

Shaping Europe's Vision for Personalised Medicine

Strategic Research and Innovation Agenda (SRIA)

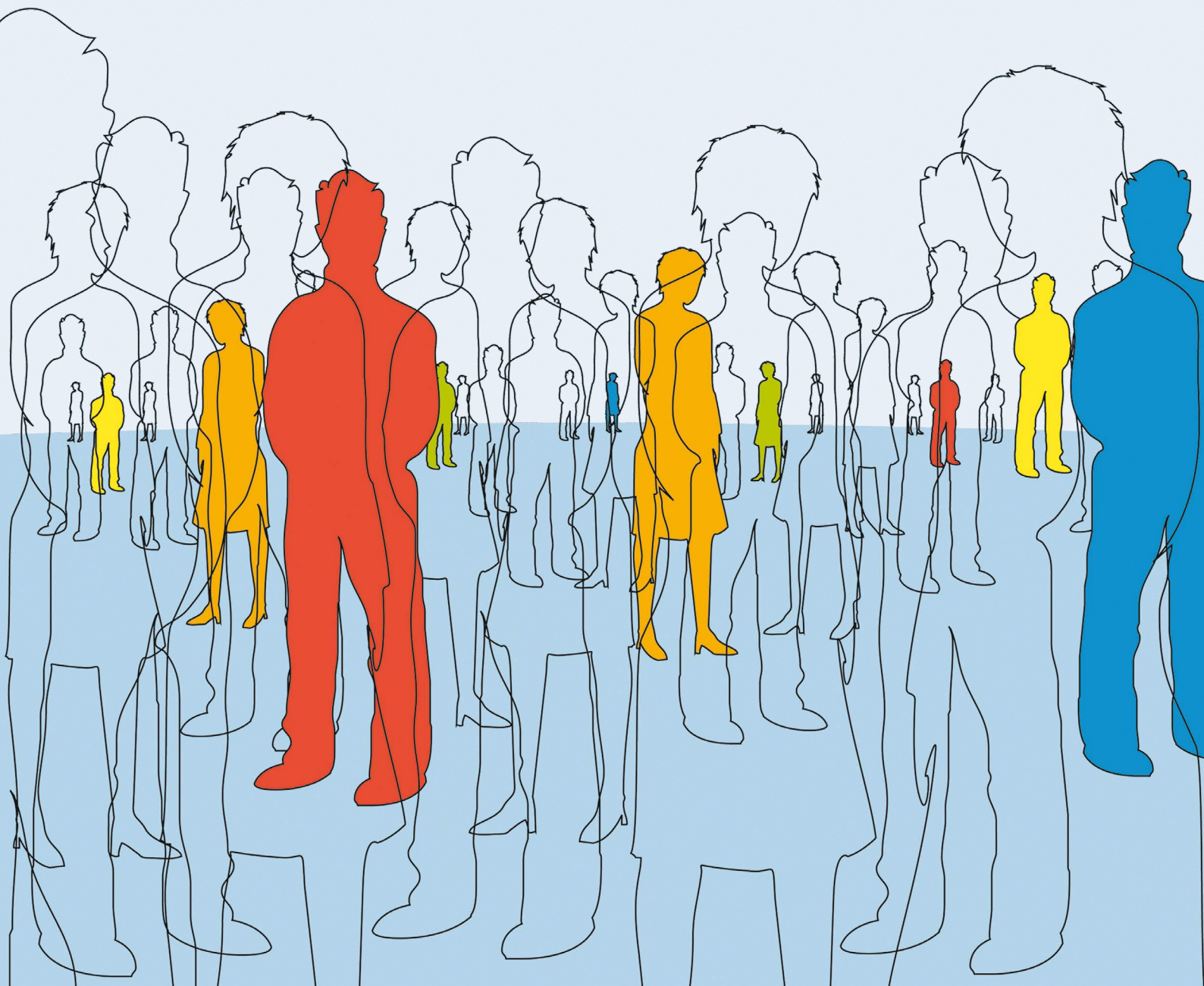


Table of Contents

1)	Executive summary	2
2)	Background	5
3)	Introduction to the five challenges	8
4)	Challenges for the further implementation of Personalised Medicine	11
	■ Challenge 1 – Developing Awareness and Empowerment	11
	■ Challenge 2 – Integrating Big Data and ICT Solutions	17
	■ Challenge 3 – Translating Basic to Clinical Research and Beyond	22
	■ Challenge 4 – Bringing Innovation to the Market	28
	■ Challenge 5 – Shaping Sustainable Healthcare	33
5)	General conclusions	40
6)	Proposed Research Activities to foster Personalised Medicine	42
7)	A glimpse into the future	45
8)	Authors and experts consulted	46
9)	Annexes	49
	Annex A: PerMed Recommendations	49
	Annex B: Strategic Reports on Personalised Medicine	51
	Annex C: Further References	52
	Annex D: References and Links	54
	Annex E: Abbreviations and Acronyms	55

Please note that a PDF version of this SRIA, including all links and hyperlinks, can be downloaded for free on the PerMed website (<http://www.permed2020.eu>).

1) Executive summary

PerMed is a Coordination and Support Action (CSA) of 27 partners representing key decision makers in research and research policy, industry, healthcare and patient organisations (www.permed2020.eu). The consortium received funding from the European Union's Seventh Framework Programme for research; technological development and demonstration to generate a Strategic Research and Innovation Agenda (SRIA) with general recommendations and research activities which could foster the further implementation of Personalised Medicine (PM).

PM approaches, particularly for diagnosis and treatment of cancer and rare diseases, are already being implemented. However, development and implementation of PM approaches for other diseases and many aspects of healthcare delivery is still far from being a reality. Thus further PM implementation will need a paradigm shift for all citizens, researchers and national healthcare systems. Taking into account that PM can only be successfully implemented when handled as a truly cross-sectoral topic, this document integrates the perspective of experts across the entire healthcare value chain. This SRIA is based on an analysis of important recent strategic reports as well as interviews and consultations with experts and representatives of all relevant sectors important to the implementation of PM. Based on recent and future developments, the SRIA contains 35 recommendations (each is numbered, and the relevant recommendations for each challenge area are shown in parentheses below and Annex A) clustered under five challenges. The SRIA also presents nine prioritised recommendations, which have the highest potential impact and outcome in facilitating the introduction of PM for the benefit of patients, citizens and society as a whole (see the paragraph Looking Forward below).

Challenge 1 – Developing Awareness and Empowerment

With the advent of PM, the role of caregivers and patients will evolve. Successful implementation of PM will be

achieved only if all stakeholders, including patients and healthcare professionals, are empowered and develop the required awareness about PM. The crucial first step is to provide the best available evidence that supports the clinical and personal utility of PM, as well as its economic value to health systems, and to enable better understanding of how the changes brought by PM will impact public health for the benefit of individual citizens and society (recommendations 1,4). Models that enable sharing, ownership and the development of a sense of responsibility towards personal health data, as well as the improvement of PM health literacy, will need to be generated along with suitable common principles, appropriate policy and regulatory frameworks (2,5,7). Public engagement in PM can be increased by enabling citizens to become actively involved in all phases of research and development ('citizen science'), and the introduction of mobile health applications will facilitate data generation about the safety and effectiveness of interventions (3,6).

Challenge 2 – Integrating Big Data and ICT Solutions

The development of PM will rely heavily on integrated 'big data' analytics and ICT solutions to generate the required knowledge and infrastructure to support the new approaches. Technologies for data capture and management and development of high quality databases will be instrumental, but there will also be a requirement for strategies to make sense of this big data for known and future purposes (8,9,10). Translational research infrastructures and data harmonisation of structured, semi-structured and unstructured data will be a central component of such strategies and should lead to new analytical methods and modelling approaches as well as innovative decision support tools such as in silico simulations to support physicians' decisions (11,12,13). To integrate all these aspects, further European big data and 'big science' frameworks need to be created and supported by suitable legislation (14).

Challenge 3 – Translating Basic to Clinical Research and Beyond

In order for PM to reach its anticipated impact on human health and wellbeing, translation of discoveries and communication across the continuum of research are required. This starts with the integration of all 'omics' data to generate and implement meaningful interventions. Such processes should be supported by re-classifying diseases at the molecular level and by developing preclinical models to validate hypotheses resulting from molecular analyses (15,16,21). A Europe-wide process to evaluate and validate biomarkers, together with longitudinal and in-depth studies to further characterise diseases and their progression would support on-going efforts towards this integration and re-classification (18,19). The development of new clinical trial designs that are adapted to these new approaches and the integration of preclinical testing with innovative clinical trials may further improve the effectiveness of interventions (20). Collaborative pre-competitive and trans-disciplinary research and cross-sector collaborations need to be promoted and supported by suitable funding mechanisms in order to truly bridge all steps of the PM research continuum (17,22).

Challenge 4 – Bringing Innovation to the Market

Bringing innovative PM solutions to the market presents a new set of challenges, including the issue of uncertainty. There will be opportunities to support the development of new risk-based approaches for the evaluation of PM in a context that encourages systematic early dialogue with

all stakeholders, including regulators, funders and innovators, providing guidance for companies to enter the market for PM (23,26,28). As is the case for the research continuum, partnerships and innovation networks need to encourage cross-disciplinary and cross-border collaboration, and these would benefit from a transparent 'open Innovation' approach (27). Finally, research on appropriate policy, regulatory and legal frameworks would ensure that the new challenges associated with PM are adequately addressed from these perspectives (25).

Challenge 5 – Shaping Sustainable Healthcare

PM needs to rely on a knowledgeable healthcare system that is able to adapt to these new approaches in a timely and socially acceptable way, and that enables the participation of all stakeholders to increase PM's effectiveness and efficiency. The starting point for this requirement is the development of training programmes on PM for health professionals, and promoting the engagement and close collaboration of all stakeholders, including patients (31,33). Patients and the citizen will play an increasingly important role in adopting and controlling the use of data from electronic health records and in developing prospective surveillance and monitoring systems for personal health data (30,32). To ensure the effectiveness of the healthcare system, health economics research relating to PM needs to be supported. In addition a flexible framework for pricing and reimbursement equitable for all patients needs to be developed (29,34), leading to an overall healthcare financing strategy that covers all aspects of PM (35).

Looking Forward

Although five distinct challenges have been described, most of the recommendations pertain to more than one challenge. This SRIA should therefore be seen as a whole that is seeking to address these multiple challenges, and to build on the numerous opportunities offered by PM. The SRIA also presents nine prioritised recommendations, which have the highest potential impact and outcome in facilitating the introduction of PM for the benefit of patients, citizens and society as a whole.

These prioritised recommendations are to:

- Demonstrate the impact and potential benefits of PM for health systems, citizens and society by supporting public health evaluations to assist decision-making and develop appropriate, equitable and sustainable access for all patients (recommendations ■ 1, ■ 4, ■ 29, ■ 34).
- Incorporate patient participation and responsibility in all phases of research and development in the healthcare system and in the ownership and control of personal health data (■ 2, ■ 6).
- Develop common principles and regulatory frameworks that enable sharing of personal data for research in a way that is ethical and acceptable to patients and the public (■ 7).
- Promote the development of high quality sustainable databases including clinical, environmental, social, health and wellbeing information (■ 10).
- Support translational research infrastructures and enforce data harmonisation fostered by specific ICT infrastructures designed to health data (■ 11).
- Develop new decision support tools and methodologies of ICT to analyse and interpret data in order to support physicians and other key stakeholders in their decision-making process (■ 13).
- Develop methods to better integrate and evaluate the information provided by genomic, epigenetic, transcriptomic, proteomic, metabolomic and micro-biome analyses (■ 15).
- Support development of new clinical trial designs taking into account best available evidence on the individual level and promote integration with concomitant preclinical testing (■ 20).
- Encourage a systematic early dialogue between innovators, citizens and decision-makers throughout all regulatory steps to provide guidance and clarity (■ 26).

2) Background

Introduction: Personalised Medicine (PM) represents one of the most innovative new concepts in healthcare. It holds real promise for more effective early diagnosis and more effective and less toxic treatments for patients, for improved medical services to citizens, and for improving the overall health of the population. As such, PM can serve as a potent engine to help drive economic growth. However, the realisation of the full potential of PM requires close collaboration between all stakeholders. These include researchers, clinicians, research institutions, healthcare providers, research and technological development (RTD) funding agencies, public health agencies, policy makers, industry, regulatory authorities, health insurers and, crucially, the citizen. PM is already finding its way into a number of specific clinical applications. Lung cancer, for example, is one disease in which enormous progress has been made in this regard. Personalised cancer therapy is based on the concept of ‘oncogene addiction’ and uses the vulnerability of molecularly defined tumour subgroups to specific inhibitors. In comparison to chemotherapy a substantially improved outcome is described in an increasing number of cancer entities with this approach. However, as things presently stand, the full potential of PM cannot be realised for a number of reasons. These include fragmentation of European efforts, nationally and regionally restricted activities, and a lack of concerted approaches in the different areas of PM. In addition, definitions and assessments of PM can differ widely, depending on factors such as scientific evidence, the particular professional context, personal experience or values, and differing applied quality standards. Therefore, in order to advance PM, it is paramount to achieve strategic interaction between key European players. These include decision-makers in diverse scientific disciplines, research policy and funding, patient interest groups, different national healthcare systems, regulatory and governmental bodies and private enterprise. Only then can a well balanced and successful development of PM be achieved.

Objective: This document is based on the work of the PerMed consortium, a Coordination and Support Action (CSA) financed by the European Commission in order to

deliver a Strategic Research and Innovation Agenda (SRIA). The aim is to develop recommendations to foster the implementation of PM in relation to research funding, the present and future potential of health systems, and, most importantly, the benefit that can accrue to the citizen. Given that PM is such a cross-sectoral topic an attempt was made to integrate the perspectives of experts across the entire healthcare value chain, beginning with the citizen and patient, through researchers and manufacturers of drugs and medical devices, and finally to healthcare providers, regulatory bodies and governmental agencies. Altogether 27 organisations from 14 countries across Europe and beyond have contributed directly to this document, making this SRIA quite comprehensive and unique.

The SRIA identifies research topics and poses relevant questions that need to be addressed in order to achieve the successful implementation of PM. Specifying the challenges and obstacles that will be faced by researchers, industry, policy makers and healthcare providers will facilitate the development of strategies and the identification of solutions to overcome these challenges and obstacles in a timely manner. The intention of the recommendations is to enable funders, insurers, policy-makers, providers and researchers to take evidence-based decisions on how they can best allocate their resources for the benefit of citizens and patients. An additional benefit is that an innovation-driven healthcare system is one of the biggest driving forces not only for a competitive healthcare industry but also other industries and the wider economy.

