in the centre for further studies and learning." (Source Interview)

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5 SCENARIOS FOR PERSONALISED MEDICINE FUTURES

The aim of scenarios is to offer parallel stories of what futures might look like for personalised medicine from a wider societal perspective. Scenarios are by no means predictions. Rather, the scenarios developed represent plausible alternatives that differ because different aspects are dominant in them. The advantage of scenarios is that they create links between future assessments (= trends, drivers) of a number of stakeholders and participants in the scenario process and can thus pictures of the future with greater density and diversity than the stringing together of individual trends. Linking trends and drivers in scenarios makes framework conditions and critical issues visible where development could take a different direction. This perspective is of importance for policy.

5.1 Methodological approach of Horizon Scanning

Personalised medicine has many aspects: next to financial implications, the future of PM depends also on megatrends such as demographic change, economic growth, innovations in medicine and (health) technologies, health literacy among citizens, but also cuts in health care costs to name just a few. The analysis of published and grey literature, forecast and foresight studies, existing scenarios and visions, policy papers etc. in combination with interviews of experts and stakeholders is the basis for this report. It sketches the main future trends and drivers of PM and provide inputs for scenarios for European models of health care. This analysis serves as the basis for identifying the critical uncertainties for the future of PM and its relation to the European health care systems in terms of access, reimbursement and affordability. Further, it helps define critical uncertainties having the highest impact and creating the highest uncertainties.

We started with a corpus of some 80 future-oriented studies, background and overview and policy papers, including some scenarios on the future of health in general and PM in particular as well as future outlooks of health systems. From these sources, we identified some 130 trend and drivers on very different levels of granularity and scope. For a better overview we condensed and categorised these trends and drivers according to a STEPV scheme: differentiating between the fields Society, Technology, Economy, Policy/regulations and Values. After assessing the greatest impact and uncertainty from these trends and drivers those with the highest scores were selected as the most promising for the scenario work (Figure 2).

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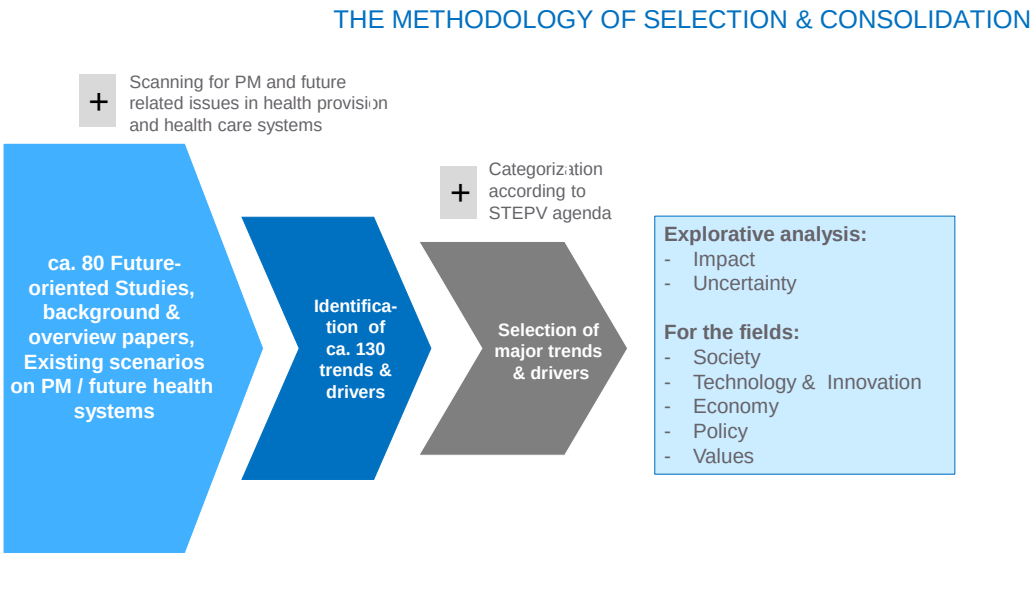
Figure 2: The Methodology of Selection and Consolidation



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5.2 Scenario: Privatisation – Boutique Medicine versus Automated Medicine

Source: Getty images, licensed.

General An over-aged society with many people over 90 years old, and with many people suffering from cancer and dementia has pushed the European social system to its limit. Private insurance affordable to only a few can hardly compensate the existing care deficit. The emergence of a “boutique medicine” where the affluent patients pick suitable and customised treatment leads to increasing inequality of health outcomes between a small rich segment and the poor majority. Multi-national diversified companies - incorporating insurance and pharmaceutical companies - offer a pan-European insurance plan and world-wide provision of health care. In this polarised health system, many services of Personalised Medicine are affordable only by the wealthy people. They live longer and healthier lives, they get access to high quality hospitals and medication.

The inequity between the small rich and large poor segment starts already at an early age, as rich people can afford full genomic sequencing right after birth, their medical treatment is based on this analysis during their life course.

Health care Medical innovation is cost-increasing rather than cost-saving. However, stratified medicine based on big data, labelled “automatic medicine”, makes diagnostics and treatment more efficient and cheaper than ever before and works for the benefit of the larger segment of the population that cannot afford boutique medicine.

There are a number of PM therapies available. The small percentage of people ascribing to boutique medicine is willing to pay a high price for granular analysis of their health-related data, thus providing incentives for start-ups to develop rapid tests and reliable interpretations. The role of private players in the production and delivery of health care services is on the rise. They might be willing to lower the price for treatments in exchange for personal data from (potential) clients.

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Financing There is no regulation by the state concerning pricing for specific treatments or tests. From the patient perspective, the free market makes shopping for the best testing and treatment internationally possible, offering a variety of solutions for those who can afford it.

PM has made considerable advances in diagnostics and treatment of diseases. A growing share of medicine is gene-mutation based. Medical and technological breakthroughs are provided not so much by the private sector, however, but by public research institutes and universities.

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5.3 Scenario: Technology-Driven Personalised Medicine by Subscription

Source: Getty images, licensed.

General The ever-growing world population has already reached 10 billion people. About 10% of the world population is over 80 years old. The top priority of the health care system is to prolong life at all costs, even if this means an increase in the number of chronically ill and care-intensive people.

Patients have great confidence in technology-driven medicine and the achievements of PM as there have been unprecedented advances in biotechnology and medical technology such as artificial intelligence, quantum computing, and new methods of analysis and visualisation of biological functional levels (genomics, proteomics, metabolomics, etc.). Health care professionals today are now dealing with genetic deficiencies rather than treating people or preventing illnesses. The processing costs of screening are low, and it has become easy to obtain enormous amounts of biological data.

Health care Health data are owned by the collecting organisation, and these data companies have become the major players in the health system. Patients readily provide their health data – whether genetic or physiological and behavioural determinants derived from wearable and (implanted) body sensors – to such companies and to pharmaceutical companies. They are convinced that by doing so the health care system can cure nearly everything in the long run. The extensive donation of personal health data has also been triggered by the fact that they are a prerequisite for patients' access to medical treatment.

For fear of a predisposition to a genetic disease, citizens are willing to participate in many of the numerous screening programs. Everybody is under great social pressure to take personal responsibility for their own health. Private companies offering screenings at low cost are flourishing. As technologies are often privately owned, care is increasingly commercialised.

Financing The government is striving to maximise the quality of health care and takes a "whatever it costs" approach. It also places great trust in PM to counteract any disease, and financially supports screening programmes and research in data-intensive health care.

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Despite tax-funded health insurance schemes, private insurance is becoming common practice, as possible genetic diseases or adverse epigenetic patterns can never be ruled out even in the healthy people. The focus of health care on the genetic causes of health problems has led to the creation of “genetic insurances” that cover all problems arising from a person’s genetic pattern. The “geneflix model” (based on the media service Netflix) is the new business model of insurance companies. People take out subscriptions, which make them direct payers of R&D on the one hand and owners of the results, i.e. the free R&D services for treatment, on the other hand.

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5.4 Scenario: Cooperation – Personalised Medicine and Holistic Medicine

Source: Getty images, licensed.

General Technological and social innovations have led to economic growth with far-reaching positive socio-economic effects on society. The society has a strong sense of community. The idea prevails that every citizen should benefit from the country's wealth. Previous crises, such as the COVID19 pandemic, have underlined the importance of the services provided by health professionals and increased their social prestige, which has also led to an increase in the number of people working in the health sector. This benefits not only the sick, but also the elderly people and those in need of care living at home. At the same time, biotechnological and biomedical developments have led to advances in PM. Transnational alliances for PM have been fostered to pool the available resources in specialised transnational centres and reduce the costs for diagnostics in large-scale settings. These centres benefit from the fact that nation states and, to some extent, pharmaceutical companies are making health data openly available worldwide. As the majority of the population uses the tax-based state health insurance system, all citizens are obliged to make their health data available to the public health centres.

Open data policy is implemented in the health systems of most countries in the world. Databases for health data are networked worldwide and data exchange has become common practice between most countries. In general, there is trust in the government and other data owners regarding the security of medical data based on clear national and international legislation, as there are strict regulations for the handling and use sensitive medical data.

Health care Collaboration and cooperation of all actors in the health care system bring together a diversity of knowledge and perspectives, thereby increasing the translation of PM to patients. However, as citizens like to put the benefits for the community before the benefits for the individual, there is little interest in PM on their part. Technological advances in PM are expected to benefit only a few patients and not the entire population.

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Disease prevention is an important driving force for health policy and is rigorously promoted by health policy makers. The population is heavily taxed to provide the resources for the health care system. In the long run, health insurers expect to save money by restricting certain treatments to patients who are likely to benefit from the therapy. The population expects the government to reallocate budgets from other sectors of the economy to the health sector. Health policy makers are still working to develop new business models and incentives for pharmaceutical companies to collaborate more closely with public centres in a public-private partnership and to balance the R&D costs for PM developments and development risks between the public funders and the economic entity who commercialises the medical product or treatment.