Methodology (see also figure 1): The methodology used to produce this SRIA was based on a systematic analysis of published key reports as well as on direct contact with experts and representatives of all relevant sectors responsible for research and implementation of PM. An inventory of activities and key players was established and a dialogue platform for stakeholders in PM was set up. Current gaps and needs for the implementation of PM strategies were identified. The details of this approach have also been published (Annex 10A, references [20](#) and [21](#)) and presented

at the PerMed workshops in Berlin and the European Health Forum Gastein ([EHFG, October 2014](#)). In summary the approach was as follows.

Evaluation of strategic reports and identification of stakeholders (see Annex B):

The European Commission and other collaborating bodies have organised conferences to tackle the challenges of PM. In addition, key European organisations and institutions have published reports, guidelines and roadmaps. Over 20 strategic reports on PM have been analysed by the PerMed consortium via a SWOT (Strengths, Weaknesses, Opportunities and Threats) and a 'gaps and needs' approach. From this analysis an inventory of recommendations was prepared and grouped into key areas. Stakeholders in important areas of research and implementation of PM were identified from these strategic reports as well as by nomination from the 27 PerMed partners. These stakeholders were invited to the PerMed workshops and/or participated in semi-structured interviews. In order to cover the entire healthcare value chain attention was paid to balance the input from all relevant sectors.

Concept of semi-structured interviews with stakeholders:

Key individuals from the stakeholder list were selected for semi-structured interviews on important issues of PM. The selection of experts interviewed has been balanced on the basis of their respective research field, their function, their gender and their geographic distribution. The semi-structured interviews focused on SWOT and gaps and needs analyses. Interviews were conducted either face-to-face or over the phone. In total 35 experts from the following four areas were interviewed: (1) basic research and new technologies, (2) translational research, (3) regulation and reimbursement, and (4) healthcare systems in general. All final interview summaries were approved by the respective experts.

Dialogue platform for PerMed partners and stakeholders – workshops in Berlin and at the European Health Forum Gastein (EHFG, see also chapter 8c):

Two workshops were organised to connect key players and stakeholders in the different areas of PM across Europe and beyond (e.g. governmental and funding bodies, researchers, the private sector, regulators and policy-makers,

payers and insurers, service providers and healthcare professionals, and citizens/patients). For the [first workshop](#) (Berlin, March 2014) the inventory of recommendations prepared from the strategic reports was merged and updated with the results of the semi-structured interviews. The workshop was attended by around 90 participants. In the keynote presentations from European and international high-level stakeholders participants were introduced to the topic and made familiar with the results of the analysis so far. The four sessions served as a discussion platform to prioritise the respective recommendations within the four identified areas. On the second day the outcomes of the sessions were presented and discussed with the entire audience to ensure that cross-sectoral issues were adequately addressed. (Links to the lectures and sessions of this workshop can be found in Chapter 8C and on: <http://www.permed2020.eu/1408.php>).

For the [second workshop](#) (EHFG, Bad Hofgastein, October 2014) the recommendations were updated based on the results of the previous workshop, and experts were selected to ensure balanced coverage between the different research areas and type of research, as well as a balanced regional distribution. This workshop was embedded into the conference of the European Health Forum Gastein ([EHFG](#)) 2014, enabling the recommendations to be revised and discussed with the target audience of policy makers (of around 120 participants, Links to the lectures of this workshop can be found in Chapter 8C and on the [PerMed webpage](#)).

Dialogue platform exclusively for funding organisations – 'Round Table PerMed':

As part of the dialogue platform the PerMed 'Round Table PerMed' was set up. The Round Table is a forum for ministries and funding organisations to exchange information about on-going and designated measures, as well as national and regional strategic agendas and interests. Based on this activity and the workshop results, the Round Table identified running and planned PM activities by a survey and some of the SRIA's priorities. It proposed common activities and potential joint funding in PM research, as well as opportunities for the alignment of existing regional, national, European and, where possible, international strategies.

External validation of SRIA by experts in the different areas of PM: After the compilation and revision of the recommendations arising from the workshops, a consultation process within the scientific community was initiated to

allow further refinement of the recommendations. Comments and input from over 25 experts (see Chapter 8B) covering the entire healthcare value chain were integrated into the SRIA.

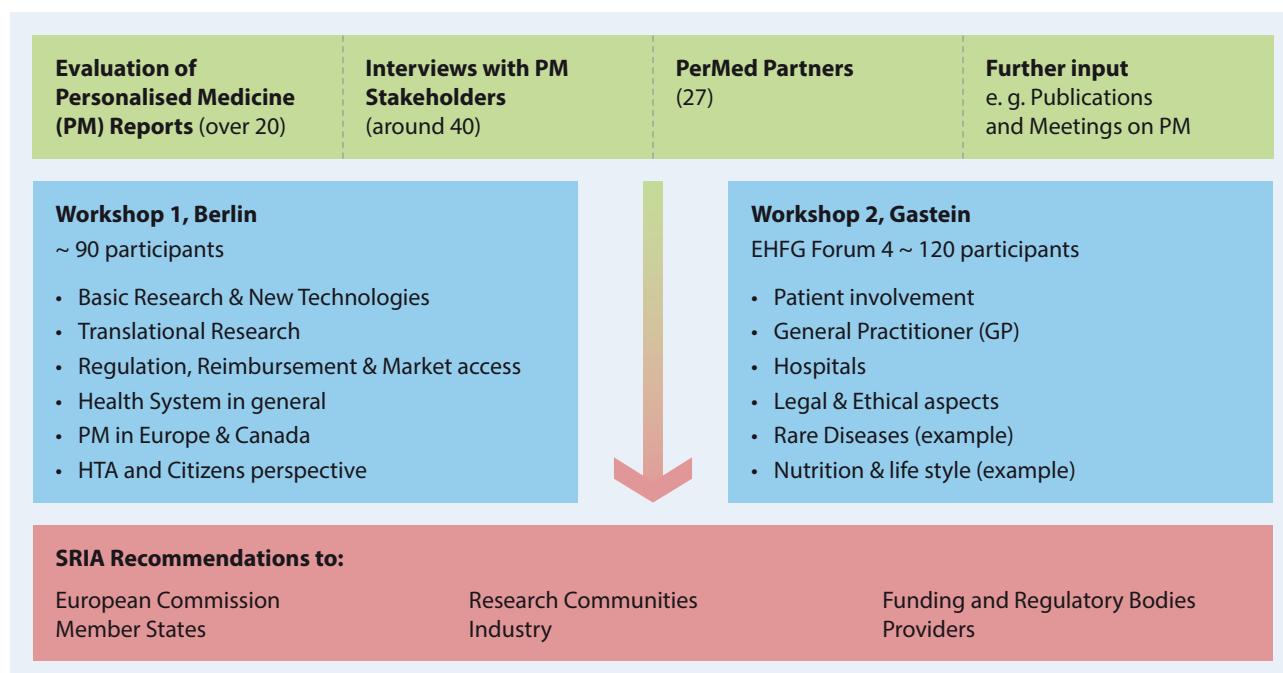


Figure 1 Process of developing the PerMed Strategic Research and Innovation Agenda (SRIA)

3) Introduction to the five challenges

Definition of PM: There is not yet a common, general definition of PM. This SRIA has adopted the recent definition used by the Horizon2020 advisory group: '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' (see Annex B, [19](#))

The future vision is to move towards prevention and prediction. PM can be achieved through different approaches: (1) stratification at the population or cohort level using biomarkers and based on traditional statistics, and (2) truly PM using omics and related technologies (e.g. imaging) and based on computer models and simulations such as the 'Virtual Patient' or other in silico models. It is likely that a combination of the two modalities will enhance the potential of PM. Moreover, PM will serve to improve the sustainability of healthcare systems. By compiling data profiles of wider populations and individuals, it will become possible to better predict the best course of treatment or prevention for each citizen, thereby introducing a radically different approach to healthcare on a broad scale. The approach has the potential to offer medium- and long-term gains – to patients and to society – and should significantly outweigh the required initial investment. PM requires stratification of patients into subgroups ('top-down') as well as 'bottom-up' big data analytics of personal data in which the effects of a particular treatment protocol and prevention strategies can be assessed based on distinct diagnostic parameters. Swift, top-down biomarker-based stratification requires the enrolment of a sufficient number of patients. This can only be achieved when standard protocols with regard to diagnostic tests and treatment are used in treatment centres; these centres can then serve as partners jointly executing a particular trial. This requires appropriate organisational alignment at all levels and ample patient buy-in.

Challenges: PM in Europe requires strategic arrangements in academic, public health and industrial research, along with organisational changes in national healthcare systems. Key issues include: the establishment of a strong culture of collaboration between all relevant research areas in a true public-private partnership, the adaptation of regulatory frameworks (e.g. for data protection, pharmaceutical innovation and in healthcare/health insurance), and the provision of tools and the development of new approaches such as Health Data Cooperatives (HDCs) to facilitate the adaptation of healthcare systems. PM will on the one hand go beyond the current broad definition of diseases: it identifies sub-types of diseases, assesses the characteristics of each person, and ultimately allows selection of the most appropriate course of action for a specific combination of disease and patient characteristics. On the other hand, diseases that display rather different symptoms and characteristics might turn out to have a common molecular cause. To exploit the full potential of PM it will therefore be necessary to develop a new definition of disease, and to take into account the person's individual lifestyle as well as other environmental factors or health determinants. These developments are occurring alongside a growing involvement of patient and citizen interests, the increased role of patient advocacy and support groups, the ubiquitous availability of information through the internet and the consequent rise in health literacy of patients and citizens. These trends are likely to change the way that healthcare clients and providers interact in the future, and this will require the definition of new responsibilities and financial models.

Objective: The generation of best available evidence in highly stratified patient groups and in single individuals will create new challenges for health research, the latter being defined as the entire range of research along the healthcare value chain. This includes not only basic and translational research, but also research relating to regulatory aspects, new flexible health technology assessment (HTA) frameworks including ethical, economic, legal and social aspects, comparative effectiveness, implementation

in health systems, public health and healthcare systems, as well as intelligent and adapted business models. This is why the aim of the CSA PerMed goes one step beyond most other initiatives and is unique in this regard. CSA partners as well as all workshop and PerMed Round Table participants have discussed specific joint actions either in research or other factors affecting the overall framework of PM implementation, such as funding vehicles to foster the translation of PM in Europe. The PerMed consortium took the view that potential joint actions in PM need to be guided by validated research questions and activities, and

that these should be formulated as recommendations. Five main challenges were identified, and each recommendation has been assigned to a given challenge.

- Challenge 1 – Developing Awareness and Empowerment
- Challenge 2 – Integrating Big Data and ICT Solutions
- Challenge 3 – Translating Basic to Clinical Research and Beyond
- Challenge 4 – Bringing Innovation to the Market
- Challenge 5 – Shaping Sustainable Healthcare

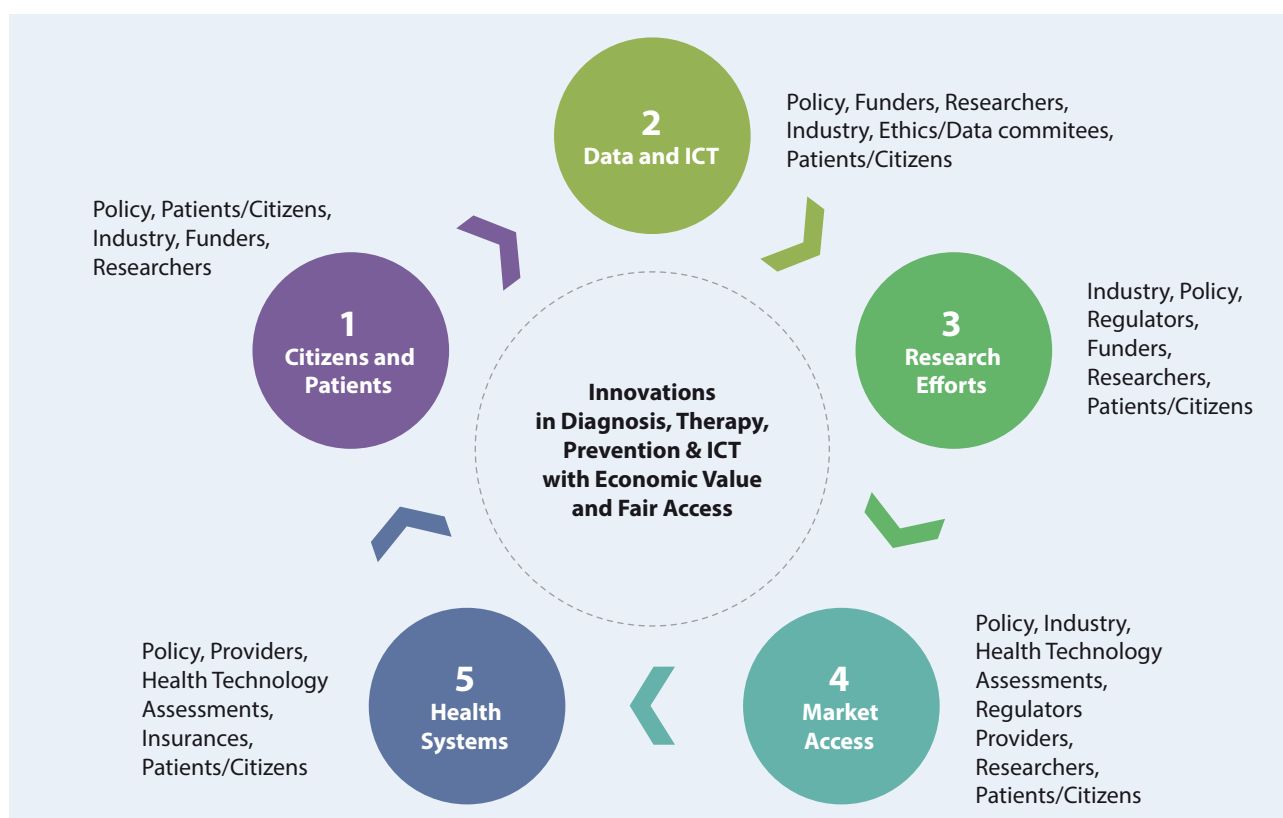




Figure 2 Circle of Challenges with important enablers and stakeholders. The overall aim of PM research and implementation is in the centre of the circle. Furthermore, there are manifold interrelations between the five challenges; these have not been indicated in order to keep the clearness of the figure.

The very nature of PM implies that research questions and the resulting recommendations inevitably cut across different challenge areas, and sometimes even across all of them. For the ease of readability of this SRIA, any given recommendation has been ascribed only to one appropriate challenge. This is not meant to imply that the particular recommendation may not be equally relevant to other challenge areas. Recommendations are linked with on-going activities and best-practice examples in EU Member States as well as enablers for future activities where possible. All recommendations have been colour-coded according to the activities referred to, which are grouped into three broad areas. However, many recommendations do have a share in two or sometimes all three types of activity (see also figure 3 in chapter 5). In these cases, the recommendation has

been assigned to the activity deemed to have the major share.

The colour-coding is as follows:

-  Recommendations on biomedical, health-related ICT and health research
-  Recommendations on humanities and social sciences research
-  Recommendations to improve the framework for implementing PM (e.g. economic, organisational, regulatory, ethical, legal and social)

4) Challenges for the further implementation of Personalised Medicine

Challenge 1 – Developing Awareness and Empowerment

Introduction

The concept of PM will bring fundamental changes to our understanding of health, disease and care. Instead of merely treating a disease, a shift to a more holistic approach is expected and needed. It seems likely that PM will increasingly be delivered in an out-patient setting, which will increase the patient's need for well-coordinated multidisciplinary care, side effect management, and access to information about, for example, expert centres, diseases, specific treatments, companion diagnostics and therapy adherence. More personalised therapies may mean that patients feel more 'left alone', becoming responsible themselves for managing complex treatment regimens, which may in turn influence their adherence. In addition they may need support from patient advocacy groups and to be in touch with patients with the same disease who are being treated in a similar personalised setting. Furthermore, a move towards more preventive approaches to healthcare is expected and needed. Such preventive measures will rely substantially on the active participation of citizens, who not only will need to collect data and make the information available, but also to own and control the personal data. This approach can only be successful if citizens, patients and healthcare professionals are aware of the concept and the potential of PM, both in terms of its benefits and challenges, and are capable and willing to support its implementation. An important aspect of genomics, nutrition, environment and lifestyle within a PM approach is to establish correlations between similar alterations in the genetic codes and epigenomic signatures of each patient and citizen, with the possibility of identifying the origin of certain diseases at the earliest possible time during the life-course to enable early secondary prevention. In addition, the study of genomics can provide information about an individual's reaction to a particular pharmaceutical product. This information can guide the optimisation of treatment for the patient – this field being termed pharmacogenomics. The European regulatory approach of MAPPs (Medicine Adap-

tive Pathways to Patients) represents a first and welcome step in this direction. For moves in this direction to bear fruit, it will be important for citizens and patient advocacy organisations to be involved in relevant discussions from the outset, because such an approach creates new challenges in the areas of patient information, data protection and data ownership. In this context, activities in two broad areas are needed if PM is to reach its full potential:

Awareness – It is vital that all stakeholders, including the citizen, fully understand the concept of PM. This compels us to discuss, establish and disseminate the applications, challenges and benefits of PM in a fully transparent, consensus-orientated process. In order to do this, it will be fundamental to establish shared practices and a communication network. Furthermore this will depend on an adapted communication between citizens, patients and general practitioners (GP) as well as other caregivers and health care provider's.

Empowerment – Providers in the health sector, citizens, patients and patient organisations should be able to make the best use of the tools of PM. This includes better and wider use of PM in diagnostics, a deeper development of ICT tools, new systematic approaches to patient information and patient consent, the integrative support of both basic and translational research, and a 'coordinated care' approach for the benefit of patients. Networks of stakeholders, researchers, clinicians and patients/citizens who share best practices and effective communication strategies will be crucial to achieve empowerment and thereby facilitate informed decisions.

Targeted achievements until 2020 and beyond – Recommendations

1. **Provide further evidence for the benefit delivered by PM to health systems.**

There is a need for further evidence about the clinical and personal utility as well as economic value of PM and its

benefits compared to standard practice. It is crucial to provide such evidence, so that health ministries and other deciders can make PM a priority area and support national and local initiatives for research that demonstrates the proof of concept of PM. Once clinical and personal utility as well as economic sustainability are proven in a precisely defined indication, a strategy for the communication and dissemination of the possibilities, challenges and potential benefits of PM needs to be developed.

2. Develop and promote models for individual responsibility, ownership and sharing of personal health data.

PM will generate significant quantities of data about an individual. An appropriate data ownership framework for patients will therefore be needed, especially given that these data – as an entity – will have a high scientific value as well as increasing economic value and will raise interest from private industry. For this reason, issues relating to data ownership, storage, handling, editing, sharing, controlling and access regulations have to be addressed. Questions such as “Should it be possible to remove past illnesses and data from your own health records?” must be adequately addressed, as does the medical, legal and ethical basis for integrating data generated about and by users into health information collected by medical professionals. Additionally, a framework for the management and communication of predictive information derived from genomic data needs to be developed. Research into the construction of national or regional citizen-owned and citizen-controlled health data cooperatives (HDC), in which citizens and patients can securely store, manage and share their data, will benefit healthcare and PM. Such a system would not only make these data more readily available, it would force data out of the incompatible data silos of national healthcare systems and so improve interoperability. Such a cooperative system represents a possible way for citizens to obtain the true value from the secondary use of their data for their own health and that of society. The cooperatives would compete in the personal data market to maximise the scientific and economic value of the data that citizens have agreed to share for the cooperative’s members. Personal and economic benefits

for cooperative members by the control of their personal data could be the new driver for the implementation of a more effective data-driven personalised healthcare system. Feasibility studies carefully weighing the pros and cons of this option will support decision-makers in this sensitive field. These developments should be supported in the light of a holistic approach carefully avoiding the risk that the citizen might only be seen as a ‘sum of data’. One example could be feasibility studies on health data cooperatives with an assessment of ethical, legal and social implications comparing different European healthcare system settings.

3. Develop mobile health applications to maximise engagement of patients with their treatment pathways and track the safety and effectiveness of these interventions.

Further development of IT applications and adequate interfaces is needed to enable the use of smartphones, tablets, other mobile services, ‘smart home’ and tele-health systems for the different user groups, such as citizens, patients and GPs (e.g. mHealth). Existing and new applications need to be tested in real-life settings to ensure safety and effectiveness. The implementation of this recommendation 2 and 3 will strengthen the finality for the patients’ benefit.

4. Understand how the changes relating to PM will impact public health and ensure that they translate directly to benefits for individual citizens and society.

PM has the potential to lead to new innovations in healthcare, but will also present challenges in terms of patient information, consent, management and care. For this reason flexible and adaptable guidelines will be needed to ensure that the implementation of PM into the healthcare system will result in benefits to the patient and citizen. In addition, social and ethical research on the effects of PM should be supported and integrated as complementary projects to proposed translational projects within this SRIA. It is essential that with time the framework can evolve and incorporate lessons from experiences of the

various stakeholders; so for example the effect in terms of justice and fairness in healthcare is difficult to predict and the highest attention should be paid to actual effects. Since PM may produce effects that are different in various social contexts, both conceptual and empirical research is needed.

5. Improve communication and education strategies to increase patient health literacy.

Health literacy is defined as the skills and knowledge of the public necessary to understand health information and services, including direct communication between patients and health professionals. Health information and services are often unfamiliar, complicated and technical, even for people with high levels of education. Moreover, limited health literacy disproportionately affects low-socioeconomic and minority groups. As it has been studied by the European Health Literacy Survey (HLS-EU, www.health-literacy.eu), health literacy is a reflection of what has been put in place by health systems, patient organisations and health professionals to make health information and services understandable and actionable. Very often, professionals, the media, and public and private sector organisations deliver information in ways that make it difficult to understand and act on, or that are even incomplete and inaccurate. Patient advocacy organisations are often the key parties that have core experience in meeting the information needs of patients, as well as generating information which is tailored to and appropriate for the target audience. Furthermore, health literacy is also based on the interaction between the skills of individuals and the requirements and assumptions of health and social systems. Consequently, the skill and competence of health professionals, patient advocacy organisations, media and government and private sector agencies to provide health information in a manner appropriate to their audiences are as equally important as an individual's skills. Improved health literacy of individuals and society can only be achieved by a multi-pronged strategy that includes 1) providing everyone with access to accurate and actionable health information; 2) delivering person-centred, lay-friendly health information resources and services involving pa-

tient advocacy organisations; 3) supporting lifelong learning and skills to promote good health. Even though this is the case for all interactions with citizens and patients, the particular nature of PM makes this need especially pressing.

6. Incorporate patient participation in the healthcare system and increase the patient's role in all phases of research and development.

Citizens and patients are key partners and stakeholders in PM, so PM cannot be fully implemented without a behavioural change of both citizens/patients and health practitioners. Patients and patient advocacy organisations must be involved across the entire development chain of PM as early in the process as possible, including: setting research priorities, clinical trial design and planning (protocol design and review, informed consent), and research conduct and implementation (information to participants, trial monitoring, post-study processes, dissemination of results, health technology assessment, patient access to PM).

7. Develop common principles and legal frameworks that enable sharing of patient-level data for research in a way that is ethical and acceptable to patients and the public.

There is a need for common principles and policies for the trans-national sharing of health/clinical data at the level of individual citizens/patients. PM requires stratification of patients into subgroups in which the effects of a particular treatment protocol or the potential of targeted preventive measures can be assessed. This stratification will greatly reduce the number of patients within any such subgroups. In view of this, international co-operation will become increasingly important in order to recruit sufficient numbers of patients for the generation of statistically significant evidence about the clinical and personal utility as well as economic value of PM approaches and their benefits and superiority to standard practice. Data protection regulation, invented mainly to protect consumers against the misuse of personal data, for example on the internet, needs to be reviewed critically in the context

of its detrimental impact on medical research, in order not to stifle data collection for research purposes, registries or cross-border sharing of research data. This may need to involve a strong voice from patient advocacy groups to adequately balance the interests of the individual patients and society as a whole.

Key Enablers for Challenge 1

Europe: e.g. EC, societies and patient organisations.
 Member States: e.g. Ministries of health, finance, research and justice, economy; institutions for public health and health insurance, medical and scientific societies, foundations, patient organisations, healthcare providers and hospital associations.
 Industry: e.g. patient involvement via EFPIA/IMI.

Conclusions

Health literacy and patient and citizen empowerment are closely linked and have to be supported in a coordinated way. The involvement of patients and patient organisations in tandem with healthcare professional training are the key factors that will enable everyone to have access to accurate and actionable health information and person-centred services. This will enable patients and citizens not only to take informed decisions within the healthcare systems, but also to interact with researchers (e.g. in delivering patient-level data). But this will only be realised through support for interdisciplinary research aimed at identifying and piloting the best channels and concepts for education and training of healthcare professionals and patients. Effectiveness of actions has to be tracked closely and adjusted appropriately. Despite all the perceived potential benefits of PM, individual citizens should still have the option of deciding whether or not they want to support this approach by providing their data and using PM themselves, without disadvantage. The incorporation of stakeholder input through various tools is thus central to PM implementation and should be seen as an essential feature without which PM cannot develop its full social impact.

Examples of on-going activities

a. Europe

In May 2011 the Health Directorate of the European Commission's Directorate General for Research and Innovation organised the conference 'European Perspectives in Personalised Medicine', which aimed to take stock of recent achievements in health-related research leading to PM, and which helped to identify and prioritise future actions needed at the European level. The conference was preceded by a series of preparatory workshops on PM held throughout 2010. The [workshops](http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html) (http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html) focused on current challenges related to omics research, stratification biomarkers, clinical trials and uptake of PM into healthcare.

In October 2013, the Commission published a staff working document that describes the progress made in PM, and the opportunities and challenges it presents for healthcare systems. The staff working document focuses on the potential for, and issues with, the use of omics technologies in PM, and related EU research funding; recent developments in EU legislation for placing medicinal products and devices on the market; and factors affecting the uptake of PM in healthcare systems.

[EuroBioForum](http://www.eurobioforum.eu/) (<http://www.eurobioforum.eu/>) is an EU-funded European platform created in 2011 to share information about initiatives, activities and the main actors in the field of PM, fostering networking, synergy and knowledge-sharing opportunities. EuroBioForum has been a vehicle for maintaining an on-going dialogue between researchers and stakeholders, with activities such as the PM [observatory](http://www.eurobioforum.eu/2028/observatory/) (<http://www.eurobioforum.eu/2028/observatory/>) annual conferences, thematic meetings and conventions. The EuroBioForum observatory is an online database which presents an overview of initiatives and provides insights into the key players and main activities in PM in Europe.

The EU funded [PERSOMED](http://www.perso-med.eu/) (<http://www.perso-med.eu/>) project is an opportunity for companies from Nord-Pas de Calais and Flanders to enhance their competitiveness and innovative capacity within PM. The activity sectors concerned by this project are therapeutics and diagnostics.

There are also a number of important European organisations aiming to promote the ideas of PM, such as the European Alliance for Personal Medicine (EAPM) and the European Personalised Medicine Association (EPEMED).

[EAPM](http://www.euapm.eu/) (<http://www.euapm.eu/>) brings together European healthcare experts and patient advocates involved with major chronic diseases. The aim is to improve patient care by accelerating the development, delivery and uptake of PM and diagnostics, through consensus. EAPM was created as a response to the need for wider understanding of priorities and a more integrated approach among stakeholders. It works on case studies, [briefing document for MEPs](#), education, training and communication to deliver practical [policy recommendations](#) designed to exploit the potential of PM to the full. Relevant departments of the EC have observer status, as does the European Medicines Agency. The EAPM Forum brings all members together to review activity and to direct [political strategy](#). Working Groups develop positions on key topics and make proposals and recommendations to the Forum. It's Specialised Treatment for Europe's Patients: [STEPS campaign, conferences](#), roundtables, [Working Groups](#), plus a Regulatory Affairs Group have raised awareness of the immense possibilities of PM.

[EPEMED](http://www.epemed.org/) (<http://www.epemed.org/>) is a non-profit organisation founded in 2009 by a group of European leaders, including academics, clinicians, SMEs (small and medium-sized enterprises) biotech companies, and major international pharmaceutical and diagnostic companies with extensive expertise in stratified medicine and the application and development of diagnostic tools. EPEMED aims to provide a platform for the harmonisation of PM development and imple-

mentation across Europe, focusing on the crucial role of diagnostics.

The European Association for Predictive, Preventive and Personalised Medicine [EPMANET](http://www.epmanet.eu/) (<http://www.epmanet.eu/>) is an industry-driven organisation comprising national institutions, patient groups, university research units, state and private hospitals, industrial groups, political representatives and insurance companies to raise awareness and recognition of PM by providing up-to-date information and educational materials as well as promoting research focused on predictive diagnostics and personalised patient treatment and standardisation.