Financing The entire health care system is rooted in the “Singapore model”, which provides every patient with every type of medical treatment, including PM. It comprises public and private health insurance schemes, both of which cover the costs of high-quality medical care. Health insurance and benefits depend on the national status of a citizen. While Europeans are entitled to subsidised public health services through a compulsory national savings scheme, employed non-Europeans can only use private insurance to obtain health insurance cover for themselves and their dependents.

5.5 Scenario: Scepticism - Personalised Medicine in a Niche

Source: Getty images, licensed.

General Due to negative experiences in the past, this society is sceptic about innovations in general. The notion prevails that “data belongs to me” and should not be shared at a level where the individual cannot control data use anymore.

Measures by some private initiatives to encounter the scepticism include more health literacy on PM, e.g involving international celebrities to show how PM has helped them. These initiatives also argue that good regulations on data ownership and privacy issues could counterbalance the concerns of the citizens. New suggestions to meet the scepticism refer to the handling of patents. Patents building on public funding should be more often owned by universities, public bodies, governments, not only by the industry.

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At international level, countries experience some isolation from other EU countries and beyond, since politicians have pursued rather protectionist strategies. For the health sector this meant less access to treatments developed abroad.

Health care Blockbuster drugs are more common than any Personalised Medicine. They are more lucrative for pharma companies and more trusted by patients. There are some private companies producing blockbuster drugs, and since the COVID19 crisis also public-private enterprises, where the government holds a considerable number of shares. This approach has helped to determine the R&D directions and financial resources in order to produce the medication required to contain epidemics and to copycat therapies of already approved medications.

PM introduces a new form of threat, namely that “you” are the one that belongs to the non-responders and thus you are denied treatment. This impression is funneled by the international trend of health treatment becoming a very expensive undertaking worldwide. Through mergers and acquisitions, the pharmaceutical market has become more and more consolidated and eventually some pharmaceutical companies have become part of “google health” and “amazon care”.

The emphasis is on prevention and healthy life styles, supported by government agencies and employers. The health insurance system is solidarity based but does not provide a lot of funds for advanced medical research, treatment or PM.

Financing As a consequence, in the skeptical society, there are reduced private investments in PM but more public investments in long-term care and “warm care”, complying to the notion that loss of length of life is compensated for increased quality of life.

Lagging behind on PM research is not necessarily bad from a country perspective, as with a time lag there is a chance of adopting evidence-based PM from other countries and gain from that experience. Once PM solutions have proven to be safe and affordable even the health policy makers in this country might integrate them into national health plans.

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6 POLICY AND PRACTICE: STATE AND OUTLOOK

With a question “Where would you see particular need for changes in public policy on the national and/or the EU level” the attempt was made to capture interviewees’ perspectives on the topic. In the following we present their thoughts and ideas. These are certainly not fully fleshed recommendations, rather a pool of current considerations and also feelings of where policy and where practice and activities could direct attention to. Especially, the section on complex systems and innovation niches was then also complemented by literature in the area to support lines of argument.

6.1 Policy from a Citizen and Patient Perspective

Patient involvement at all levels.

In general patients’ expectation is that as experts of their own lives and disease they should naturally be involved in all stages that lead up to the implementation and institutionalisation of personalised medicine approaches in health care systems. Patients are an integral part of the diverse stakeholder landscape together with health care professionals, industry representatives, regulators, European and national health policy, and HTA bodies.

In order to get people to accept new technologies, especially in genomics, patients have to be engaged in the processes leading up to their implementation. Citizens panels are seen as very important here, especially fin the Nordic region. There have to be deliberative ways of introducing new technologies to the population. In Finland, the Finish academy flagships, which have a focus on precision medicine, are in the process of incorporating patient panels and stakeholders in the basic research path. Engagement from the very beginning is deemed as extremely important as different perspectives are needed for developing public health policy, especially for complicated issues like genomics or precision medicine.

Scientific journalism.

According to patient representatives, scientific journalism is underestimated in its importance. Scientific journalists are important translators of science to the wider public, however currently this type of profession is underfinanced. Left to media companies, these journalists have often been laid off in the past. As a consequence, science communication is more often produced by those who have high interest in products themselves. Especially in health developments and connections are very complicated, it needs independent, high-level translation of personalised medicine for the citizens and readers. (IP05)

*White paper update***.**

An update of the white paper on personalised medicine, as was published by (Golubnitschaja and Costigliola, 2012) and the creation of European guidelines was considered as an essential. these documents have been an important first step in Europe in building up an understanding also among citizens. The definition and common understanding of what is this personalised medicine, specific medicine for a specific disease, explaining differences between a personalised approach from the standard approach, and objectivity on the positive and negative aspects are needed as a basis for decision making.

A European clinical patient management system.

This is supposed to enable patients to do consultations across borders. Understanding has to be created that these treatments are important for the patient population and also how to provide them in the concrete country.

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Social integration of patients with chronic diseases.

Alongside with treatment itself also measures for the social integration of patients in everyday social life were emphasised, also to the benefit of the whole society. Easy access to normal schools rather than institutions for people with special needs, or implementation of school nurses, information campaigns starting at school level together with patient organisations.

6.2 Personalised Medicine: Transforming Health Care Systems

European health care systems are seen as multi-layered complex systems of great diversity. (IP04, IP07, IP09, IP10) Hence, there is no single best pathway to achieve change towards any desirable goal. Already a definition of what is a desirable goal requires complex negotiation processes between diverse stakeholders. Providing market access for personalised medicine and implementing personalised medicine in public health care systems has been a bottleneck for years. It means radical changes in health care systems and processes of system innovation. Processes of system innovation comprise all stages of innovation - from R&D, to inventions, their implementation as innovations and their wider diffusion – distributed among a variety of actors in the system with diverse incentives and rationalities. (Schot and Steinmueller, 2018)

In such a complex setting, policy is more likely to exert functions of mediation instead of top-down steering powers. (Smits and Kuhlmann, 2004) In this mediation function where policy actors have limited knowledge themselves as all other actors in the system, the governance mode is tentative: it provides guidance and stimulates strategic approaches by missions and vision development, it provides room for experimentation and implements structures for scaling up learning processes, it manages interdependencies and contingencies that have been identified as bottlenecks. The notion of 'tentative governance' wants to create spaces of openness, probing and learning, it does not try to prescribe ways forward for actors, institutions and processes (Kuhlmann and Rip, 2014).

In the area of personalised medicine, many stakeholders realise that complex systems dynamics and organisational structures are at the core of transformation processes towards personalised medicine in all its variety. Many countries develop roadmaps and implement foresight processes. Sweden launched its Vision Zero Cancer[11] in 2019, the European Commission presented Europe's Beating Cancer Plan in 2021[12], but also stakeholder networks like ICPerMed developed a vision paper on personalised medicine (PM) research and implementation by 2030[13] (Vicente et al., 2020, 2019). Thereby their intention is to apply a long-term perspective and identify and formulate elements of a desirable future and be bold and comprehensive. Mutual understanding and the knowledge of the cornerstones of a desirable future shall initiate self-organisation processes, experimenting and accumulation of experience that ultimately leads to acceptable pathway/s of transforming the system.

[11] https://visionzerocancer.com/, last accessed 28/03/22.
[12] https://ec.europa.eu/info/strategy/priorities-2019-2024/promoting-our-european-way-life/european-health-union/cancer-plan-europe_en, last accessed 28/03/22.
[13] https://www.icpermed.eu/en/activities-vision-paper.php, last accessed 28/03/22.

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6.3 Innovation Niches – Setting up Experiments and Learn from Them

In the end, the challenge is that treatments reach a patient in a concrete hospital. (IP07, IP09) Yet, there is still a lot to learn on how experimentation can be structured and set up to generate system transformation. The question of anchoring and scaling up of experiments is multiply emphasised in the interviews (IP09, IP10), but not sufficiently understood, neither in theory nor in practice. Instead, one might be overwhelmed by the amount of interlinked processes that take place from patients, caretakers and primary care local levels, to hospitals, regional organisations, processes of commercialisation, to European and global drug development processes, approval mechanisms worldwide, reimbursement authorities on country levels, hospitals and different kinds of networks all these actors are part of. (IP09)

Personalised medicine is still in its early days. Research applications in an early stage tend to have poor performance and high costs, yet they are hopeful because of valued functionalities. (Mokyr 1990) These valued functionalities may induce actors to invest in their further implementation and spread, however, this may take time and the crossover can be rough. Innovation niches are an instrument of research and innovation (R&I) policy for the phase of crossover. The concept has been introduced from the 1990ies, the idea is to provide spaces for experimentation and learn from these experiences in an organised form.