The European Society of Pharmacogenomics and Personalised Therapy ([ESPT](http://www.esptnet.eu/)) (<http://www.esptnet.eu/>) represents 850 members from all European countries, working with 22 corporate members from pharmaceutical and biotech companies. Twelve scientific groups are closely involved with the organisation of meetings, summer schools and work committees. Other organisations such as the European Federation of Clinical Chemistry and Laboratory Medicine ([EFLM](http://www.efccim.org/)) (<http://www.efccim.org/>) and the International Federation of Clinical Chemistry and Laboratory Medicine ([IFCC](http://www.ifcc.org/)) (<http://www.ifcc.org/>) deal with the challenges of PM for laboratory medicine. Recently members of these societies have published an [opinion paper](#) with a survey on laboratory medicine and PM.

b. Member States and other countries

In Germany the Federal Ministry of Education and Research (BMBF) is supporting research on ethical, legal and social issues arising from the development of PM with a special focus on patient data.

The United Kingdom has the Stratified Medicine Innovation Platform supported by Innovate UK (formerly the Technology Strategy Board, TSB), the Medical Research Council's Stratified Medicine Initiative and the Stratified Medicine Programme supported by Cancer Research UK. Together, these organisations have de-

veloped the UK Stratified Medicine Roadmap, comprising the following nine themes: 1. Incentivising adoption; 2. Increasing awareness; 3. Patient recruitment – consents and ethics; 4. Clinical trials; 5. Data – collection, management and use; 6. Regulation and standards; 7. Intellectual property; 8. Biobanks and biomarkers; and 9. Increasing the impact of research and development investment.

Within the [Risks and Benefits Citizens' Jury Project](#) by the Genetic Alliance UK patient organisations, facilitated by the University of Glamorgan, brought together a panel of 12 jurors from across the UK, either patients themselves or family members, and presented them with case studies of new medicines (<http://www.geneticalliance.org.uk/docs/citizens-jury-press-release.pdf>). The aim was to see how those directly affected would assess the risks and benefits of a new medication, and whether their opinion differed from regulators – essentially asking whether patients should be strategically involved in risk–benefit assessments so that their preferences

would be better reflected in regulatory decisions.

In Canada, the Canadian Institutes for Health Research (CIHR) and Genome Canada recently launched the Genomics and Personalized Health: 2012 Large-Scale Applied Research Project Competition. A total of 17 projects in various diseases areas were funded through investments of over 165 MioC\$ from federal sources and partnering organisations. By their completion, these projects need to demonstrate the clinical utility of PM approaches and contribute to develop a more evidence-based cost-effective healthcare system. In order to do this, all projects either have an integrated Genomics and its Ethical, Environmental, Economic, Legal and Social Aspects (GE3LS) component or are stand-alone GE3LS projects.

In the United States and internationally the Personalized Medicine Coalition (PMC) (<http://www.personalizedmedicinecoalition.org>) is an important platform and stakeholder in the area of PM.

Challenge 2 – Integrating Big Data and ICT Solutions

Introduction

The datasets generated by large-scale sequencing and omics technologies are extensive and when combined with clinical, imaging, nutritional, life style and environmental exposure data produce truly 'big data'. Through careful integration of all of these data and thorough interpretation, the basis of disease stratification as well as understanding personal health will be achieved; identifying patients with the apparent same disease but different prognosis and further investigation of the data at the individual's genetic level will lead to true PM. The role of information and communication technologies (ICT) is therefore crucial, and recognised as such in a publication of the EC in 2013 on the Use of '-omics' technologies in the development of PM (http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf)

Most of the 35 recommendations in this SRIA are dependent on the efficient use of ICT solutions. These include comprehensive cataloguing of high quality biobank specimens and biomarkers, and their use in all large-scale studies on patient and population cohorts ('top-down approach') as well as big data analytics ('bottom-up approach'). Development of PM is dependent on heterogeneous types of data: a) data available in various databases (e.g. [NCBI](http://www.ncbi.nlm.nih.gov/), [EMBL-EBI](http://www.ebi.ac.uk/) and <https://clinicaltrials.gov/>), b) data extracted from semantic web or images; c) data extracted from various 'internet of things' objects monitoring health status (e.g. sleep, activity, nutrition); and d) the integration of data from basic and clinical research (e.g. www.guidetopharmacology.org/). Thus it is not only omics or imaging technologies that will generate vast amounts of data. The potential of this wealth of information can only be maximised by its integration with information from other sources, such as electronic health records data from different types of registries and emerging flows of unstructured data coming from, for example, connected objects or social media. Development of novel ICT solutions for integration of these big data is at the very core of introducing PM into healthcare. Even though the launch of translational projects as a main driver for products and services development is key, market successes

or otherwise remain closely related to barriers such as the access and deployment of relevant interoperable ICT and telecom infrastructures, the fragmentation of health systems and services together with the heterogeneity of regulatory regimes, the lack of significant business and economic cases, and the resistance of end-users to change.

One of the challenges of PM is a scientific one that relates to our capacity to integrate big data through efficient and user-friendly ICT solutions and thereby create sustainable knowledge. On the other side is a challenge driven by the business models and the necessarily long time it takes for a product or service to reach the market, together with the associated costs (for example for clinical validation). New and interesting opportunities are emerging through e-solutions for the health and wellbeing sectors, which may be subject to less regulation and which have demonstrated some major successes on the market (such as 'connected objects' like a smart watch). These have been able to generate revenues, as well as gaining trust and acceptance among users. The same is true for the development and introduction of pharmacogenomics into clinics. Development of prospective surveillance and monitoring systems for personal health data will also contribute to the accumulation of data on individuals across their life course. This all means that medical practice will become increasingly dependent on decision-support mechanisms, which requires all medical professionals to strengthen their ICT proficiency. ICT professionals on the other hand need to develop easy-to-use interfaces that allow management of the underlying complexity of data and make application in clinical routine possible. At the same time lay people have access to an overwhelming amount of information and misinformation on diseases, their symptoms and potential treatments, including harmful ones, through the internet.

So the ICT challenge is multiple. Aspects include: (1) how to store and provide access to huge amounts of human health-related sensitive data under a secure and common standard; (2) how to optimise and support the computing capacity needed to perform the actual computation of huge datasets taking into account the fact that storage may be either centralised or decentralised; (3) how to interrogate such data; and (4) how to link such data to ex-

perimental data. Furthermore it needs to be determined who finances such activities and who will reap the benefits. New solutions, such as cloud computing and secure user authentication, have been developed to cope with the multiple ICT challenges in a number of EU- and Member-State-funded consortia. Yet most of these still have to demonstrate their applicability, especially in the health sector. Several EU-funded activities exist in this area; these include the Research Data Alliance ([RDA](#)), the European Data Infrastructure ([EUDAT](#)) and the Committee on Data for Science and Technology ([CODATA](#)). Some public–private partnership projects of the Innovative Medicines Initiative ([IMI](#)), such as Electronic Health Records for Clinical Research ([EHR4CR](#)), are also working towards solutions such as tools and services for reusing data from electronic health record systems for clinical research. In addition regional e-infrastructure networks exist in the ITC domain, such as the Nordic e-Infrastructure Collaboration ([NeIC](#)) facilitating the development of advanced IT tools and services in areas of importance to Nordic researchers.

Targeted achievements until 2020 and beyond – Recommendation

8. Promote strategies to make sense of ‘big data’.

Existing and emerging multi-scale methods which are in use in other big data areas, for example finance, marketing, aerospace, meteorology, and so forth, need to be applied and propagated so as to become standard practice in health. In addition to bioinformatics, expertise is also needed for modelling, molecular classification and sub-classification of diseases and for designing new approaches for monitoring disease development and targeting prevention, as well as for secure storage of sensitive data that can still be accessed by the research community in the public and private sectors.

9. Develop and encourage the fast uptake of technologies for data capture, storage, management and processing.

There is a need to promote database-driven research and technologies that reduce costs. In detail this means to:

- Create a framework for data usage and connect it to a digital environment to facilitate and improve medical data sharing while ensuring transparency and data protection.
- Facilitate re-use of data, if possible across Europe.
- Support an appropriate infrastructure to collect and store the huge amount of information generated. Improve and control data quality and maintenance and ensure the appropriateness of related legislation.
- Involve big data organisations in research, motivate and stimulate them to invest in research.
- Support storage centres guaranteeing cybersecurity, e.g. by crypto-computing and software safety.

10. Promote the development of high quality sustainable databases including clinical, health and wellbeing information.

For these databases the citizen’s and patient’s lifecycle should be considered not only when an episode of severe or acute disease occurs. This recommendation also includes a laboratory quality control nationwide and if possible Europe-wide. This will produce a setting that is not only suitable for adequate diagnosis, therapy decision and care, but also for developing standards in the respective datasets.

11. Support translational research infrastructures and enforce data harmonisation fostered by specific ICT infrastructures designed to the health data.

The need for translational research infrastructure and data harmonisation is not specific for PM, but is nevertheless very urgent in this field. In particular stakeholders should:

- Give access to data from silos by encouraging and facilitating data sharing.
- Support and coordinate data harmonisation to enable the identification of best practice examples as well as guidelines for treating the data generated (e.g. in meta-genomics).

12. Support analytical methods and modelling approaches to develop new disease models, e.g. 'Computerised Twins' or a 'Virtual Patient'.

The use of genomics and molecular data as an individual fingerprint can enable the identification in databases of another patient who has the same fingerprint ('electronic twin'), whose electronic medical record of natural history of disease and treatment outcome will help medical decision-making through modelling and prediction. Such a data set can follow the person during the whole life-course through the healthcare systems enabling health care professionals to virtually simulate and optimize treatments. In the end, medical decision-making might finally turn into in silico decision-making.

13. Develop new decision support tools and methodologies of ICT to analyse and interpret data in order to support physicians in their decision-making process.

The introduction of genomic (sequence) and molecular information, and medical as well as real world data into medical practice will bring huge amounts of predictive information to physicians. Computerised decision-making tools will be needed to make sense of this increasing amount of diverse information. Development of these tools will need the following:

- Collaboration between clinicians, researchers and ICT specialists.
- Matching of clinical and genomic and molecular information by means of vice-versa exchange between laboratory medicine and decision-making in the clinic.
- Evaluation of the extent to which this process contributes to the accuracy of the diagnosis/treatment scheme, e.g. quality of care, cost-efficiency and knowledge gain.

14. Create a European 'big data' framework and adapt legislation.

There is a huge need to standardise practices in generating data for medical decisions and also harmonise the

way that data are stored, secured and shared, respecting the irrevocable rights of patients. Medical doctors and researchers in the public as well as the private sector from each EU country should be able to access data collected from across Europe in a way that respects anonymity and confidentiality. This requires the following actions:

- Harmonise the format in which big data are collected and stored.
- Harmonise clinical records and medical information, if possible in English.
- Ensure the interoperability of procedures and IT systems, e.g. by a reference test (regularly referenced and improved from the latest discoveries) against which all data will be compared to.
- In certain cases create centralised databases with nodes distributed in different countries to ensure that data are stored and accessed in a standard way (e.g. genomes in the European Genome-phenome Archive, [EGA](#)).
- Decide which data will be needed (e.g. genome, epigenome, transcriptome, meta-genome, meta-proteome, images or medical records) and for each one decide on the best framework to store and access it.
- Create a common legislative and ethical framework for such big data endeavours.

Key Enablers for Challenge 2

Europe: e.g. EC, European research infrastructures, large consortia/cluster projects, medical and scientific societies, patient organisations, standardisation authorities and organisations.

Member States: e.g. Ministries of health, research and justice; institutions for public health and health insurance, national computing centres, industry, medical and scientific societies, ethics and data committees, patient organisations, hospitals, universities, public research bodies including systems biology/medicine, research technology organisations.

Industry: e.g. ICT and telecommunication, healthcare industry, eHealth and mHealth.

Conclusions

The increasing amount of available health data will support the paradigmatic shift towards preventive strategies. To leverage this huge potential benefit for patients and citizens, healthcare professionals need to strengthen their ICT proficiency. In parallel they need suitable decision-support tools with an easy-to-use interface to make their use in clinical routine possible. Big data organisations need to be motivated and stimulated to invest in ICT-related biomedical research. This has to be flanked by efforts towards incentivising ICT harmonisation across large translational research and healthcare infrastructures. The aim should be to not only trigger and support this process nationally but at the European level where ESFRIs are paving the way. Furthermore, analytical methods and modelling approaches should be developed to make use of individual datasets and support the decision-making process.

Examples of on-going activities

It is almost impossible to envisage the development of PM without digitised information. Electronic health records are being introduced into public and private healthcare in most Member States. Laboratory tests and medical images are stored in digital health records. Population/patient-derived samples can be collected into biobanks, where analytical data derived from the specimens are also being stored. For research purposes biobanked samples throughout Europe are being catalogued and now also stored at the national and EU level in biobanks (national nodes of the pan-European biobank, [BBMRI-ERIC](#)). The availability of very large sample collections with corresponding data, on factors such as the donors' health, diseases, lifestyle, nutrition, and environmental exposure, from national registries makes it possible to start to stratify current disease diagnoses into subgroups based on their molecular characteristics. National biobanks and registries of different size also exist in countries that are not part of BBMRI-ERIC. Furthermore, national nodes of several other research infrastructures on the [ESFRI roadmap](#) play an important role in paving the way for PM as outlined below under 'Examples of on-going European/international activities'. Furthermore Member States

support research on integration and modelling of omics data via information science and mathematical methods.

a. Europe

The establishment of the pan-European Research Infrastructures (particularly those participating in the European Strategy Forum on Research Infrastructures – [ESFRI roadmaps](#) 2006, 2008 and 2010) has introduced an important group of new actors for the provision of infrastructure services in the fields of biological information and data storage ([ELIXIR](#)), biobanking (BBMRI-ERIC), translational research ([EATRIS-ERIC](#)), clinical trials ([ECRIN-ERIC](#)), structural biology ([Instruct](#)), animal models ([Infrafrontier](#)), biological and medical imaging ([Euro-Biolmaging](#)), chemical biology ([EU-Openscreen](#)), and so on. These infrastructures are primarily joint activities of Member States but are also supported by the EC in the preparatory phase. Essentially all ESFRI research infrastructures are involved in the production of big data in support of research and PM; thus they are also major players in standardisation, harmonisation and interoperability of big data generated by the research infrastructures and communities. Large 'cluster' projects, such as [BioMedBridges](#), funded by the EC, play an important role in coordinating the big data generated by the ESFRI research infrastructures. Thus ESFRI infrastructures and [BioMedBridges](#) play an increasingly important structuring, harmonising and standardising role in biomedical research, which is likely to extend to clinical practice, given that the process of disease stratification is dependent on the results of such research. Another EU-funded project in this field is [P-medicine](#) – (<http://p-medicine.eu/>) supporting data sharing and integration via Virtual Physiological Human (VPH) models to PM, launched in 2011. The main drivers for such an infrastructure are clinicians as they have direct contact with patients and need to take an active part in sharing data for the benefit of the patient. The goal is to provide the necessary tools and processes for clinically driven multi-scale VPH modelling. Many European and global research consortia and networks currently work on collections of very large disea-

se-specific sample and data collections. These include consortia such as the International Rare Diseases Research Consortium ([IRDiRC](#)), which teams up researchers and organisations in rare diseases research, and the International Cancer Genome Consortium ([ICGC](#)). The Global Alliance for Genomics and Health ([GA4GH](#)) and the Genomic Medicine Alliance ([GMA](#)) aim to enable responsible sharing of genomic and clinical data.

b. Member States and other countries

In France the National Research Strategy (April 2015), announced a concentration of research efforts in the integration of non-biased and high quality massive data (omics, patient and general population data, imaging) offering a systemic vision of the living (Systems Biology). This programme is part of a national action framework launched in 2014, making 100 million € available for five years. As examples, for omics, MetaboHUB (<http://www.metabohub.fr/en>) is a national infrastructure of metabolomics and fluxomics that provides tools and services to academic research teams and industrial partners particularly in the fields of health, nutrition, agriculture, environment and biotechnology. The France Génomique infrastructure brings together most of the French sequencing and bioinformatics platforms within a consortium gathering the CEA (coordinator), INRA, CNRS, INSERM, INRIA, the Pasteur Institute, the Curie Institute, the Ecole Normale Supérieure (Paris) and 4 universities (Aix-Marseille, Strasbourg, Lille 1 and Claude Bernard in Lyon). And CATI is a service platform supporting more than 30 multicenter neuroimaging studies in the fields of neurodegenerative diseases and psychiatry (AD, Parkinson, Huntington, ALS, Bipolar, etc.) including several therapeutic trials.

In Germany, the e:Med-research and funding concept of the BMBF supports with 200 Mio € research consortia and junior research groups to enhance the understanding of molecular networks within pathophysiological processes with state-of-the-art information technologies. 'Demonstrator' pilot projects show how data from high-throughput research directly feed into personalised prevention, diagnosis and therapy.

In the UK, the Medical Research Council alongside the Health Department has invested £20m in the [Farr Institute](#) (<http://www.farrinstitute.org/>). This is a national network of centres of excellence linking clinical and research data to address a range of research questions. Some Member States are also active in promoting different types of health registries, such as national cancer registries, occupational health registries, and so on. However, collection of such data varies between Member States, and interoperability of health-related registries and health records is a major challenge for ICT. At Member State level most health information is recorded in national languages, which produces another challenge for integration of all the data available.

Beside many European partners, Canada is strongly involved in the [IRDiRC](#) as well as in the [ICGC](#) (e.g. [Genome Canada/CIHR](#)). Furthermore Canada is implementing PM to accelerate drug discovery through research on invention and development of the next generation of technologies, computational tools and devices in cancer, infection and immunity, and neurodegeneration affecting cognition. Finally, the Phenome Central platform has been developed through the Care for Rare project; this platform enables phenotypic and genotypic international data-sharing to identify the genetic basis of undiagnosed rare diseases.

Challenge 3 – Translating Basic to Clinical Research and Beyond

Introduction

PM will only be realised through the integration of excellent basic science with clinical and public health research and through product development and communication in both directions. This will require the concerted action of a number of sectors, disciplines and agencies. In recent years, there have been a number of scientific and technological breakthroughs underpinning the usefulness of PM, for example in treating specific tumours and subpopulations, and in developing drugs for orphan or cardiovascular diseases or hepatitis. These have been achieved through a number of largely 'bottom-up', investigator-driven studies. Research into the underlying genetics of diseases must continue as this will identify new targets for treatment as well as new biomarkers of disease. It is evident that basic research has a crucial impact on clinical research and its subsequent translation into products and policies.

Targeted achievements until 2020 and beyond – Recommendations

15. Develop methods to better integrate and evaluate the information provided by genomic, epigenetic, transcriptomic, proteomic, metabolomic and microbiome analyses.

Whereas the capacity to create large datasets accurately describing gene sequences, mutations and expression patterns – even at the single cell level – is growing exponentially, there are great difficulties in interpreting this information. To make sense of these datasets, more sophisticated systems biology approaches are needed that create hypotheses which can subsequently be validated by biochemical and cell biological methods, and by experiments in suitable disease/animal models. Thus research is needed on such models with a short development cycle ('living test tubes') for mono- or oligogenic diseases to improve the understanding of genetic variants. The development of PM derives from an understanding of the genetic characteristics of the individual coupled with

the individual's interaction with the environment or the context in which the person lives and acts (i.e. the person's lifestyle). In this sense some of the mechanisms of expression are mediated by the context within which the expression occurs. This context can include micro-organisms and their characteristics. Given that some of the mechanisms of expression, interaction and significance are not well understood, it is crucial to continue to seek not only to improve the knowledge base, but to develop meaningful interventions that will positively impact upon an individual's health. In this regard, research on correlations between genotype and phenotype, aimed at gaining a better understanding of the influence of the environment on the evolution of disease could have significant clinical impact.

16. Support research in preclinical models to validate hypotheses resulting from molecular analyses of patient samples and treatment outcomes.

Translational research is a two-way street. Basic research can result in new insights that need to be explored in a clinical setting. However, nature is often more complicated than we realise, and therefore it is of critical importance that clinical observations resulting from the translation of basic insights are fed back into the laboratory in order to improve our understanding of underlying mechanisms. This feedback constitutes an extremely important step in the process; it might, for example, explain why a therapeutic intervention based on solid basic research has failed or does not lead to the expected benefits for the patient. This information can then be used to adapt protocols resulting in more effective treatments. Illustrative examples of this already exist in the treatment of cancer, e.g. by studying the underlying mechanisms of intrinsic and acquired resistance as observed in a number of biomarker-based therapies. For example research in human induced pluripotent stem cells (iPS), stem cells and human cell lines can obtain information which is valuable for patient treatment within PM approaches.

17. Promote collaborative pre-competitive and trans-disciplinary research in all disease areas to gain trustworthy and objective information.

To make PM a reality, it is vital to ensure coordination between researchers across disciplines and always having in mind the patients' needs. These include basic and clinical researchers, pathologists, radiologists, bio-informaticians, bio-engineers, trial designers, epidemiologists, mathematicians, public health experts and many others. Academia must work with not only the pharmaceutical and biotech industries, but also data-based industries and start-ups such as those focusing on big data handling and web design. Collaborative, pre-competitive multidisciplinary, trans-sectorial research consortia should be encouraged. The focus could be around a particular disease or technology, but all the actors must share the common vision of the consortium, having the patients' best care in mind. Template agreements dealing with partnerships, intellectual property (IP), publication policy, personal data protection and data access arrangements should be established to help expedite consortia development and activation. There is also a need for professional project management to ensure effective collaboration between the academic and private sector groups. These new research partnerships must define how clinical data will be collected, curated and shared for research purposes, and also how this information can be shared with outside groups and fed into clinical practice. An environment in which data is shared securely needs to be encouraged, standardised in terms of language, item collection and storage, and its value maximised through low-threshold access while ensuring appropriate levels of security, privacy and confidentiality.

18. Instigate a European-wide biomarker evaluation and validation process.

Biomarkers are our window into disease, offering possibilities for prevention, early detection, response monitoring and treatment. Identification, evaluation, validation and adoption of biomarkers are a critical driver of PM. Identification of new biomarker candidates through basic research needs to continue but evaluation, validation and adoption is a complex process with many obstacles. A biomarker should be able to predict susceptibility to a certain disease (termed a susceptibility/risk biomarker), to diagnose the disease itself (diagnostic biomarker), to

assess the stage and the evolution of a disease (prognostic biomarker) and to predict the response to treatment (predictive biomarker). There should be a concerted effort to share biomarker information across research groups and across the public and private sectors. Even more challenging is the identification of a combination of several biomarkers to identify the most effective therapy or preventive measure (biomarker signature). Biomarkers can come from a range of sources, including genetic, phenotypic, imaging, and behavioural sources. Data from these different sources have to be integrated in order to create optimal diagnostic tools. Information on validated biomarkers should be compiled in databases that highlight the stage of evaluation that a particular biomarker has reached. These databases should be seen as 'living' – allowing them to be continually updated, for example through automated literature searches. Biomarker research will be accelerated by access to established cohorts and biobanks. Again, there are many of these across the EU and there should be an attempt to catalogue and harmonise these resources, while ensuring a broadly accessible (where feasible with full open access), high quality dataset of adequate size. [See Challenge 2 for further discussion and recommendations on this aspect.].

19. Promote longitudinal studies in the areas of PM.

Following patients during the various stages of disease progression (and relapse) and the monitoring of side effects that might ensue many years later (for example cardio-toxicity or secondary tumours as a result of previous chemotherapy) is of critical importance to fully assess the effectiveness and safety of interventions. This requires long-term follow-up of patients. Funding mechanisms need to be put in place to enable such long-term studies that can extend over several decades. Some examples of such follow-up programmes are underway, especially large cohort follow-up, including genetic data. These include the HUNT study in Norway, and several other large long-term cohorts in Europe, which mostly, but not solely collaborate in the [BBMRI-LPC](#) project. The extensive characterisation of diseases and their evolution should be extended and enhanced.

20. Support development of new clinical trial designs and promote integration with concomitant preclinical testing.

Traditional clinical trials test for safety first, usually in healthy volunteers and efficacy later. However, this approach fails to take advantage of continuing advances in pharmacogenomics. According to expert opinion, clinical trials need to be designed in such a way that it becomes clear if a drug is effective after treatment of the first few patients (see, for example, *Nature Medicine* (2005, 22)). The development of PM with targeted therapies should allow for this early identification of efficacy, e.g. by early clinical trials including on-going analysis of patients' tissue and blood samples. If a drug fails, scientists can determine whether it does not work because the target is inappropriate, or because genetic differences prevent the drug from hitting the target in some individuals. The new models may shift the focus from patient groups to the development of diagnostic tools along with new drugs. Other important clinical trial models for PM are adaptive clinical trial designs which are becoming increasingly used (e.g. Bayesian designs that use decision theoretical approaches). Given the inherent characteristics of more personalised treatments, innovative designs have to cope with smaller populations for these trials. These new models should be covered by guidelines and reflection papers to enable their inclusion in the regulatory framework of clinical trial legislation. The acceptance of data coming from innovative trial designs by regulatory authorities for the marketing authorisation of medicines is essential for these trials to be increasingly used in drug development. So drug developer need to seek advice on how to best use this trials via the protocol scientific advice procedures offered by both, the EMA and the FDA.

Since many of the new clinical trial design strategies are being developed and applied in current or completed trials, and some are being used to provide the data package for marketing authorisation applications (MAA), research is needed to investigate the different trial designs, their results, whether they have been successful in addressing the question they were designed to answer, whether they have been used for marketing authorisation purposes,

and whether these applications have succeeded. Such an investigation could inform both the regulatory process and the drug development process.

Programmes in methodology research, trial design and social science should be supported in order to maximise the information that can be gathered from clinical trials. New clinical trial methodologies, for example adaptive trial design such as MAPPs (Medicines Adaptive Pathways to Patients) with the incorporation of biomarker information on individual level, should be strongly encouraged and supported. Clinical trial networks should be developed and coordinated across the EU.

As the stratification of patient cohorts into subgroups increases, the focus should shift from 'finding patients for a clinical trial' to 'finding the best trials for the patients'. Methods in which tissue samples of patients can be used to directly test interventions hold significant promise. Our ability to propagate cells from patients in culture (e.g. organoid cultures or induced pluripotent stem cells – iPS – technology) or in xenografts in mice offers important new opportunities in this regard. Such approaches may substantially improve the predictability and effectiveness of interventions, an especially pressing issue in the field. Finally, and importantly, patients must become involved in all stages of the clinical trial process, from design and implementation to the consideration of regulatory issues. Only under these conditions will patients occupy their rightful position.

21. Re-classify diseases at the molecular level.

Genetic analysis represents an important parameter for grouping diseases. Moving from a symptom-, phenotype- and organ-based approach towards a network- and systems-based classification offers a number of advantages. In this way complex diseases might be described as 'multiple rare diseases', thereby benefiting from the methodological and clinical advances achieved in the rare diseases field in terms of clinical trial design, drug development processes and the most efficient use of limited patient data. To support such research, pre-disease data for prevention and better understanding of disease mechanisms in the patient have to be provided.

22. Develop suitable funding models to enable cross-sector working in PM research.

This will enable new partnerships, among others between clinicians, patients, and health insurers and regulatory agencies, to develop more rapidly and allow standardisation of processes. A first step could be to elaborate suitable template agreements. Recognition of the importance of translational research for the integration of PM into European health systems should lead to the development of a European Translational Research Platform (ETRP) that enables the efficient conversion of exciting research discoveries into innovative diagnostics, therapeutics, products, services and processes that will benefit European patients, industries and societies. This platform should be part of the pipeline envisaged by the H2020 Advisory Group (Health, Demographic Change and Wellbeing) for the implementation of PM in Europe and be informed by already existing infrastructures in Europe such as EATRIS. To encourage cross-disciplinary research, funders must work together to create a stimulating and transparent funding environment. Governments, charities, not-for-profit and private funders should join forces to foster a collaborative culture in which resources are shared and a dynamic flow of ideas between the participants becomes the norm. Continuity of high quality research lines has to be ensured by installing sustainable funding schemes that allow basic researchers to take their findings through the subsequent development stages.

Key Enablers for Challenge 3

Europe: e.g. EC, European research centres, European research infrastructures, societies, healthcare providers, foundations/charities, patient organisations.

Member states: e.g. national research centres, ministries of health and research; institutions for public health and health insurance, healthcare providers, societies, patient organisations, ethics committees, registries, agencies responsible for biobanks and data-banks.

Industry: e.g. pharmaceutical, biotech and IT industry.

Conclusions

PM must be underpinned by robust knowledge of the disease and the patient. This will only be realised through support for excellent basic research conducted across Europe, and by harnessing data and outcomes to enable translational opportunities to be identified. Collaboration between sectors and the provision of the best possible environment, resources and infrastructure should be promoted. Furthermore it must be ensured that an open, sharing culture is established – including the sharing of both risks and gains. This will create an environment for the translational research that will be needed to keep Europe at the forefront of PM.

Examples of on-going activities

a. Europe

The [EMA](#) offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development relating to pharmaceuticals. This process can also be used to evaluate and validate biomarkers. Within the Innovative Medicine Initiative (IMI-2) a Strategic Research Agenda entitled 'The right prevention and treatment for the right patient at the right time' was published in 2013 (<http://www.imi.europa.eu/content/imi-2#SRA>).