Several experts in the interviews for this project labelled the Catch-22 problem of personalised medicine: In evidence-based health care systems, the idea is to first have the evidence to implement some innovative service. But in order to generate the evidence, it has to be implemented before. When health care systems do not invest in PM because it is not cost-effective, it cannot be implemented and become cost -effective over time through practice, learning by doing and economies of scale. (IP08, IP09)

The way forward can be to implement innovation niches, testbeds, pilots. Although these are implemented locally, they should be designed to induce learning on a European level. Mostly, but not necessarily, these innovation niches are still funded through research and innovation funds, not through healthcare budgets. They are loci where it is possible to deviate from existing paths and approaches, including approaches to evaluation of how they work in a setting of very small patient cohorts. Innovation niches are implemented to develop a common understanding through monitoring, evaluating and learning in terms of preferences of all actors involved, adverse infrastructure versus necessary infrastructure, and mobilisation of actors to be integrated. (Rotmans, 2006). They can be combined with regulatory sandboxes, with legal experiments and related phenomena of regulation to test hindering or conducive regulation of these experiments. (Makarov and Davydova, 2020)

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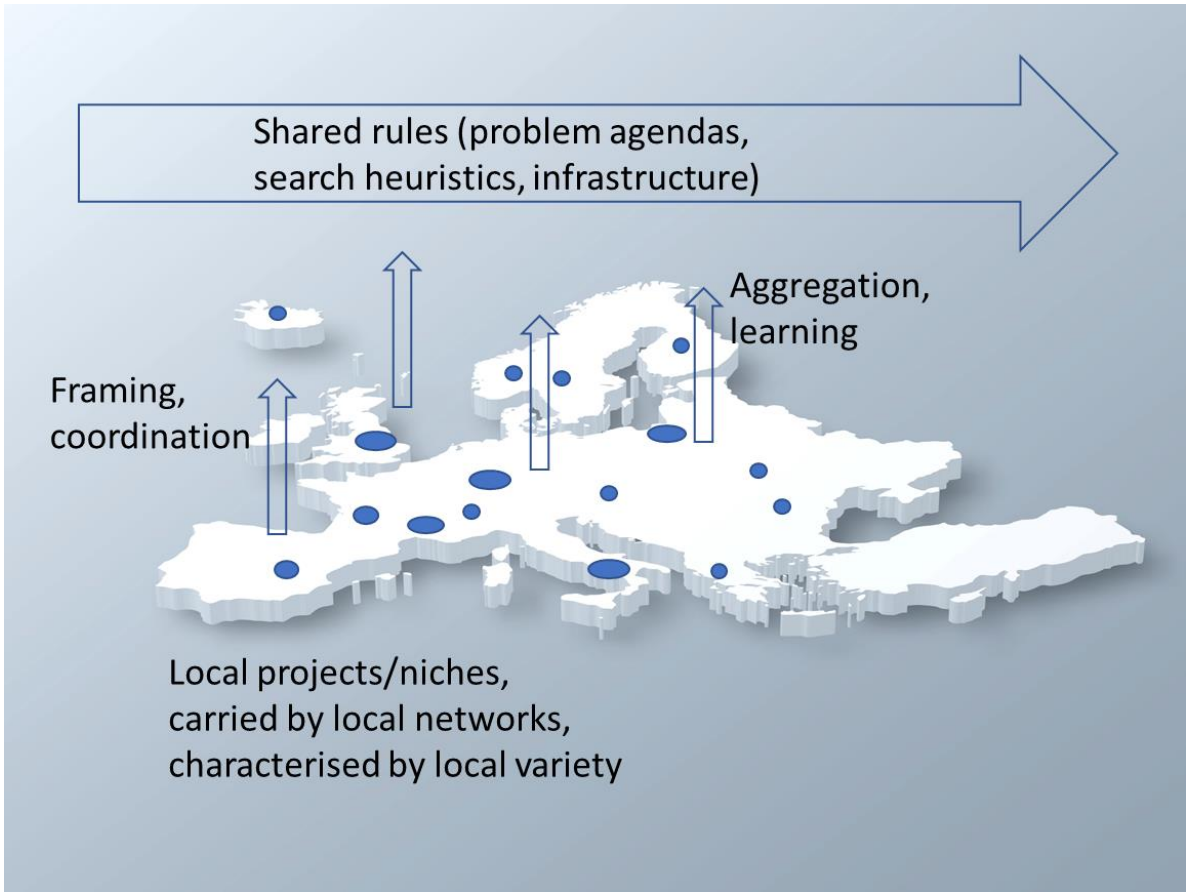
Figure 3: The role of innovation niches for system transformation



Source: Adapted from (Geels and Raven, 2006)

The crossover from the innovation niche to further institutionalisation (i.e. from niche to regime level, (Geels, 2004; Geels and Schot, 2010)) is then associated with diffusion of novel solutions, increasing codification of knowledge and learning and increased cost-effectiveness, established of communities of practice, workable infrastructure and regulative framework.

Countries approach innovation niches from different logic angles, and it may be worthwhile to discuss the concept further and balance the different benefits and issues of the approaches:

- **Innovation niches around infrastructure**. In Switzerland there are attempts to start the process from the infrastructure side in trying to identify critical infrastructure, setting up the infrastructure and then implementing pilot projects that use the infrastructure. This leads to insights of where issues are and what should be developed further and included. To finance research before the infrastructure was ready, did not turn out to be as productive. Now that infrastructure and the services are maturing, “driver projects” are funded that help test, grow, and identify gaps in the existing services and infrastructure.
- **Innovation niches around stages of the disease**. In some pilots they try to introduce molecular profiling late in the disease, when patients are basically out of options. If, based on the analysis of the DNA of the tumor, a therapy is chosen that has not yet been approved, i.e. off-label use, then this has to be included in a data base to generate evidence. Other initiatives do molecular profiling very early after the diagnosis, early in the treatment pathway, to direct and optimise treatment strategies.

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- **Innovation niches around a catalogue of criteria**. According to European procurement law every hospital that fulfils the criteria has to be included. In Germany the catalogue of criteria for establishing a testbed comprised first) requirements that the specialists themselves considered necessary, these were negotiated and operationalised in a way that they can be checked. Second) the quality of diagnostics had to be proven through interlaboratory tests. Third) a minimum quantity of cases of a certain disease, e.g. at least 500 lung cancer cases per year to assert the necessary clinical experience, and fourth) scientific activity in order to be on the edge of research in terms of phase 1 and phase II studies.
- **Innovation niches around particular promising technologies**. Further countries or regions (Sweden, Spain, Italy, more) implement particular technologies, like whole genome sequencing or liquid biopsies etc, because they expect future benefits. These countries/regions simply accept that they have to do this today otherwise they will not be competitive in the future. Thereby they follow the line of argument that the technologies will serve mainly research purposes in the near future, but it is expected that this will change in the long run. Such a line of thinking and implementation seems easier in settings where healthcare and R&I funding is closely interconnected.

Around these loci of experimentation there should be structures designed to continuously iterate and enhance experiments or parts thereof that are promising and less of the experiments that are not promising. This will require collaboration, not only across different types of stakeholders, but also across countries in Europe because often local experimentation has to be integrated into European evidence generation structures. How these may look like will have to be discussed in stakeholder processes. To connect evidence generated in a distributed way across Europe, fuel prosperous experiments and channel these into (national) health care systems needs a strategic multi-level governance approach to set up the connections and loops in the system/s.

Although learning also includes learning from good practice examples, it is important to note that these will not readily translate to other country or regional settings. Any guidelines, White Papers, good practices can only be a source of ideas for individual countries and regions.

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6.4 The European Role for Personalised Medicine

Despite health essentially being a national agenda, there is a general agreement that there are several roles for European level governance in personalised medicine. Although some countries and politicians approach personalised medicine as a competitive strategy, wanting their country to become world leaders in genomic medicine, collaboration across several countries, European and worldwide will become more important. Below are several lines of argument.

Maintaining pace: agenda and priority setting.

Although personalised medicine approaches are very much in line with many strategies on the European level and the SDGs in terms of 'Leave no one behind', and social inclusiveness is already anchored in that respect and on the top level in this type of strategy, the risk is that in terms of daily policy making and priority setting, it does not always have the highest commitment. Politically hot topics like the mitigation of the COVID-19 pandemic or hospital staffing in emergency may take all the oxygen for policy responsibles to discuss which makes it very difficult to prioritise genetically guided treatments today that will unfold its full potential possibly in ten years' time. At the same time, there is a lot of awareness that in order to make it happen by 2035, there has to be investment today.

Here, EU level organisations function as leaders in the debate. They are organisers of events which allows facilitating role and at the same time - in connection with member states - self-organisation processes at the level of member states. Apart from the roleof the European Commission itself, ICPerMed promotes the establishment of a European partnership for Personalised Medicine. A co-funded European Partnership for Personalised Medicine (EP PerMed[14]) is supposed to bring together commitments of EU member states and participating organisations. And hence will work on the political level and maintain pace by priority and agenda setting, organising debates and taking them forward by sharing of information, evidence, know-how.

Setting up European Learning Structures/Platforms for Sharing Evidence

In experimentation, the insights gained from this must be shared and used in a knowledge-generating way. Evidence must be collected and shared so it is possible to identify what has worked and what has not. Therefore, these experimental programmes should always have substantial translational aspect, an aspect of systematic learning. This should be implemented on a European level - the European Reference Centre Network (ERN) can be a role model here.

With extreme patient stratification, the European level will become more important here. Associated with small patient cohorts, but not only, is the large number of different protocols and treatments that are provided to similar patients across countries. Often these are based on trial and error, but have to be used in an evidence enhancing way to generate information and learning. Thereby the idea is not to share data on individual patients, but sharing results of groups of patients and also being able to make decisions on a broader basis.

[14] https://www.icpermed.eu/en/ep-permed.php, last accessed 29/03/22

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Cross-border collaboration and treatments

The above entails setting up cross-country structures on how to coordinate research, evidence and care and find the right level for solving the same problem. In such a setting, patients can travel to other countries and get treatments at a specialised centre. In order to provide equal access and organise diagnostics and treatments efficiently across Europe, stakeholders expect there will be different ways of financing and also cross-border reimbursement for diagnostics and treatments. Today, this may be a problem, apparently also within some countries, even more across countries. It needs balancing of population size and numbers of patients required in terms of providing particular services.

Education and training through exchange

Interviewees stressed that implementation of personalised medicine will also need an experimental mindset in established professions, experimental mindsets. Training through international exchange is extremely relevant here as European and international research projects seem to have highly positive effects on the training of health professionals and related areas relevant for personalised medicine.

Horizon 2020, mobility through Marie Curie programmes and of course, Erasmus+, are exchange formats in place that seem to work well already. They add to capacity building of professionals in providing secondments, this also creates a consciousness of Europe as a whole. To foster exchange with industry as part of these formats could even add new perspectives and flow of information and exchange that does not seem to be covered to its full potential now.