In Europe, the [EPIC study](#) is a large cohort study on nutrition and cancer, which could be also used for other purposes and has started incorporating genetic data. The ERA-Net on rare diseases ([E-Rare](#)) launched a call in 2014 on innovative therapies (gene therapy, cell therapy and pharmaceutical therapy) for rare diseases.

b. Member States and other countries

The Academy of Finland's research programme [Personalised Health](#) (2014–2019, <http://www.aka.fi/en-GB/A/Programmes-and-cooperation/Academy-programmes/Open-for-Application/Personalised-medicine-/>) explores the application of genome data and other personal health information to maintain and promote

an individual's health and to prevent and treat diseases. In addition, the programme will look into the medical, treatment-related, technological, judicial, ethical, social and societal issues and impacts relating to data generation, collection, storage and use. By creating and providing a platform for multidisciplinary research consortia, the programme will aim to connect different scientific disciplines to contribute to unearthing new kinds of research perspectives.

In France, 8 French cancer research sites [SIRIC](#) (Integrated Cancer Research Sites) were designated for a 5-year period (starting from 2011 and 2012), and then became national centres of reference for cancer research. This designation is aimed at offering new opportunities for conducting translational cancer research, thus helping to optimise and hasten the production of new knowledge and promote its dissemination and application to cancer care. The French Alliance for Research in Life Sciences ([Aviesan](#)) has set up two strategic valorisation fields on biomarkers and companion tests on the one hand and on biomarkers in neurology and psychiatry on the other hand (in French 'domaine de valorisation stratégique, [DVS](#)') to bring together all relevant players across the value chain to: (1) identify the teams involved in biomarker research and validation (pathological or technological); (2) make an inventory of biomarkers and order them according to their development stage with regard to medical validation (identified, verified, validated) and technical validation (reproducibility, sensitivity, specificity, robustness of the analysis) and to offer support in all project modes; (3) work alongside pharmaceutical, diagnostics and device manufacturers to assess the development stage and level of interaction needed between these players and academics; (4) identify analysis methods or biomarker measures and the players who can develop them; (5) work with manufacturers concerning molecules upon which they would like to conduct specific biomarker research; and (6) drive thoughts on issues concerning business models and reimbursement based on real cases and an exact definition of 'clinical utility'.

In Germany, the BMBF is supporting translational research with over 40 Mio € for validating biomarkers as

well as driving personalised therapies and biomedical devices from the preclinical phase into clinical trials. In order to facilitate research in this field methods and tools for integrating data from research need to be improved further. BMBF is supporting the development of new methods, tools and services for preclinical and clinical research in PM with a focus on data integration and security.

A network of German research institutes has launched a large-scale, nationwide, long-term population study, the so-called [German National Cohort](#). The aim of this study is (1) to explain the causes of widespread diseases such as cardiovascular disease, cancer, diabetes, dementia, and infectious diseases; (2) to identify risk factors; (3) to highlight effective forms of prevention; and (4) to identify options for the early detection of diseases. In this cohort study, 200,000 people aged between 20 and 69 from across Germany will be medically examined and questioned on their living habits (e.g. physical activity, smoking, diet, occupation). In addition, all participants will supply blood samples, which will be stored in a central biobank for later research projects. In the course of their observation over a period of 10–20 years, some of the participants are certain to develop diseases, which can then be correlated with the data collected.

In Norway, the [HUNT Study](#) – a longitudinal population health study – is one of the largest health studies ever performed. It is a unique database of personal and family medical histories collected during three intensive studies. In the third phase genetic data is being collected, and will be combined with clinical records and cancer, stroke and death registries.

In Spain, the National Institute of Health Carlos III (ISCIII) launches yearly calls for integrated projects of excellence on predictive and personalised medicine for accredited Health Research Institutes (6 M€ per year). These institutes are collaborative structures that bring together basic research groups from academia and clinical research groups from hospitals. ISCIII also supports omics and bio-informatics platforms, a biobanking network and a Genotyping platform ([CeGen](#)).

In the UK, the Medical Research Council has recently invested £60m in disease-specific multidisciplinary research consortia. These bring academic and private partners together with the aim to identify distinct groups of patients within a particular disease that share a set of defined molecular markers. This encompasses patient cohorts, biomarker analyses, genotypic and phenotypic analyses and bioinformatics. The UK has established a number of biobanks, cohorts and disease registries as resources for both academic and private sector researchers. Examples are the UK Biobank and the UK Brain Banks Network. Innovate UK (formerly the Technology Strategy Board) has invested £50m over the past five years through a stratified medicine innovation platform – see Challenge 1 above for details. Cancer Research UK has also invested significantly in stratified medicine. Phase one aimed to demonstrate on a small scale how routine testing of patients' tumours could be scaled up to provide a national service across the National Health Service (NHS), while at the same time gathering data on patients' genetic test results and their treatments to boost research in PM. Phase two now aims to:

- Genetically screen up to 2,000 non-small-cell lung cancer patients a year to identify the key genetic faults driving the growth of their cancer;
- Continue to pioneer the use of Next Generation Sequencing technology in the NHS;

- Use this information to match patients to the best treatment option from the multiple arms of the National Lung Matrix Trial.

The UK has also recently set up the [100,000 genome project](#) led by Genomics England, to deliver the sequencing of 100,000 whole genomes from NHS patients by 2017. Its four main aims are: to create an ethical and transparent programme based on consent; to bring benefit to patients and set up a genomic medicine service for the NHS; to enable new scientific discovery and medical insights; and to kick start the development of a UK genomics industry.

In Canada, as discussed in Challenge 1, a Genome Canada/CIHR partnership led to the launch of 'Genomics and Personalised Health: 2012 Large-scale Applied Research Project Competition'. Following a competitive call, 17 such projects – for a total budget of 165 MioC\$ over four years – have been funded. These should illustrate how genomics-based research can contribute to a more evidence-based approach towards healthcare and improve the cost-effectiveness of the healthcare system. More recently, the CIHR Ethics Advisory Committee on Innovative Clinical Trials has been mandated to develop a white paper on clinical trial methodologies. This will provide a common understanding among regulators, clinicians and ethics review boards on the development and management of PM clinical trials and facilitate international trials.

Challenge 4 – Bringing Innovation to the Market

Introduction

Bringing innovation to the market has traditionally been viewed as a linear process proceeding from research and development to regulatory approval, and then to health technology assessment (HTA) and on to the final reimbursement or implementation decision. However, this linear process does not take into account the inherent uncertainties of innovation. More rapid introduction of innovations into health systems needs to be based on regulatory and reimbursement pathways that take into account evolving knowledge on safety, efficacy, efficiency and the necessary conditions of the health system that allow the promise of the innovation to be realised. For these approaches – both for drug and non-pharmaceutical products – processes need to be able to evaluate the use of in vitro and companion diagnostics, innovative clinical trial designs and the balance between the inherent higher uncertainty due to smaller sample size of target groups and the contrary inherent lower uncertainty due to higher impact or effectiveness on target groups.

Historically, the drug cycle has reached optimal development levels. However, new times demand different solutions. In the development of a new drug there are now two sectors that are becoming increasingly important: health technology with in vitro diagnostics (with a decisive role in the sustainability of healthcare systems) and biotechnology. This is why European and country-specific regulatory authorities must urgently adapt their structures and regulations to this new reality. European regulators need to find adequate approaches for assessing and regulating companion diagnostics, which do not put European companies at a disadvantage relative to non-European companies, while at the same time providing European patients with safe, effective and affordable diagnostics. Another, at least equally important, challenge for European regulators is the detection of rare adverse events during the post-marketing surveillance phase. The EMA has already raised the possibility of staggered approval schemes in its published roadmap to 2015, and announced in March

2014 the launch of a pilot project on Adaptive Pathways. This pilot will be combined with new tools within the new EU Pharmacovigilance Regulation and stringent Post-Approval Safety Studies and Post-Approval Efficacy Studies. Time will tell if this approach can live up to its high expectations and whether it should be adapted to the needs of PM.

Within the concept of PM, work is done with therapeutic targets and the paired diagnostic companion and novel molecule, which inevitably leads to the optimisation of processes, an increase in efficiency and security and a decrease in adverse events, both in quantity and quality. Moreover, there is a reduction in the number of patients in clinical studies, due to the inclusion of their genotype and phenotype, resulting in an optimisation of resources and, most importantly, a contraction in the time needed. But the resulting high cost and the lack of knowledge in clinical outcomes if such a therapeutic proposition were to be extended to a larger number of patients will require the pharmaceutical, technological and biotechnological industries to come up with innovative formulas with the different administrations, regulatory bodies, decision-makers, healthcare professionals, patients and the rest of society. Another crucial decision point for PM lies in HTA, as also discussed in Challenge 5. HTA has hitherto been considered as a decision which is made at a single point in time. Now, however, with the on-going implementation of PM it needs to evolve to life-cycle approaches and to be part of a systematic early dialogue covering the whole pipeline from technology transfer (TT) to implementation in health systems. In order to fulfil this requirement, HTA and value considerations have to be included early in the research design process to ensure the appropriate data is captured, both for market authorisation and for HTA. Regulatory and HTA authorities need to receive and assess all necessary information for the decision process in order to successfully bring innovation to the market (Rosenkötter et al., 2011).

If PM is to be implemented, evidence-based decisions have to be taken by national or regional authorities as well as by clinicians and their patients. Both the evidence

and the rationale for taking the decision should be publicly available. The inclusion of economic dimensions into the decision-making process calls for public deliberation on patient and societal values that are essential for coherent and politically and socially acceptable decisions. PM will have an effect across the entire healthcare model. Citizens as well as patients will be significantly confronted with it in 'digital health' (by information and training), in the 'internet of things' (by devices) and in social networks (by influence). The coherent and cost-effective introduction of PM into health systems must be based on an explicit examination of what is necessary in order to allow the promise of the innovation to be realised. For example, well-defined patient pathways are needed for the appropriate use of innovative technologies. The safety and efficacy of the diagnostic component of PM depends on the presence of stringent quality control measures being applied within laboratories.

Targeted achievements until 2020 and beyond – Recommendations

23. Formalise a risk-based approach for the evaluation of PM.

A combination of benefit–risk evaluation with real-time data and the use of observational, epidemiological or in silico studies to demonstrate effectiveness even on individual level will enable the introduction of new models of innovation into the healthcare system. These evaluations will also enable post-marketing surveillance to spot rare adverse events and include spontaneous reporting and analysis of electronic health records. This post-marketing surveillance is particularly important for PM as the initial uncertainty is often higher given the smaller subgroups. Such an evaluation will also reinforce the shift of HTA from being viewed as a single point in time to a means to inform decisions from the initial introduction of a technology to its retirement. It is impossible to speak about PM without considering the global perspective. For example studies to interpret variants in populations could be a benefit with the help of multi-national trusted biobank networks, working around the same guidelines and operating procedures.

24. Optimise individual drug therapies and poly-pharmacy especially in the case of multi-morbidity.

All EU Member States are facing the same demographic change: an increasing elderly population with multiple chronic diseases and poly-pharmacy. For this growing group of patients, ways must be identified to evaluate benefits and risks of medication which are usually tested in younger and healthier populations and where the evidence base is weak. This may include pragmatic clinical trials and particularly epidemiological studies using healthcare databases. Moreover, approaches for individualisation of drug therapy in the light of several comorbidities and patients' preferences should be tested and validated. These approaches may include omics testing to determine the probability of response and benefit on one hand and an exploration of patients' preferences on the other. Systems biology may contribute to better understanding of the interference of multiple chronic conditions and facilitate optimal drug choice for the individual patient. Participation of patients and their empowerment must play a crucial role in improving adherence; otherwise the best drugs will not be effective.

25. Support research on an adequate regulatory and legal framework for PM.

Research on regulatory and legal issues should be supported in order to update and adapt current regulations. There should be a simplified, harmonised and predictable regulatory procedure across all regulators, taking into account ethical, legal and social aspects. This would lead to reduced costs and fewer administrative hurdles and ensure coordination between authorities and coherence across legislative jurisdictions for medicines, diagnostics and medical devices, as well as for data protection and clinical trials. The updated regulations will need to allow coordinated marketing authorisation application (MAA) approval and a reimbursement process for PM approaches. Those approaches often include a combination of drug and companion diagnostics (CDx), a combination that is difficult to manage in the current system. Introduction of new models, such as value-based pricing (VBP), managed entry agreements; conditional approvals, adaptive pathways and conditional reimbursement also

need to be considered. Overall, this will enable a cohesive approach that takes into consideration the specificities of PM evaluation. These new models are based on a continuous adaptation of the use of new technologies to the evolution of knowledge. Without limiting itself only to the competent regulatory and assistance authorities, this adaptation must be extended to the postgraduate level in universities and to healthcare professionals, given that PM is likely to become integrated into day-to-day practice, from diagnosis to treatment, without existent specific training curricula for healthcare professionals. European harmonisation in these areas would also facilitate international coordination within the field of PM. Innovation in the area of rare diseases has recently benefited from such international coordination through the International Rare Diseases Consortium. Many regulatory hurdles common to rare diseases, including smaller sample size and higher uncertainty, are similar to those facing PM. The rare disease field offers many 'lessons learned' and can help to ensure that similar international structures can be established. These best practices as well as all the new regulatory approaches have to be adequately evaluated and assessed for the benefit of patients and citizens and for European competitiveness.

26. Encourage a systematic early dialogue between innovators, patients and decision-makers throughout all regulatory steps to provide guidance and clarity.

This recommendation is closely allied to the revision of the regulatory and legal framework to produce a clearer and harmonised approach with interconnected components. Systematic early dialogue with innovators – both from the public and private sectors – is essential to ensure that research, even at an early stage, considers the regulatory and reimbursement evaluation needs, e.g. data required, trial design, or choice of comparator. This early dialogue will decrease the time required to meet the regulatory requirements, facilitate reimbursement decisions, and avoid duplication and misalignment of expectations. It is of key importance to involve patients in this dialogue, especially in terms of defining endpoints, patient-relevant outcomes and intended comparative value.

27. Facilitate partnerships and innovation networks to encourage cross-disciplinary and cross-border collaboration in research and development using an 'Open Innovation' approach.

Trust has to be fostered by supporting research collaborations and public–private partnerships (PPP) and by bringing public and private funding together. The appropriate framework for a collaborative culture has to be created throughout the sector with shared resources, dynamic bi-directional flow of ideas and interchange between companies. The approach of 'living labs', with open public, private and user partnerships, seems to be particularly interesting for enabling the introduction of promising innovation, where the added value is of high plausibility. Open innovation processes are particularly useful for accelerating the introduction of innovation into health systems accompanied by research that reduces the inherent uncertainties under real-world conditions. Peer reviewed collaborative research using open data is a model that should be promoted.