Public Procurement: the Corona Vaccine Model

How public procurement worked on a European level for COVID-19 vaccines led many interviewees to think that this is a desirable and viable model for future procurement. Here it was highly appreciated that the EU safeguarded the vaccines also for smaller countries despite fierce competition at the beginning between some countries worldwide. (IP05) It could be of support in several ways: One, for conditional approvals where the evidence requirements that are demanded are often not met. If the low level of evidence then also leads to price reductions, then joint procurement in Europe would generate more weight in negotiations vis-à-vis the manufacturers. (IP10) Two, in joining on a European level, health care systems could adopt a more proactive approach. Instead of being at the receiving end, joint procurement would allow to have a joint entry platform harmonising an important step in the conditions under which drugs enter health care systems. (IP09)

Standardisation

If countries are going to cooperate on this kind of research, including front edge issues and smaller cohorts, using the vast data that are available in the patient databases, these then have to be organised in a comparable way. There are now competing initiatives of which route this kind of standardisation process is going to take (IP06).

- One is through the EU system and through the joint action on the EU Cancer Mission
- Another route is through corporate collaborational systems
- A third route is through direct research projects cooperation.

Within countries there are different advocacies of which route to go. Some advocate for the official channels, especially the official channels, where the European registries are involved in. At the same time, there are also debates going on that the official national or international

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standards will always lag behind. However, those are two different strategies that have to be taken into account. (IP07)

6.5 The European Role in Data Regulation

Digital Health challenges in Personalised Medicine

Data and its management by digital health solutions and infrastructures is an indispensable resource to facilitate Personalised Medicine (PM). As with “classical” medicine, this is the case both for developing diagnostic and therapeutic concepts for PM, and for establishing PM based healthcare. Since PM is defined as tailoring healthcare to the particular needs of an individual patient, this requires detailed information on this particular patient in order to be able to personalise the healthcare concept. This already – and in the future likely even more so - includes data from Whole Genome Sequencing, complex medical imaging, or longitudinal vital signs telemonitoring, i.e., datasets which are currently not routinely collected in standard healthcare. In a broader sense, this may also include data from the context of the patient, i.e., sociodemographic data, data on activities of daily living, nutritional data, data on environmental aspects and behavioural data, e.g., when it comes to mental diseases.

In summary, PM requires the collection, management, and processing of large, long, diverse, deep and big healthcare data sets, often distributed among different sources.

Therefore, PM is tied to data needs in order to allow patient identification and stratification, to finding relevant data sources and, subsequently, aggregating data from multiple sources. Potential solutions are still in their infancy.

Connected national/regional Electronic Health Records (EHR)

EHR, in many countries are designed to overcome the particular challenge of segmented healthcare systems as they are typical for Europe, where healthcare services are offered by multiple, independent healthcare providers which in many countries have only started the processes of sharing data in a common format. However, even in countries where this is advanced, data from electronic health records must not be shared for research purposes. Furthermore, data formats in electronic health records differ between countries, which is of disadvantage in personalised medicine that due to small cohorts would very much benefit from data exchange between countries. A dedicated set of initiatives and projects on the European level was initiated to facilitate interoperability between existing and upcoming national/regional EHRs[15].

The European Health Data Space

The European Health Data Space is an ambitious project but has still a far way to go. Rare diseases and personalised medicine are important drivers behind a current initiative by the European Commission to set-up a European wide infrastructure named the European Health Data Space to:

- promote safe exchange of patients' data (including when they travel abroad) and citizens' control over their health data
- support research on treatments, medicines, medical devices and outcomes
- encourage the access to and use of health data for research, policymaking and regulation, with a trusted governance framework and upholding data-protection rules

[15] X-eHealth – Exchanging Electronic Health Records in a Common Framework

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- support digital health services, and
- clarify the safety and liability of artificial intelligence in health.

However, all large-scale data sharing endeavours, especially in the healthcare domain and including the PM use case, face multiple and massive challenges like:

- Regulatory compliance, e.g., with data protection and privacy regulations (GDPR in Europe)
- Governance and data ownership questions
- Information security, i.e., to strike a balance in between Confidentiality, Integrity and Availability, also known as the CIA triad[16]
- data integrity, harmonisation, standardisation, and interoperability[17]

The Rare Disease Model for Personalised Medicine

Both in the diagnostic and therapeutic phase of PM, data challenges are similar to the rare disease challenge, since full personalisation, eventually, leads to each person's disease being classified into a unique, i.e., a very rare, disease.

- *Coding systems:* Hence, PM often shares the struggle of the Rare Diseases communities when it comes to information management. One issue is the need to develop proper coding systems to characterise the disease which may require to define, new and more specific coding systems. In the RD field, this led to classification concepts like the Orphanet nomenclature[18], since the classical general coding systems, like ICD10, or even specific ones, like ICD-O-3[19], turned out to be to coarse. They do typically not take into account biomolecular aspects of the disease and sometimes they are also not up to date to identify newly defined/discovered rare diseases.
- *Data Sharing Platforms & European Reference Networks***:** Also, large scale and geographically widespread data sharing concepts are required, which the European Commission addresses by supporting the Joint Programme on Rare Diseases (EJP-RD)[20] and its upcoming infrastructures like the Virtual Platform[21] or cross border healthcare structures like the European Reference Networks to pool knowledge and resources on a European scale[22].

The way forward

To achieve the above-mentioned goals and to help overcoming some of the related information management challenges, advanced ICT concepts like connected health technologies, Digital twins[23], the Internet of Things[24], Blockchain-based distributed and immutable ledgers[25], FAIR data initiatives[26], and many sorts of advanced analytics, including Artificial Intelligence, need to become part of the solution.

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[16] Information Security
[17] eHealth Network - Refined eHealth European Interoperability Framework
[18] http://www.rd-code.eu/introduction/
[19] International Classification of Diseases for Oncology
[20] https://www.ejprarediseases.org/
[21] https://www.ejprarediseases.org/what-is-it/
[22] https://ec.europa.eu/health/european-reference-networks_en
Digital Twins: From Personalised Medicine to Precision Public Health
[24] The internet of things in healthcare: An overview
[25] Blockchain in healthcare and health sciences—A scoping review
[26] From Big Data to Precision Medicine

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6.6 The Future of Health Care Systems

Personalised medicine approaches have the potential to increase the wellbeing of societies. Thereby they change the way health care systems are structured. This will change the way patients are treated. It will move away from the sort of one size fits all approach to treating diseases, which will require a large number of policy changes in re-engineering parts of health care systems. Forming alliances within Europe will be crucial and solve some issues related to personalised medicine.

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7 REFERENCES

Aula, V., 2019. Institutions, infrastructures, and data friction–Reforming secondary use of health data in Finland. Big Data Soc. 6, 2053951719875980.

Budin-Ljøsne, I., Harris, J.R., 2016. Patient and interest organizations' views on personalized medicine: a qualitative study. BMC Med. Ethics 17, 1–10.

Cambrosio, A., Campbell, J., Bourret, P., 2021. Beyond nosology? Molecular tumor boards, singularization, and the conflation of diagnosis and therapy. New Genet. Soc. 40, 95–111.

Cambrosio, A., Campbell, J., Keating, P., Polk, J.B., Aguilar-Mahecha, A., Basik, M., 2022. Healthcare policy by other means: Cancer clinical research as "oncopolicy." Soc. Sci. Med. 292, 114576.

Colombage, D., Lee, S., 2018. Companion diagnostics: requirements under the new IVD regulation. Regul Rapp. 15, 18–23.

Custers, J.A., Davis, L., Messiou, C., Prins, J.B., van der Graaf, W.T., 2021. The patient perspective in the era of personalized medicine: What about scanxiety? Cancer Med. 10, 2943–2945.

Erdmann, A., Rehmann-Sutter, C., Bozzaro, C., 2021. Patients' and professionals' views related to ethical issues in precision medicine: a mixed research synthesis. BMC Med. Ethics 22, 1–18.

Frezza, A.M., Trama, A., Blay, J.-Y., Casali, P.G., 2019. Networking in rare cancers: What was done, what's next. Spec. Issue Rare Cancers 45, 16–18. https://doi.org/10.1016/j.ejso.2018.03.030

Fujimura, J.H., 1988. The molecular biological bandwagon in cancer research: Where social worlds meet. Soc. Probl. 35, 261–283.

Geels, F., Raven, R., 2006. Non-linearity and expectations in niche-development trajectories: ups and downs in Dutch biogas development (1973–2003). Technol. Anal. Strateg. Manag. 18, 375–392.

Geels, F.W., 2004. From sectoral systems of innovation to socio-technical systems - Insights about dynamics and change from sociology and institutional theory. Res. Policy 33, 897–920. https://doi.org/10.1016/j.respol.2004.01.015

Geels, F.W., Schot, J., 2010. The Dynamics of Socio-Technical Transitions: A Socio-Technical Perspective, in: Grin, J., Rotmans, J., Schot, Johan (Eds.), Transitions to Sustainable Development: New Directions in the Study of Long Term Transformative Change. Routledge, New York, London.

Golubnitschaja, O., Costigliola, V., 2012. General report & recommendations in predictive, preventive and personalised medicine 2012: white paper of the European Association for Predictive, Preventive and Personalised Medicine. EPMA J. 3, 1–53.

Gulbrandsen, M., Hopkins, M., Thune, T., Valentin, F., 2016. Hospitals and innovation: Introduction to the special section. Res. Policy 45, 1493–1498. http://dx.doi.org/10.1016/j.respol.2016.05.010

This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No 824997.

Héon-Klin, V., 2017. European Reference networks for rare diseases: what is the conceptual framework? Orphanet J. Rare Dis. 12, 1–9.

Hutchings, E., Loomes, M., Butow, P., Boyle, F.M., 2021. A systematic literature review of attitudes towards secondary use and sharing of health administrative and clinical trial data: a focus on consent. Syst. Rev. 10, 132. https://doi.org/10.1186/s13643-021-01663-z

ICPerMed, 2017. Action Plan. Actionable Research and Support Activities identified by the International Consortium for Personlised Medicine.

ICPerMed, 2015. Shaping Europe's Vision for Personalised Medicine. Strategic Research and Innovation Agenda (SRIA).

Jungkunz, M., Köngeter, A., Mehlis, K., Winkler, E.C., Schickhardt, C., 2021. Secondary use of clinical data in data-gathering, non-interventional research or learning activities: Definition, types, and a framework for risk assessment. J. Med. Internet Res. 23, e26631.

Kuhlmann, S., Rip, A., 2014. The challenge of addressing Grand Challenges. A think piece on how innovation can be driven towards the "Grand Challenges" as defined under the prospective European Union Framework Programme Horizon 2020.

Lehtimäki, H., Helén, I., Snell, K., Eriksson, P., Montonen, T., 2019. Sustainable value creation in the commercialisation of innovation: the case of Auria Biobank. Int. J. Entrep. Innov. Manag. 23, 451–465.

Lipponen, S., 2021. Is Genomic Speech to Hopeful?

Makarov, V.O., Davydova, M.L., 2020. On the concept of regulatory sandboxes. Presented at the Institute of Scientific Communications Conference, Springer, pp. 1014–1020.

Moretti, A., Cianci, P., De Paoli, A., Meroni, F., Tajè, S., Mariani, M., Selicorni, A., 2021. Burden of care in families of patients with rare genetic diseases: analysis of a large Italian cohort. Eur. J. Med. Genet. 64, 104230.

Nordforsk, 2019. NOS-M Report: Personalised Medicine in the Nordic Countries.

Ritzhaupt, A., Hayes, I., Ehmann, F., 2020. Implementing the EU in vitro diagnostic regulation–a European regulatory perspective on companion diagnostics. Expert Rev. Mol. Diagn. 20, 565–567.

Robertson, A.R.R., Nurmatov, U., Sood, H.S., Cresswell, K., Smith, P., Sheikh, A., 2016. A systematic scoping review of the domains and innovations in secondary uses of digitised health-related data. BMJ Health Amp Care Inform. 23, 611. https://doi.org/10.14236/jhi.v23i3.841

Rotmans, J., 2006. Societal Innovation: Between dream and reality lies complexity. Erasmus University, Rotterdam.

Russo, A., Incorvaia, L., Capoluongo, E., Tagliaferri, P., Galvano, A., Del Re, M., Malapelle, U., Chiari, R., Conte, P., Danesi, R., 2022. The challenge of the Molecular Tumor Board empowerment in clinical oncology practice: A Position Paper on behalf of the AIOM-SIAPEC/IAP-SIBioC-SIC-SIF-SIGU-SIRM Italian Scientific Societies. Crit. Rev. Oncol. Hematol. 169, 103567.

Safran, C., Bloomrosen, M., Hammond, W.E., Labkoff, S., Markel-Fox, S., Tang, P.C., Detmer, D.E., 2007. Toward a National Framework for the Secondary Use of Health Data: An

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American Medical Informatics Association White Paper. J. Am. Med. Inform. Assoc. 14, 1–9. https://doi.org/10.1197/jamia.M2273

Schot, J., Steinmueller, W.E., 2018. Three frames for innovation policy: R&D, systems of innovation and transformative change. Res. Policy 47, 1554–1567. https://doi.org/10.1016/j.respol.2018.08.011

Shah, R., Ali, F., Finlay, A., Salek, M., 2021. Family reported outcomes, an unmet need in the management of a patient's disease: appraisal of the literature. Health Qual. Life Outcomes 19, 1–35.

Smits, R., Kuhlmann, S., 2004. The rise of systemic instruments in innovation policy. Int J Foresight Innov. Policy 1, 4–32.

Thune, T., Mina, A., 2016. Hospitals as innovators in the health-care system: A literature review and research agenda. Res. Policy 45, 1545–1557. http://dx.doi.org/10.1016/j.respol.2016.03.010

Vellekoop, H., Huygens, S., Versteegh, M., Szilberhorn, L., Zelei, T., Nagy, B., Koleva-Kolarova, R., Tsiachristas, A., Wordsworth, S., Rutten-van Mölken, M., 2021. Guidance for the harmonisation and improvement of economic evaluations of personalised medicine. PharmacoEconomics 39, 771–788.

Venne, J., Busshoff, U., Poschadel, S., Menschel, R., Evangelatos, N., Vysyaraju, K., Brand, A., 2020. International consortium for personalized medicine: an international survey about the future of personalized medicine. Pers. Med. 17, 89–100.

Vicente, A.M., Ballensiefen, W., Jönsson, J.-I., 2020. How personalised medicine will transform healthcare by 2030: the ICPerMed vision. J. Transl. Med. 18, 1–4.

Vicente, A.M., Ballensiefen, Wolfgang, Donertas, Derya, Eklund, Malin, Ivask, Angela, Jönsson, Jan, Kuhlmann, Katja, Lawrence, Adrien, O'Driscoll, Mairead, Richer, Etienne, Trivella, Giovanna, 2019. The ICPerMed vision for 2030. How can personalised approaches pave the way to Next-Generation Medicine? https://www.icpermed.eu/en/activities-vision-paper.php.

Vreman, R.A., Heikkinen, I., Schuurman, A., Sapede, C., Garcia, J.L., Hedberg, N., Athanasiou, D., Grueger, J., Leufkens, H.G., Goettsch, W.G., 2019. Unmet medical need: an introduction to definitions and stakeholder perceptions. Value Health 22, 1275–1282.

Wijnen, R., Anzelewicz, S.M., Petersen, C., Czauderna, P., 2017. European Reference Networks: Share, Care, and Cure—Future or Dream? Eur. J. Pediatr. Surg. 27, 388–394.

Zimmermann, B.M., Fanderl, J., Koné, I., Rabaglio, M., Bürki, N., Shaw, D., Elger, B., 2021. Examining information-seeking behavior in genetic testing for cancer predisposition: a qualitative interview study. Patient Educ. Couns. 104, 257–264.

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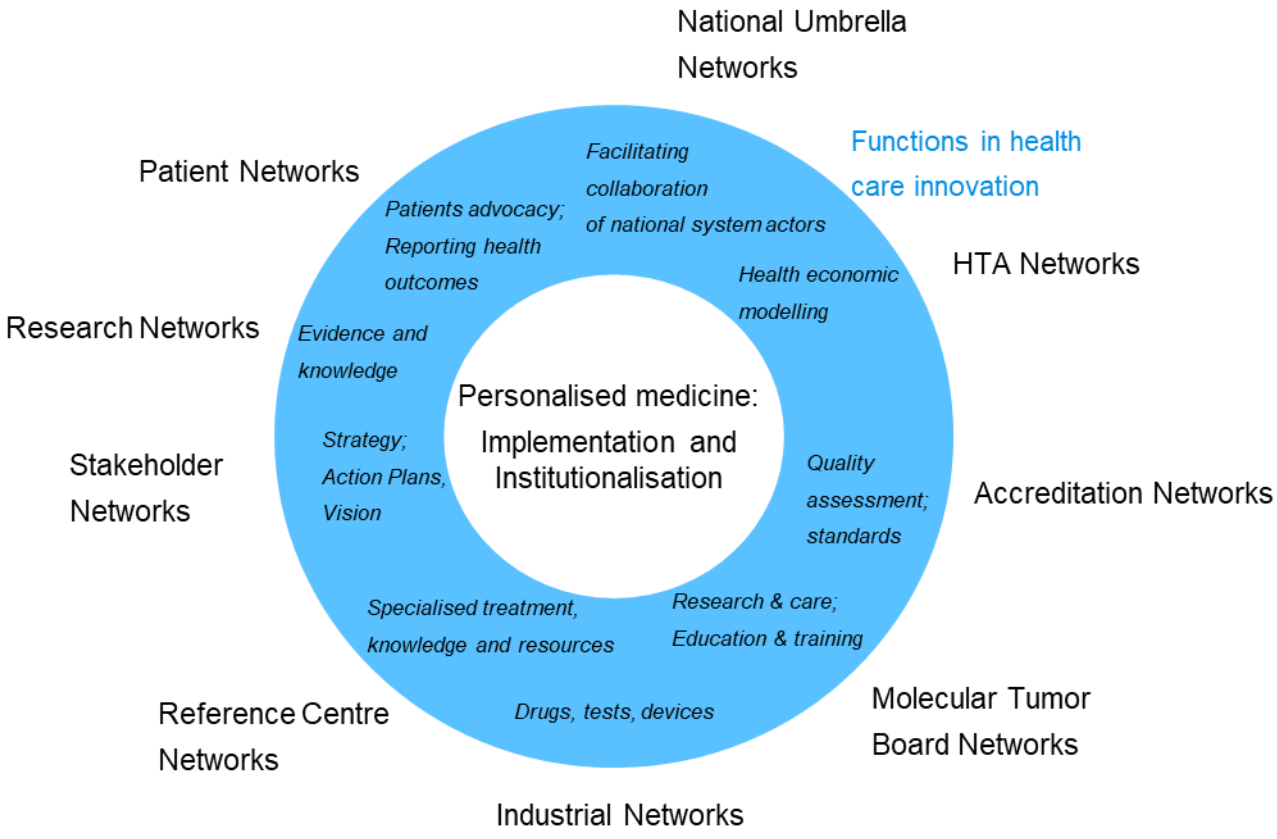
ANNEX: NETWORKS ENHANCING PERSONALISED MEDICINE FOR HEALTH BENEFITS

This section - without any claim to completeness –provides an overview of diverse types of networks that are operative and have influence on institutionalisation and implementation of personalised medicine. Interlinked networks play a crucial role in governing change in multi-layered complex systems like European health care systems. Different kinds of networks are of importance because they may be instrumental/essential for further policy development. The below tentative Figure gives an overview of how networks enhance implementation and institutionalisation of personalised medicine approaches through fulfilling crucial functions for health care innovation.