28. Provide support and guidance for companies to enter the market for PM with sustainable business cases.

In this context translational projects closer to the patient/market should be driven by the end-users' needs. In addition to encouraging early dialogue, specific support to companies needs to be developed. Companies are hesitant to access the market due to the limited understanding of certification, validation and regulations: for example, guidance is needed with regard to regulatory and reimbursement issues, as well as current and envisaged health policies. Innovators and companies should be encouraged to seek guidance early in relation to options and approaches. Collaboration between innovators of diagnostics and therapeutics is a crucial aspect for PM to move forward. In addition to this guidance, a framework to aid the development of PM for companies and to facilitate access to finance needs to be developed. This will facilitate access to resources and competences, both of which are lacking among the different actors involved in the development of PM.

Key Enablers for Challenge 4

Europe: e.g. EC, EMA, IMI, FDA and patient organisations.

Member States: e.g. Ministries of health, justice and economics, national regulation authorities including notified bodies, HTA, standardisation authorities and organisations, academia, patient organisations and research centres.

Industry: e.g. the pharmaceutical (e.g. EFPIA or EBE), diagnostic (e.g. EDMA), medical technologies (e.g. Eucomed) and biotechnology industries (e.g. EuropaBio).

Conclusions

The development of PM entails a new research and development model for drugs. Regulators, researchers, healthcare professionals and businesses have to collaborate to achieve optimal patient access (both in time and manner) to PM. Patients, the media and society in general must also take responsibility for the successful introduction of PM. Society as a whole, and each individual in the realm of his or her responsibilities, must adapt to a new approach towards diagnosis and new treatment options, including the prevention of an illness before its onset. Prevalent and complex diseases as well as rare diseases will not only become more controlled (chronicity as opposed to death), but their patients might even experience absolute recovery. The paradigmatic shift caused by PM calls for research, guidance and new collaborations in the regulatory field, especially regarding post-launch requirements and surveillance of pharmaceuticals and medical devices. Market entry pathways have to be adapted in order to assure a safe, effective and competitive environment for patients and industry.

Examples of on-going activities

a. Europe

At the EMA there are several platforms and tools that have been created to facilitate early dialogue and ultimately timely patient access to safe and efficacious medicines:

The Adaptive Pathways approach is part of the EMA's efforts to improve timely access for patients to new medicines. Adaptive Pathways foresees either an initial approval in a well-defined patient subgroup with a high medical need and subsequent widening of the indication to a larger patient population, or an early regulatory approval (e.g. conditional approval) which is prospectively planned, and where uncertainty is reduced through the collection of post-approval data on the medicine's use in patients. The Adaptive Pathways approach builds on regulatory processes already in place within the existing European Union legal framework. A pilot project is on-going already entering phase II with 10 of the 34 applications accepted for the next phase of discussions.

The Innovation Task Force provides a platform for early dialogue with the agency. It is open to industry, academia and other interested parties that want to discuss a product or technology related to the development of pharmaceuticals. It offers a safe harbour and open dialogue with expert regulators who offer their personal views and recommendations on the topic of discussion.

Scientific Advice procedures, including the method qualification programme (e.g. for biomarkers or innovative development methods or trial designs), offer an official response to very specific scientific questions from companies relating to the appropriateness of

their development programme, biomarker, trial design, data package for a certain indication, and so on. There are special discount schemes, for example for SMEs, orphan diseases or paediatrics.

Joint Scientific Advice with HTAs and with FDA: Companies have the possibility to request parallel scientific advice with the EMA and national HTA bodies or with the EMA and FDA. The discussions in these joint procedures are carried out jointly, facilitating convergence in requirements and the dialogue between all stakeholders involved.

[SEED](#) (Shaping European Early Dialogue for health technologies) is a project financed by the EC with the objective to reduce the risk of production of data that would be inadequate to support the company's future reimbursement request. SEED aims to conduct pilots on early dialogue between its member HTA agencies and developers of health products (pharmaceuticals and medical devices) whose products are currently in the development stage. In total, ten early dialogues are planned with the aim to conduct seven on drugs and three on medical devices.

[PROTECT](#) is an IMI-funded consortium coordinated by the European Medicines Agency (EMA) conducting pharmaco-epidemiological research on outcomes of therapeutics. The project will enhance the monitoring of the safety of medicinal products by studying combinations of drugs and adverse events in several databases with the aim to explain discrepancies between the reported outcomes from pharmaco-epidemiology studies.

The IMI-funded European programme in Pharmaco-vigilance and Pharmaco-epidemiology ([Eu2P](#)) is a partnership between universities, companies, and the

French and European medicines agencies covering courses in pharmaco-vigilance and pharmaco-epidemiology and targeting experienced professionals as well as non-specialists such as journalists, the public and patients.

b. Member States and other countries

In Germany the BMBF is supporting three 'Leading-Edge Clusters' in PM with 120 Mio€. These clusters facilitate networking of industry and academic research for biomarker-based drug development within a region, thereby creating best practice on how to drive innovations to the market.

Spain founded in 2009 the 'Predictive and PM against [Cancer Institute](#)' with the goal to change current diagnostic and treatment models within preventive and PM with a focus on cancer research. Its core activity is to carry out basic and translational research as well as the instruction and distribution of new genomics medicine knowledge among healthcare professionals and society in general. Hospitals, universities and private businesses involved in PM are integrated by the Spanish Bellvitge Biomedical Research Institute ([IDIBELL](#)).

In the United Kingdom, Innovate UK has established a Stratified Medicine Programme coordination group, including all the relevant funders, together with regulators and representatives of health departments. This group ensures that there is coordination between research, regulations and health delivery. There is also significant engagement of the pharmaceutical and biotech industries across all of the UK activities to help with routes to translation and uptake.

Challenge 5 – Shaping Sustainable Healthcare

Introduction

There are today several policy tools to manage the diffusion of innovations in healthcare, one of which is payment mechanisms. The challenges faced by payment authorities are manifold. How can promising innovations be driven forward while avoiding the diffusion of undesirable ones? How can the execution of studies required for sound reimbursement decision-making be encouraged? And how can appropriate utilisation and diffusion of these innovations be ensured in terms of patient population and provider setting? Affordability is a central element for reimbursement, and thus an additional challenge of bringing innovation to the market. Inevitably competing policy goals have to be balanced: maximising health benefits for the population as a whole and ensuring that innovation is financially rewarded, while at the same time containing costs.

In principle, PM creates a high expectation from the perspective of healthcare systems. The possibility of providing diagnostics and care that are tailored to the characteristics of the individual has been one of the main goals of healthcare since its inception. There is the promise of better outcomes; each patient will be given only what he or she needs, avoiding the at times trial-and-error based 'classical personalised medicine'. There is also the prospect of a reduction in costs related to this trial-and-error paradigm, together with a reduction in resources required to address risks such as adverse events and incomplete benefits that might arise from not applying the best available option. However, it does not follow that there will be an overall reduction in budgets, at least in the early stages of the introduction of PM. Initially, there will be a need for investment in quality assurance, organisational aspects and capacity building. Shaping sustainable healthcare is mostly based on a balance between resources and achievements, in other words costs and outcomes. Healthcare systems should provide services with sufficient guarantees of safety and quality and, in principle, on the basis of supporting the paradigm of the [general assembly of United Nations on Universal Health Coverage](#) that includes a system for

financing health services. In this sense, some major drivers should be considered: a) the technology itself; b) the system and its organisation (including its workforce); and c) the interaction between the system and the client.

The technology or group of technologies, if we consider treatments and companion diagnostics, by itself offers benefits that are linked to its inherent characteristics: the capacity of creating tailored solutions that increase the safety and efficacy of treatments and the generation of further data that could help in improving current standards of practice. However, there are still some challenges that have not been solved and health systems have not yet produced a harmonised and common definition of what represents added value (Henshall et al., 2013). The definition of added value from the perspective of healthcare systems is very much linked to the expression 'clinical utility' as well as 'personal utility' and when diagnostics and treatments go hand-in-hand, there is a need to consider how the existence and determination of well-defined sub-populations will change our standards of care or clinical pathways (Teutsch et al., 2009). That is, if we can effectively and correctly categorise patients, will other therapeutic or preventive measures be taken and will that improve the health of the affected patients? One question is related to the capacity of the system, its organisation and its workforce to assume and ensure the adequate implementation of this technology and paradigm. This includes the completion, quality control and interoperability of existing clinical record databases for this new purpose (see Challenge 2); the ability of health professionals to build the capacity required for them to assume their new role (see Challenge 1); and appropriate systems that allow the transmission of information to patients on what the new findings are supposed to generate (Godman et al., 2013). Finally, according to best standards of care and ethical practices, there is a need for a trustworthy and transparent interaction between healthcare systems and clients, including patients and care-givers. The key to a successful transition to PM is that patients are well-informed and at the same time health literacy is promoted. For this purpose, the analysis of the target population and its characteristics, the development of adapted materials and improved health literacy are crucial. While there are no one-size-fits-all solutions, good practice can be shared (see also Challenge 1).

Targeted achievements until 2020 and beyond – Recommendations

29. Support health economics research of PM to support decision-makers.

New models for pricing and reimbursement have to be discussed. Where patients provide their personal health data and Member States invest in infrastructure, the pricing of products and services that bring innovation to market has to be adapted. Reimbursement has to ensure fair rewards for the research investment and risks taken by the producer, but also affordability for the entire health system as well as equity for each patient. Decision-makers need sound economic and medical evidence to support their decision-making process. Funding organisations should collaborate with healthcare providers to identify a disease or group of diseases as a paradigm for PM and fund research on relevant health economics related to PM (Haycox et al., 2014).

30. Develop prospective surveillance systems for personal health data that facilitate accurate and on-going assessment of highly dynamic health information across the life course.

In this case, major challenges can be identified: accuracy of data, interoperability of databases, which includes the capacity to trace individuals while securing anonymity, and appropriate storage capacities. Another limiting factor is the capacity to analyse and integrate big data (see Challenge 2). There are initiatives paving the way by establishing supercomputing centres in order to solve this problem of storage, integration and analysis (Merelli, 2014).

31. Develop training programmes on PM for health professionals.

Education and continuous training are indispensable if the potential of PM is to be realised. Informed health professionals will be the key to increasing public awareness of PM and ensuring patient rights. Patients must be adequately informed and their health literacy needs to improve. This can be achieved by promoting collabo-

orative partnerships between health professionals and patients. Hence health professionals, and especially practitioners, need to learn how to communicate PM in an understandable way to patients and the broader public (Public Health Genomics Guidelines. Brand A, Lal JA; Public Health Genomics European Network. European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies: 2012 Declaration of Rome., 2012).

There is a need to establish informative public health campaigns, support patient groups and recognise the patient's right to seek information. This should be done by initiating and supporting constructive and informative public debate. At the same time, health systems have to shift focus from acute disease treatment to preventive health management in parallel with treatment of disease. This requires training of healthcare professionals and students in PM. For adequate training to be given, changing relationships, for example between care-givers and patients, have to be fully understood and best practice must be evaluated. Since disease definitions will change it is crucial to promote inter-, trans- and multi-disciplinarity in healthcare providers (e.g. Golubnitschaja et al., 2013).

32. Encourage a citizen-driven framework for the adoption of electronic health records.

As has been pointed out earlier, the interaction between health system and client is one of the major points to analyse, especially considering that the owners of the data are the patients. There are initiatives in place to provide electronic data storage and data-sharing; this is relevant when there is a need to combine clinical data with other data such as lifestyle and environmental exposure (e.g. Chute et al., 2013). Recommendations on possible legal/regulatory initiatives relating to data collection, storage and sharing will need to balance the different interests at stake: patients' rights, health professionals' obligations, and the need for an efficient healthcare system (see Challenges 1 and 3). Such recommendations should also take into account national and European initiatives related to non-legal aspects of electronic health records (EHRs). In its 2008 recommendation on cross-border interoperability of EHR systems, the EC recognised that in order to

achieve the objectives of the European eHealth Action Plan, legal initiatives should go hand in hand with financial measures, agreement on an organisational framework, promotion of the use of technical standards and architectures, the establishment of common interoperability platforms, coordination at the semantic level and, finally, education mechanisms and awareness raising. Recommendations on legal structures relating to EHRs need to take into account the wider legal issues with regard to eHealth and in particular the delivery of cross-border eHealth services (Commission Recommendation of 2 July 2008 on cross-border interoperability of electronic health record systems notified under document number C(2008) 3282). In the [Calliope Roadmap](http://www.ehgi.eu/Pages/download.aspx) (2013, <http://www.ehgi.eu/Pages/download.aspx>), these wider legal issues are illustrated by the following example: “When an eHealth solution is the primary vehicle for delivery of [cross-border] care, for example a second opinion delivered by video conferencing with simultaneous capture and transfer of bio-data, then the legal and ethical issues are wide and will arise not only in terms of the data sharing, but also in terms of identity certification, professional accreditation, liability for shared care and other issues yet to be identified. The legal and regulatory issues include also administrative regulations such as those of reimbursement, and – in the context of cross-border care – the mutual recognition of professional qualifications and the complex issue of entitlement to care”. With regard to EHR interoperability, considerable efforts have been made by the eHealth European Interoperability Framework (eEIF) and by many other initiatives (e.g. eHGI, epSOS, HITCH, ISA, semantic Healthnet, Antilope, eSens, Expand, STORK 2.0). One of the results of these initiatives is a better understanding of the interoperability needs and of the layers on which interoperability needs to be achieved (making the distinction between technical, semantic, organisational and legal interoperability). These layers will now be populated with standards, specifications, case studies, workflows, subsets of terminologies, interoperability agreements, guidelines developed by specialised organisations, fora, consortia or EU funded projects after they have been identified or endorsed by the relevant EU governance bodies (e.g. eHealth Network, ICT Standards multi-stakeholders platform and later the Connecting Europe Facility – CEF – gover-

nance). In doing so they have to connect with PM translational research results in order to feed in and cross-fertilise (see Challenge 3).

33. Promote engagement and close collaboration between patients, stakeholders and healthcare actors across sciences, sectors and borders.

Patient communication should be adapted to the specifics of PM. Therefore a collaborative partnership between healthcare professionals and patients should be sought. Patients should be helped to become active managers of their own health, and healthcare professionals should learn how to communicate PM in an understandable way. Healthcare professionals need to be involved at an early stage of the development of PM to draft an implementation plan. Better collaboration between primary care, secondary care and hospital care and the coordination of health and social care services should be encouraged (Godman et al., 2013).

34. Develop a framework for pricing and reimbursement for PM that ensures equitable access for all patients – regardless of economic or geographic status – and is sustainable for health systems.