Figure 4: Networks and Functions in Health Care Innovation



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Patient Networks

The following patient networks were collected from interviews and in desk research and stand as examples for national, European and international network organisations. Patient organisations have been formed for specific diseases or to coordinate joint efforts over a spectrum of diseases.

National Patient Networks

The following national networks can only exemplify the large variety of national networks.

VSOP - Patient Alliance for Rare and Genetic Diseases) is the national patient alliance for rare and genetic diseases in the Netherlands. Their mission is to contribute to the quality of life of people living with a rare and/or genetic disease, their families and generations to come, by prevention, early diagnosis, therapeutic research, better health care and more societal awareness. VSOP was founded in 1979. At European level, VSOP works together with Eurordis and the European Patient Forum. When active in European projects, VSOP acts also on behalf of EGAN (European Patients Network for Medical Research and Health). VSOP is committed to all people with rare or genetic diseases and their families. It represents their interests from a patient perspective in the areas of quality of care, diagnostics and prevention, medical scientific research, heredity and pregnancy. For this VSOP develops various instruments and offers various forms of service. These include the special GP brochures on rare diseases, the development of quality standards, the organisation of several platform meetings, the appointment of special chairs and specific project websites.

Source: All information from the website https://vsop.nl/english/, last accessed 15/03/22

Lobby4Kids Austria is a self-help group formed mostly by families with children with disabilities or chronic illnesses. Lobby4Kids is an Austrian network that connects families and unites initiatives to raise public awareness on the one hand, and to create a network on the other. Parents and carers have to voice their children's concerns and fight for them. Especially in the case of children with disabilities or chronic illnesses, carers often no longer have the strength to achieve improvements. This self-help network helps directly with care, access to medicine and state support. Lobby4Kids offers individual care support including telephone support, referral to the right authorities, assistance in the clinic, and mediation between affected persons, doctors or authorities. Furthermore, they provide quick help through a helpline and online databank with individual information collected by members and public relations work.

Source: All information from the website https://www.lobby4kids.at/ , last accessed 28/03/22

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iCAN Digital Precision Cancer Medicine Flagship is part of the Finnish national R&D flagship program funded by the Academy of Finland providing solutions to the cancer challenge through a discovery and innovation cluster at the interface of precision cancer medicine and digital health. The iCAN discovery platform links molecular profiling of tumors with broader health data of cancer patients, acting as a catalyst for breakthrough research and technologies. Cancer patients are engaged through participation at all stages of iCAN to ensure research quality, relevance, and effective dissemination and application of the results. The purpose is to ensure relevance and impact of the project for cancer patients. A Patient and Citizen Advisory Board was established, that enables patients and researchers to share their perspectives and priorities and facilitates two-way interaction and dialogue. Its members act as a link between the broader public, citizens, cancer patients and patient organisations and the iCAN research, management and project teams. They are based in various parts of Finland and represent several cancer patient organisations.

iCAN hosts research projects aligned with the iCAN aims and carried out by iCAN partners for discoveries, innovations and improved treatments. However, iCAN is implemented as a partnership between academic research, healthcare system, life science industry partners and patients and at the core of iCAN is the Flagship project, a large pan-cancer public-private research partnership. The active participation of patients at all levels is a key element of the flagship, ensuring impact and benefits to the patients. Partnerships with companies from pharma, biotech, and AI sectors are critical and enable the inclusion of early drug leads, new technologies, and new competencies.

Source: All information from the website https://ican.fi/patient-engagement/, last accessed 25/05/22

European Patient Networks

Especially EUPATI was mentioned in various interviews as a kind of public private network that is deemed important in playing a key role in policy processes. Such organisations also provide education for and understanding of the patients. Other umbrella organisations such as EURORDIS, the European Patient Organisation for Rare Diseases. and organisations on national level, for example the VSOP, were considered as important partners for involvement in round table discussions with various other stakeholders.

The European Patients' Academy on Therapeutic Innovation (EUPATI) is a multi-stakeholder public-private partnership originally launched by the IMI-EUPATI project (2012-2017) and hosted by the European Patients' Forum (EPF) from 2017 to 2020. EUPATI is today established as an independent non-profit Foundation in the Netherlands. It is a successful programme that provides education and training to increase the capacity and capability of patients and patient representatives to understand and meaningfully contribute to medicines research and development (R&D), and to improve the availability of medical information for patients and other stakeholders. EUPATI provides a broad range of training and education to increase the capacity and capability of patients and patient representatives

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to understand and meaningfully contribute to medicines R&D, to improve the availability of medical information for patients and furthermore. a broad training portfolio for industry representatives and academic representatives.

Source: All information from the website https://eupati.eu/, last accessed 28/03/22

The Melanoma Patient Network Europe (MPNE) is an organically growing multidimensional network system of predominantly European Melanoma patients, carers and advocates and operates effectively across cultural and language barriers according to subsidiarity and shared principles. Their mission is to systematically address problems faced by the European Melanoma community in a constructive, result-oriented and evidence-based manner by providing platforms for communication and collaboration. MPNE provides high-quality education so that Melanoma patients are not only able to actively participate in their own care but are also enabled to shape the systems around them to the benefit of the entire Melanoma patient community- from research to policy.

Source: All information from the website http://www.melanomapatientnetworkeu.org/home.html, last accessed 28/03/22

EURORDIS, the European Patient Organisation for Rare Diseases, is a non-governmental patient-driven alliance of patient organisations representing 988 rare disease patient organisations in 74 countries. Its mission is to build a strong pan-European community of patient organisations and people living with rare diseases, to be their voice at the European level. EURORDIS seeks to improve the quality of life for people living with rare diseases in Europe through advocacy at the European level, support for research and medicines development, facilitating networking amongst patient groups, raising awareness, and many other actions designed to reduce the impact of rare diseases on the lives of patients and family.

Source: All information from the website https://www.eurordis.org/, last accessed 28/03/2

European Patients' Forum (EPF) is an independent non-profit, non-governmental umbrella organisation of patient organisations across Europe and across disease-areas. The 77 members include disease-specific patient groups active at EU level and national coalitions of patients. The mission is to advance the interests of patients and patients' communities by strengthening their collective impact across Europe through effective advocacy, education, empowerment, and partnership. EPF focuses on patients with chronic conditions and has established a role as initiator, e.g., for EUPATI or the Patient Access Partnership PACT. They directly represent the interests and views of the members, which are umbrella patient organisations across Europe and inter alia, the interests of all patients with chronic conditions

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in Europe, also through cooperation with online communities. EPF indirectly represents the interests of all patients with acute conditions, bringing unique experience and expertise as patients living with long-term conditions to help strengthen health systems and ensure patient safety and multi- stakeholder collaboration. EPF focuses on promotion of meaningful, systematic and structured patient involvement in policymaking, research and in shaping healthcare practice that empower patients to be active partners in care. EPF advances patient involvement through campaigns, advocacy, education, research, and projects and advocates for equitable and affordable access to high-quality, state of the art, inclusive care for all and for the eradication of discrimination and stigma.

Source: All information from the website https://www.eu-patient.eu/, last accessed 28/03/22

Patient focused medicines development (PFMD) is a not-for-profit collaborative initiative benefiting patients and stakeholders from the health care system by designing a patient-centred healthcare system with patients, healthcare professionals, patient advocates, life science representatives and regulators. Its mission is to bring together initiatives and best practices that integrate the voice of the patient thereby speeding up the creation and implementation of an effective, globally standardized framework for patient engagement – that involves patients as partners – as well as the necessary tools, services and support to allow the adoption of the framework by various stakeholders. The strategic approach includes scaling patient engagement in drug development, building the conditions and enablers of patient engagement and patient engagement in digital health and data.

Source: All information from the website https://patientfocusedmedicine.org/, last accessed 28/03/22

The **Patvocates Network** is a think tank, consultancy and social enterprise in the area of patient advocacy and patient engagement. They deliver insights, experience, connections and projects to empower all stakeholders to establish effective engagement frameworks, policies, processes and projects for the involvement of patients, patient advocates and patient organisations in research, healthcare institutions and the private sector. Patvocates is run by a team of leading pan-European patient advocates with extensive knowledge of pan-European healthcare systems, institutions, stakeholders, cultures and the pan-European patient community. Patvocates also offer training and consultancy to authorities, healthcare institutions and companies and for patient advocates.

Source: All information from the website https://www.patvocates.net/, last accessed 27/03/22

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Strategic Platforms and Stakeholder Networks

Stakeholder networks play a crucial role in strategic reflection, forming a common understanding of the potentials and issues around personalised medicine, making connections with the higher policy levels, and organising events around stakeholders presenting different aspects around personalised medicine.

International Consortium for Personalised Medicine (ICPerMed)

ICPerMed is a strategic platform and promotes the reasonable and fair implementation of personalised medicine approaches into health care systems, with the aim of PM benefitting patients, citizens and society as a whole. Members of ICPerMed are public organisations like funding agencies, ministries of health etc from the different countries and regions.

ICPerMed has developed over the last decade, an important milestone was the CSA PerMed financed by the 7th European Research Framework Programme. It was initiated to increase coordination efforts between European key stakeholders in order to allow synergies.

ICPerMed works in close collaboration with several Coordination and Support Actions (CSAs) funded by the European Commission (=ICPerMed Family). At the same time, it works in close cooperation with the ERA Net on Personalised Medicine, ERA PerMed. ERA PerMed is supported by 32 partners from 23 countries and co-funded by the European Commission. It aims at funding transnational research projects and to align national and regional research strategies.

ICPerMed launched a Strategic Research and Innovation Agenda (SRIA) (ICPerMed, 2015) covering the whole value chain of personalised medicine, bringing forward challenges and recommendations for advancing the area. Furthermore, ICPerMed developed an *Action Plan* (ICPerMed, 2017), based on the PerMed recommendations, with concrete suggestions for research that can be rather directly taken up by research funding programmes on national, regional, European or even international level.

Source: All information from the websites https://www.icpermed.eu/en/related-initiatives.php, https://www.icpermed.eu/en/icpermed-about.php, last accessed 30/03/22

The European Alliance for Personalised Medicine (EAPM)

EAPM was launched in 2012 and mediates for a wider understanding of priorities in personalised medicine through a more integrated approach among lay as well as professional stakeholders. EAPM organises regular major events and media interaction, and also the publication of Special Issues. The Alliance has a broad mix of members, like patient groups, academia, health professionals and industry.

Source: All information from the website https://euapm.eu/who-we-are.html, last accessed 30/03/22.

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Global Research Networks

Clinical researchers, especially from research hospitals, report challenges in participating in global research networks due to GDPR. “When we make clinical trials, we open the trials to other countries, like Japan, China, U.S., South America, and also in European countries. What we need is that Europe, European centres can participate to global clinical trials. Today, there is a lot of constraint with GDPR. We are less and less invited to participate in clinical trials.” (IP01)

Pharmacogenomics Global Research Network (PGRN)

The Pharmacogenomics Global Research Network (PGRN) targets to facilitate research in precision medicine with a specific focus of how genomic variation influences therapeutic and adverse drug effects. Members of the PGRN are international and come from diverse clinical and scientific disciplines and may be working in research, education, non-profit organisations, industry and governments. The network offers events for members (online and in person) to update them on research in progress and best practices.

Source: All information from the website https://www.pgrn.org/what-is-pgrn.html, last accessed 25/03/22

The Personalised Medicine Network

The personalised medicine network is embedded in the Faculty of Health at Aarhus University, Denmark. It aims to foster research but also teaching in this area to allow a faster progress of scientific developments to benefitting the patient. Regional, national and international initiatives are part of the network. Everybody can join who is interested in the research area and currently there are experts from “genetics, molecular biology, bioninformatics, supercomputing, epidemiology, pharmacology, law and ethics”. The network regularly offers seminars and started a series called “Approaches to personalized medicine at health”.

Source: All information from the website https://health.au.dk/en/research/research-networks/the-personalised-medicine-network/, last accessed 25/03/22

Regional Networks

It is a major concern that in some regions in Europe, there will be poor access to certain services, for example to new generation sequencing. This is partly related to low numbers of population, hence insufficient critical mass to justify the investment in such technologies where at the very beginning the level of investment is substantial. One possibility here is some kind of agreement amongst European regions and also across countries in order to

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reach sufficient critical mass. Here, in a Europe of regions, cross-country and cross border coordination and investment may be a solution. (IP04, IP05)

The Nordic countries may serve as an example of how to foster cooperation between countries, also on a regional level.

Personalised Medicine in the Nordic countries

In the Nordic countries, the Nordforsk, an organisation under the Nordic Council of Ministers that provides funding for and facilitates Nordic cooperation on research and research infrastructure (see https://www.nordforsk.org/about), raised the importance of cooperation in personalised medicine across Nordic countries. Cooperation here might entail fewer challenges as the Nordic countries in many respects have very similar systems compared to e.g. at the EU level.

A Mapping report by the Nordforsk came to the following conclusions: (p4)

- There are national strategies in all Nordic countries directed either specifically towards personalised medicine or to closely related areas.

- It is clear that the Nordic countries have a number of advantages to facilitate the realisation of personalised medicine, e.g. high-quality epidemiology and clinical research, unique health data infrastructures in registers, cohorts and biobanks.

- The many similarities between the Nordic countries, e.g. similar public health care systems, a population that is generally very positive towards participating in and has trust in research, etc., implies a strong added value in collaboration between the Nordic countries in personalised medicine.

- The unique Nordic biobanks and health registers have the potential to make the Nordic region competitive at the global level. There are several ongoing initiatives at the Nordic level addressing handling and sharing of health data, clinical data as well as large data generated from genomic/omics projects.

- A number of obstacles to Nordic cooperation need to be overcome. One such obstacle is the utilisation of data from registers and biobanks at the Nordic level.

Common Nordic Initiatives

- Nordic Society for Human Genetics and Precision Medicine
- Nordic Trial Alliance
- Nordic Health Research and Innovation Networks
- Nordic Alliance for Clinical Genomics
- Nordic Biobank Network
- Nordic Collaboration for Sensitive Data (Tryggve)
- NORIA-net on Registries
- Common Nordic Calls for innovation projects

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- Common Nordic conferences for personalised medicine

Source: All information from the report (Nordforsk, 2019)

National Umbrella Networks

Several countries entertain national networks that either have the main task of implementing and institutionalising personalised medicine-based health care in their country (e.g., Swiss Personalised Medicine Network) or they are broader, but have the implementation of personalised medicine in their country among their goals (e.g., Cancer Society Finland). Some examples for individual countries are given, but there are numerous others, that are working on non-profit or profit bases.

Cancer Society Finland

Cancer Society Finland is an example for a national umbrella organisation, it is the headquarter of a network of different components. It is a very broad umbrella, hence like a network because different types of organisations that function separately and then come together in the umbrella of Cancer Society Finland. Network nodes are the clinics, biobanks, the cancer registry, and also patient organisations.

Cancer Society Finland

Aims, approach, history

- Cancer Society Finland was founded 1936, and from the1950s/60s established Finish cancer registry, furthermore first provincial cancer associations, and patient organisations.

- The mission statement is to promote health/survival, prevent cancer, support people with cancer and their relatives, and reduce adverse effects of cancer.

- Regional associations and national patient organisations activities provide “counselling for cancer patients and family, arranging peer support, rehabilitation and orientation courses and recreational activities”.

Funding, ownership, governance

Cancer Society Finland is financed through income from fundraising and private investments; grants; and open-ended agreement with National Institute for Health and Welfare.

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Impacts

General impacts are health promotion, advice service, advocacy.

Impacts related to research are the Finnish Cancer Registry as “a national and internationally important research body. The Cancer Registry is a statistical and epidemiological cancer research institute. It runs a database of all cases of cancer in Finland. Part of the Cancer Registry comprises the mass screening registry, which directs cancer screening work and evaluates screenings nationally.”

Source: All information from the website Cancersociety 2022 https://www.cancersociety.fi/ , last accessed 15/03/22

French Cancer Plan and French National Cancer Institute

The French cancer plan may also serve as an example of a national network as it interconnects all hospitals treating cancer in France. A particular cancer patient with a particular type of cancer will be treated similarly across all of France, no matter which region s/he is in. There is a central exchange of data between all cancer care providers. (IP07)

French National Cancer Institute

Aims, approach history

The French National Cancer Institute was founded in 2004. Several national cancer control strategies were developed since then while the latest cancer control strategy considers the longest time horizon with 10 years (2021-2030).

The strategic goals are set regarding research, public health and cancer care with three dedicated priorities: “improved prevention; Limiting side-effects of treatment and improving patients’ quality of life; Fighting cancers with the worst prognosis for both adults and children”

Funding, ownership, governance

The French national Cancer Institute partners with state representatives, charities, health insurance funds, hospital federations and research organisations. It is governed by senior leaderships, a board of directors (27 directors), a scientific board, a general assembly (12 representatives of the public interest group), an ethics committee, and a health democracy committee.

The available budget is approximately €100 million with the majority provided by the ministries for Health and for Research, contributions from other GIP members and funds from partnerships with public and private organisations.

About half of this budget is allocated to research funding, remainder healthcare initiatives, public health and public information.

Impacts

The institute accredited the national data sharing project (OSIRIS) to create a network of searchable federated databases.

Source: All information from the website https://en.e-cancer.fr/ , last accessed 15/03/22

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Austrian Platforms for Personalised Medicine and Rare Diseases

In Austria there are several platforms organising issues around personalised Medicine and patient organisations.

Austrian Platform for Personalised Medicine https://www.personalized-medicine.at/ is financed by the Ministry for Education, Science and Research with the aim to establish a networking platform for all actors across disciplinary and sectoral boundaries in order to advance the discussion of the topic of Personalised Medicine in Austria, in the European and in the international context through increased strategic cooperation. The platform is open for membership to individuals as well as organisations. Through active cooperation of the participating research facilities, clinics and institutions biomedical basic research, clinical and translational research in Austria is promoted. In *four working groups* different topics are addressed, this includes academic research, medical practice as well as education and training. In addition, the discussion of societal or socio-political implications of Personalised Medicine and ethical issues as well as the stimulation of a broader public discussion about possibilities and risks are promoted.

Source: All information from the website https://www.personalizedpersonalised-medicine.at/, last accessed 15/03/22

Pro Rare Austria - Alliance for Rare Diseases - was founded at the end of 2011 as an Austria-wide umbrella organisation for patient organisations and self-help groups in the field of rare diseases by directly affected people and parents of affected children. Pro Rare Austria is a non-profit association, has around 80 members and sees itself as an active platform, pro-active action alliance and, above all, as a mouthpiece for the many concerns of people with rare diseases. The fact that both medical and social framework conditions in care and reimbursement for the 400,000 Austrian patients are in need of improvement is their mandate for action. Their tasks are member support and networking, representation of interests and voice for members, contact point for the public sector; international networking, public relations, information, awareness raising, initiation of projects & scientific work, fundraising and sustainable operation of the association (https://www.prorare-austria.org/)

Source: All information from the website https://www.prorare-austria.org/), last accessed 15/03/22

HTA Networks

There is a huge diversity within the Europe in terms of how to conduct health technology assessments. However, “the European level has already shown with this HTA network how good cooperation can work. One would actually wish for such a network of experts in personalised medicine.” (IP10)

As personalised medicine brings forward a lot of methodological issues that are solved differently between HTA exercises, many experts mention the EUneTHA as a model for

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cooperation and instrument of harmonising the methodology in HTAs in the personalised medicine field. Here, an HTA core model adhering to EUnetHTA methods and joint clinical assessments could be linked to country/region-specific assessments of patient pathways, budget impact and cost-effectiveness.

EUneHTA

EUneHTA was initialised in 2004 by call of EC and Council of Ministers.

Its mission is to support collaboration between European HTA organisations and to add value to healthcare systems at the European, national and regional level.

EUneHTA was initiated by EC and project funding. It impacts on joint clinical assessment (and dissemination) and joint scientific consultations before the start of pivotal clinical trials.

Activities as stated on the website:

- Support of efficient production and use of HTA in countries across Europe;

- Provision of an independent and science-based platform for HTA agencies in countries across Europe to exchange and develop HTA information and methodology;

- Provision of an access point for communication with stakeholders to promote transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations;

- Development of alliances with contributing fields of research to support a stronger and broader evidence base for HTA while using the best available scientific competence.

Source: All information from the website https://www.eunethta.eu/ , last accessed 15/03/22

Internationally HTA organisations are cooperating in networks such as the HTAi.

Health Technology Assessment international (HTAi) is the global, non-profit, scientific and professional society for all those who produce, use or encounter health technology assessment (HTA). They represent 82 organisations and over 2,500 individual members from 65 countries around the world. These stakeholders include researchers, policy makers, industry, academia, health service providers, agencies and patients, and they contribute to balanced conversation around HTA across different areas of practice and jurisdictions.

Their vision is to continue to be the leading global society for all stakeholders engaged in the production and use of HTA in decision-making.

This will be achieved through their mission to promote the development, communication, understanding, and use of HTA around the world through four areas of focus:

- Expand and grow the presence of HTAi globally through our membership
- Expand HTA through knowledge sharing and information dissemination through partnerships

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- Advance scientific knowledge and support capacity development
- Ensure continued financial stability and good governance

Source: All information from the website https://htai.org/. Last accessed 25/03/22

EPEMED

EPEMED aims to represent a diverse group of members from industry (including diagnostic, pharmaceutical and device sectors), academia, research as well as patient groups and professional service firms.

EPEMED intends to be a catalyst who acts for advancing personalised medicine in Europe and the breakthrough role of diagnostics and co-dependent drug-companion diagnostics technologies in improving patient outcomes.

Source: All information from the website http://www.epemed.org/online/www/content/ENG/index.html, last accessed 29/03/22

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Industrial Networks

Relevant here are pharma companies, but it is also expected that the new, big players will be the technology companies in the health area. Pharmaceutical companies will be under increasing pressure to provide those drugs that are needed at prices that are affordable. (IP11)

European Biopharmaceutical Enterprises (EBE) was established in 2000 and is a network representing biopharmaceutical companies in Europe. It is part of the **European Federation of Pharmaceutical Industries and Associations (EFPIA)**.

EFPIA together with the European Commission launched a partnership, the Innovative Medicines Initiative (IMI, 2008-2024) which is also active in the area of personalised medicine.

EBE has issued a White Paper highlighting the components needed for the future:

- greater investment in e-health and big data infrastructure, for innovative regulatory science and access mechanisms for the benefit of patients;
- establishing data privacy and protection laws, which effectively protect patients while also allowing for pan-European research initiatives;
- appropriate European regulation to ensure access to reliable methods for correct diagnosis; the ongoing trilogue on a medical devices and in-vitro diagnostics regulation provides a unique opportunity for progress.

Source: All information from the website https://www.efpia.eu/news-events/the-efpia-view/efpia-news/ebe-releases-white-paper-on-personalised-medicine-with-a-focus-on-key-challenges/, last accessed 30/03/22

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Accreditation networks

Accreditation networks are an important instrument in order to develop and implement standards and assure quality. In the field of personalised medicine they may help cancer centres and institutes to implement a quality system e.g. for oncology care. In developing and adapting standards for this, improvements in translational and clinical cancer research are fostered and accelerated.

Organisation of European Cancer Institutes (OECI) Accreditation Programme

The goals are equal access to high quality cancer care by overcoming differences in access to diagnostics, treatment and therapeutic options within Europe. In using OECI standards, centres and cliniques are supported in the implementation of a quality system for oncology care.

OECI quality assessment programme is a supportive voluntary measure for cancer centres/institutes. OECI has a special accreditation programme in multidisciplinary integrated cancer care and research including goverancne, organisational quality, patient involvement and empowerment, multidisciplinarity, prevention and early detection, diagnosis, treatment and care, research, education and training

In order to apply for a comprehensive cancer centre, “OECI membership is required, as well as a strong commitment to quality improvement (signature of Director/ Board of Directors), dedicated staff (contact person, project group, all involved employees), stable management structure (no interim management), no major changes/problems (expected management change, merger, housing movements, financial crisis), following the steps of the A&D programme with care and within the required timeline, involvement in oncology research and education programmes, provision of oncology surgery, radiation therapy and medical oncology. Cancer care has to be performed in an identifiable unit with an identifiable budget, management and organisational structure”

Necessary steps include screening, self-assessment, approval, peer review and designation assessment, reporting, approval accreditation and designation certificate.

Reference (all information from the website), https://www.oeci.eu/Accreditation, last accessed 21/03/22.

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ANNEX: INTERVIEW GUIDELINES

Questions on Patient Perspective

Benefits/challenges of PM for the patient

- **What do you think are patients'/relatives' expectations concerning personalised medicine?**
  - What benefits and challenges do patients/relatives expect from PM-based services/therapies?
  - What benefits and challenges have patients/relatives experienced from PM-based services/therapies already? Examples?
- Which benefits/perspectives for patients/relatives are particularly important for personalised medicine? (What values can be added to the value proposition?)
- How can benefits for patient be identified and assessed?
- From a patient's perspective, where is additional R&D particularly needed?

Empowerment

- How are patients be involved in PM? Are there distinct differences for certain PM approaches? **What are good/best practices to involve patients in PM?**
  - Research and implementation?
  - **Additionally, relatives?**
- What are the **key aspects of patient/relative empowerment related to PM**? HOW is the patient empowered, are there several lines of thinking?
- Does PM only have empowering aspects, or also weakening? Scanxiety
  - Who might have disadvantages by the implementation of PM (and how)?

Financial accessibilities

- **From the patients'/relatives' perspective, how do you assess the financial accessibilities of personalised medicine for patients (in general)?**
- What challenges do patients/relatives expect/experience by the financing of PM services/therapies?
- Are you aware of any documented approaches?
- What would this mean for insurance companies and reimbursement schemes?

Policy

- **Where would you see particular need for public policy action? At regional, national or EU level? Are there any collaborations (needed)?**
  - What types of policies are required to promote PM **implementation**?
  - Is there anything in the regional or national or European policy context (or economic context) that has influenced the development of PM and benefits for patients so far?
  - Is there anything the regional or national of European policy context (or economic context) that could influence the development of PM and benefits for patients so far?

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- On a policy level, who are the key players/ carrying organisations in the change process?
    - How can they influence /drive the change process towards more implementation / institutionalisation of PM?
- Considering the national character of health care,
    - What is the specific role of members states in PM related policy?
    - what is the specific role of the European Union in PM-related policy?
    - What is the specific role of patient organisations in PM-related policy?

Support

- **Do you know any support scheme for patients/relatives** that undergo a PM specific therapy/treatment?
    - Personal, medical, organisational, financial, etc.?

Future

- **Is there anything that should change / become better in PM to increase the benefit/value for the patients?**
- To what extent can patients /patient organisations contribute to the development of PM based services/therapies? How?
- Who is PM for and is there a danger of creating a two-class health care system?

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Questions on Institutionalisation Aspects

Block 1: Implementation/Institutionalisation

- **Could you please shortly characterise your organisation and role therein?**
- **Do you have experience with PM and related approaches in your job?**
- **Do you have experiences in processes of implementing new health care services in general? Is PM different?**
- **Which activities or strategies could enhance the chances and speed of successfully implementing PM approaches into the health systems?**
- To what extent does health economic modelling/HTA support or hinder this process? Cost-effectiveness? Budget impact? Patient needs? Other aspects?
- Are you aware of effects/benefits of PM that should be reflected in the evaluation (HE modelling/HTAs) of PM?

Block 2: Decision making processes in public health care

- **Recent health economic modelling results indicate that PM might not be as cost-effective as we maybe would like it to be. How could this affect the implementation of PM in public healthcare (in your country/region)? How will you or your institution proceed?**

Block 3: Innovation

- **From your perspective, where is <u>additional R&D</u> in the context of personalised medicine particularly necessary?**
- **What are the arrangements for funding <u>education and training (certification)</u> related to personalised medicine?**
- **How can academia, industry, and regulatory authorities <u>collaborate</u> to further support and promote innovation?**

Block 4: Innovation: Niche perspective

- *Pilot projects/references cases/strategic niche management and studies for implementation*

- **Where would you set up pilots/niches for PM care, what should be the selection criteria**
- **What should be criteria for <u>not</u> implementing PM approaches as niches?**

Block 5: Role of regulation/legislation (Note for self: -> Roadmap!)

- **What regulations/legislation may be particularly important to facilitate or prevent the implementation of PM?**
  - **If you think about the future (10, 20, 30 years), would there be other regulations/legislation beneficial for the implementation of PM?**

Block 6: Role of policy

- **Where would you see particular need for changes in public policy? National, and also EU?**

Closure: Past and Future

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- Is there something surprising in the development of PM so far, something you did not expect at all?
- Is there anything that should be particularly considered for the future of PM/health/QoL?

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