We appreciate that at the European level this recommendation represents a significant challenge, bearing in mind the huge differences between European Member States in terms of wealth and in terms of share of healthcare expenses. Given this situation, equitable access for all patients should initially be developed at the national level. While this recommendation is not exclusive to PM, it does particularly affect PM. Current methods of calculating prices are far from transparent and are not directly linked to a given technology’s added value and performance (Henshall & Schuller, HTAi Policy Forum., 2013; Dranitsaris et al., 2014). In the case of reimbursement, the main problem centres on budget constraints and single technologies analyses; in many cases the prices of reference limit the improvement of methods to define prices and gain reimbursement. Mostly prices are calculated on the basis of existing comparator and standards of care costs. This limits the possibility of paying per performance or per outcome reached on an individual patient (Raftery, 2013). There is a need to explore

new methods of pricing and budget prioritisation based on pathologies and pathways much more than single technologies analysis and pricing, and budget impact analysis of these single technologies (Leopold et al., 2013).

35. Develop an optimised overall healthcare financing strategy.

For example, a shared risk-and-benefit mechanism could be elaborated. Additionally a 'full cost of the patient' view should be established and adopted. Sustainable technology transfer capacities could ensure faster patient access to innovative technologies and cost-effective translation, which could reduce the overall costs of new medicines. Evidence generation: Current costs of evidence generation to manufacturers, especially trials design and development, could be minimised by establishing agreements between manufacturers and healthcare systems (Goldman, 2012; Said & Zerhouni, 2014). This is key when we consider designs that include a reduced number of patients involved, for example in the case of rare diseases and stratification. Gaps of evidence and uncertainty management: When uncertainties regarding outcomes are still in the pipeline and added value from existing evidence is expected from new solutions, there is still a chance to speed the process without compromising budget and safety to patients. Mechanisms exist that can be valuable in the case of new evidence generation while ensuring access to innovation. These mechanisms have been called conditional coverage agreements (CCA) and include a range of practices including 'coverage with evidence agreements' or 'risk sharing agreements' (Hutton et al., 2007; Klemp et al., HTAi Policy Forum, 2011). A thorough assessment should be run to test the applicability of these approaches for PM.

Key Enablers for Challenge 5

Europe: e.g. EC, EMA and patient organisations.

Member states: e.g. Ministries of health, regulatory authorities' (e.g. national authorities, including notified bodies); HTA; insurances; hospitals and other health providers; academia; patient organisations.

Industry: e.g. pharmaceutical, companion diagnostic technologies, manufacturers, ICT and health providers.

Conclusions

PM poses a challenge to healthcare systems. This is in principle positive because of its promise to reduce uncertainties and increase benefits in the balance between risks and benefits. However, the current landscape on pricing and determination of added value and the difficulties in establishing agreements for reimbursement based on performance do not favour its broad implementation. There is also a lack of knowledge among professionals and citizens about the significance and consequences of these new technologies. The most innovative approaches with their strong intellectual property protection are especially complicating for shared decision-making processes. While not exclusive to PM, shared decision-making processes are particularly crucial to implement PM services without putting at risk the sustainability of the systems and the outcomes to be achieved. Therefore, public-private partnerships are important in evidence generation and innovation implementation. Thus, managed entry-agreements, coverage with evidence schemes and new ways of innovative public procurement processes are good candidates for addressing most of the issues that are currently under debate.

Examples of on-going activities

a. Europe

The Public Health Genomics European Network ([PH-GEN](#)) is a cornerstone in the development of Public Health Genomics in Europe and has endorsed the first European best practice guidelines on PM ('Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies'). The implementation of the concept of public health genomics, being the responsible and effective translation of genome-based knowledge and technologies for the benefit of population health, requires modifications to public health and health governance systems on all levels. Whereas PHGEN I identified the need for European best practice guidelines ('mapping exercise'), PHGEN II developed the first edition of these European best practices, which became a scientific benchmark in Europe. In this concept, genome-based

information is highly holistic and includes not only all 'omics' data but also environmental, socioeconomic and lifestyle factors, as well as information on health systems, and promotes a big data analytics approach and in silico simulations/modelling. Furthermore, on the regulatory level in 2009 PHGEN developed the concept of personal utility, citizen ownership and control of personal data, addressing the need for systematic early dialogue, 'truly' public-private partnerships and proactive and bottom-up policy-making. In 2012, experts from across the field of public health genomics representing key European and national competent authorities in policy making from all Member States, academia and the private sector, came together at the final meeting in Rome – amongst them the ESPT and the EMA – to discuss the future of public health genomics and to endorse the Declaration of Rome 2012, a summary of European Best [Practice Guidelines](#) for Quality Assurance, Provision and Use of Genome-based Information and Technologies.

[EUnetHTA](#) was established to create an effective and sustainable network for HTA across Europe. The partners work together to help develop reliable, timely, transparent and transferable information to contribute to HTAs in European countries thereby supporting HTA knowledge-sharing and promoting good practice in HTA methods and processes. EUnetHTA-JA2 is currently developing methodological guidelines relevant to PM such as: how to evaluate medical devices, individual technologies joint assessment and the early advice initiative and examples of evidence- and risk-sharing agreements (Examples of evidence and risk sharing agreements: Annex C, 24 – 27).

The EU funds the project [AdHopHTA](#) (Adopting Hospital based HTA in the EU) under FP7. Hospitals are the main entry point for new technologies in healthcare. However, hospitals often lack the knowledge and resources to evaluate these technologies. AdHopHTA will foster the application of high-quality HTA in hospital settings. Decision-makers in hospitals are thereby informed of the likely value of a health technology for a specific healthcare organisation. This will promote

the adoption of technologies with proven value in hospitals. AdHopHTA will in addition develop tools for formal coordination among existing hospital-based HTA initiatives and for improved liaison with national and regional HTA agencies.

One of [EAPM's](#) key aims is the development of a patient-centred European Translational Research Platform that maximises the impact of new and existing activities at European and national levels, thus ensuring the efficient translation of research promise into innovative PM care for European patients (see Challenge 3). Establishment of this platform is a central component of the EAPM Research Policy Roadmap. The goals are to: (1) embed PM in European health systems; (2) develop a patient-centred European Translational Research Platform; (3) empower patients as advocates for PM integration; (4) inform relevant stakeholders on the benefits and challenges of PM; (5) provide an evidence base for the clinical, health economic and societal advantage of PM; and (6) engage with regulatory authorities, healthcare providers and policy makers to enable more rapid translation of PM approaches into clinical practice.

The Innovative Medicines Initiative ([IMI](#)) is Europe's largest public-private initiative aiming to speed up the development of better and safer medicines. IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. IMI is a joint undertaking between the European Union and the pharmaceutical industry association EFPIA. It is focused on drug development, although IMI-2 also concerns medical devices development.

Public Procurement of innovations ([PPI](#)) is a European-wide initiative that is not exclusively targeted at the healthcare sector. An initiative within this framework is [Pre-Commercial Procurement](#) (<http://ec.europa.eu/digital-agenda/pre-commercial-procurement>) Some of the projects in health sector that are already in place can be viewed at <http://www.innovation-procurement.org/projects/health-elderly-care/>.

The [EUROREC](#) Institute is an independent not-for-profit organisation, promoting within Europe the use of high quality EHRs. One of its main missions is to support, as the European certification body, EHR quality labelling and the defining of functional and other criteria. EuroRec is organised as a permanent network of national centres and provides services to industry (developers and vendors), healthcare providers (buyers), policy makers and patients. European projects in which EuroRec is involved, include ARGOS; [HITCH](#), Healthcare Interoperability Testing and Conformance Harmonisation; Q-REC, European Quality Labelling and Certification of Electronic Health Record systems (EHRs); RIDE, A roadmap for interoperability of eHealth systems with special emphasis on semantic interoperability; and EHR-IMPLEMENT, national policies for EHR implementation in the European area – social and organisational issues.

The European Genome-Phenome Archive (EGA) is available at the European Bioinformatics Institute ([EBI](#), <https://www.ebi.ac.uk/ega/home>) and the Centre for Genomic Regulation ([CRG](#), <http://www.crg.eu/>). The EGA provides a service for the permanent archiving and distribution of personally identifiable genetic and phenotypic data resulting from biomedical research projects. Data at EGA have been collected from individuals whose consent agreements authorise data release only for specific research use to bona fide researchers. Strict protocols govern how information is managed, stored and distributed by the EBI. The EGA currently stores genome and phenome data on over 100,000 people, from 200 centres and research groups from around the world, and is a fundamental resource for the advancement of PM. Currently, the EGA stores the data generated by over 700 scientific studies on cancer, diabetes, autoimmune diseases, cardiovascular problems and neurological disorders, amongst other illnesses. These data, which add up to around 1 Mio Gigabytes, will be stored in the Barcelona Supercomputing Centre (BSC-CNS) facilities and subsequently analysed by the MareNostrum supercomputer (see also Challenge 2).

b. Member States and other countries

In United Kingdom [NHS Choices](#) is the UK's biggest health website. It is a clear example of well-presented information for patients and professionals and provides a comprehensive health information service to help put individuals in control of their healthcare. The website helps people make choices about health, from decisions about lifestyle, such as smoking, drinking and exercise, to finding and using NHS services in England. NHS Choices includes more than 20,000 regularly updated articles. There are also hundreds of thousands of entries in more than 50 directories.

The Health Technology Assessment International ([HTAi](#)) Policy Forum provides a unique opportunity for senior people from public and private sector organisations using HTA to support decisions or recommendations about product development and coverage to meet one another, members of the HTAi Board, and invited international experts, for strategic discussions about the present state of HTA, its development and implications for healthcare systems, industry, patients and other stakeholders. The forum has published [various papers](#) that address value-based pricing and adaptive licensing (<http://www.htai.org/policy-forum/about-htai-policy-forum.html>).

The Agency for Healthcare Research and Quality in the United States (AHRQ) published a report with recommendations for a health information technology infrastructure that could not only achieve interoperability among EHRs but also integrate data. Such data could include information from personal health devices, patient collaborative networks and social media, and environmental, demographic and genomic data. 'Data for Individual Health' examines how health information is used and shared across the healthcare system and makes recommendations about the use of standards and incentives to allow information sharing. The report, supported through a partnership between AHRQ, the Office of the National Coordinator for Health Information Technology (ONC) and the Robert Wood Johnson Foundation, comes as ONC is developing a federal he-

alth IT [strategic plan](#) for a shared, nationwide interoperability roadmap to ensure that information can be securely shared across an emerging health IT infrastructure (<http://healthit.ahrq.gov/sites/default/files/docs/publication/2014-jason-data-for-individual-health.pdf>).

MedlinePlus is the National Institutes of Health's Web site for patients and their families and friends.

Produced by the National Library of Medicine, it provides information about diseases, conditions, and wellness issues in language understandable to patients and care-givers. [MedlinePlus](#) offers free reliable, up-to-date health information and as such is a global initiative and clear example of information prepared for citizens (<http://www.nlm.nih.gov/medlineplus/>).

5) General conclusions

The recommendations reflect the expertise of the partners, participants and experts, representing key decision-makers from all relevant areas brought together and consulted by the PerMed initiative. This SRIA identifies 35 general recommendations and research sectors, topics and some of the instruments that will be needed for the further development and implementation of PM (see chapter 6). However the recommendations not only focus on potential research topics, but also highlight general developments and aspects that will foster innovation by PM approaches. To this end, stakeholders representing all relevant perspectives were included, such as research policy and funding, healthcare provision, and citizens'/patients' needs and interests. As a result of this comprehensive participation, a very broad spectrum of recommendations and potential fields of action has been identified. Given that PM encompasses multiple topics and developments; it has been a significant challenge to pinpoint reasonable concrete actions. Therefore most of the recommendations of this SRIA should be seen in the context of the entire proposed package of activities. To tackle the five challenges as well as the 35 recommendations several enablers have to join forces on either European or national level. Fortunately in several important areas this already is an ongoing process.

Several recommendations relate to more than one of the defined five challenges or cut across more than one of the three broad areas of activity which have been identified (see figure 3 below). In these cases, the recommendations have been ascribed to the challenge or activity area to which they mainly relate, in the interest of producing a clearer picture. However, only a well-balanced and inter-linked package of measures will provide sufficient impact on the wellbeing of citizens, the sustainability of healthcare systems and the competitiveness of relevant industries in Europe and beyond. Therefore the very nature of PM should be borne in mind by decision-makers to ensure that actions take account of the inherent multi-disciplinarity of this broad area of research. The disease-specific definition of research fields is becoming increasingly less

relevant, and parallel, cross-sectoral and interdisciplinary research from basic research to actual healthcare is becoming inevitable.

Thus, funding measures need to provide incentives not only to reach the next step in translational research but also to bridge the entire healthcare value chain (see table in chapter 6). Successful implementation of PM will still demand 'classical', well-funded research consortia to accelerate the introduction of safe new diagnostics and therapies, for example by the validation of biomarkers. But too many current approaches result in failure at some point along the development pipeline or do not demonstrate sufficient health benefits. For these reasons, additional funding for clinical implementation and 'real-world' assessment of these new personalised diagnostics and therapies is urgently needed. Research projects that are carried out in close collaboration with, for example, regulatory bodies, healthcare providers, policy-makers, ethical, legal and social experts and patient organisations can drive the kind of innovation that is needed. This will confront researchers with hitherto unfamiliar communication and cooperation requirements and funders with the need to finance research teams and institutions that are far beyond traditional research organisations.

As a result, the challenge for research funders and decision-makers will be to fund research beyond the classical funding schemes. There will be a need to include more communication and training modules, more outreach activities, and more non-research cross-sectoral projects to complement 'classical' basic and translational research activities. Funding also needs to provide incentives to include specialists from a wide range of areas such as:

- Big data and information and communication technologies including data sharing and integration
- Public health
- ELSA (ethical, legal and social aspects)
- Regulatory affairs
- Industry, including SMEs

National activities alone will not be sufficient to include all relevant stakeholders and to reach the ambitious goal of high-quality research and implementation across all areas of the healthcare system. ESFRI (European Strategy Forum on Research Infrastructures) is a successful and established example of an activity on a European level whose results and achievements can be developed further and applied for the needs of PM. This is especially true in the area of data integration and sharing, either between diffe-

rent European research infrastructures or between research infrastructures and other stakeholders in the field of PM. In this context especially important ESFRI infrastructures are BBMRI (Biobanking and BioMolecular Resources Research Infrastructure), ELIXIR (European Life Science Infrastructure for Biological Information), EATRIS (European Advanced Translational Research Infrastructure in Medicine) and ECRIN (European Clinical Research Infrastructure Network).

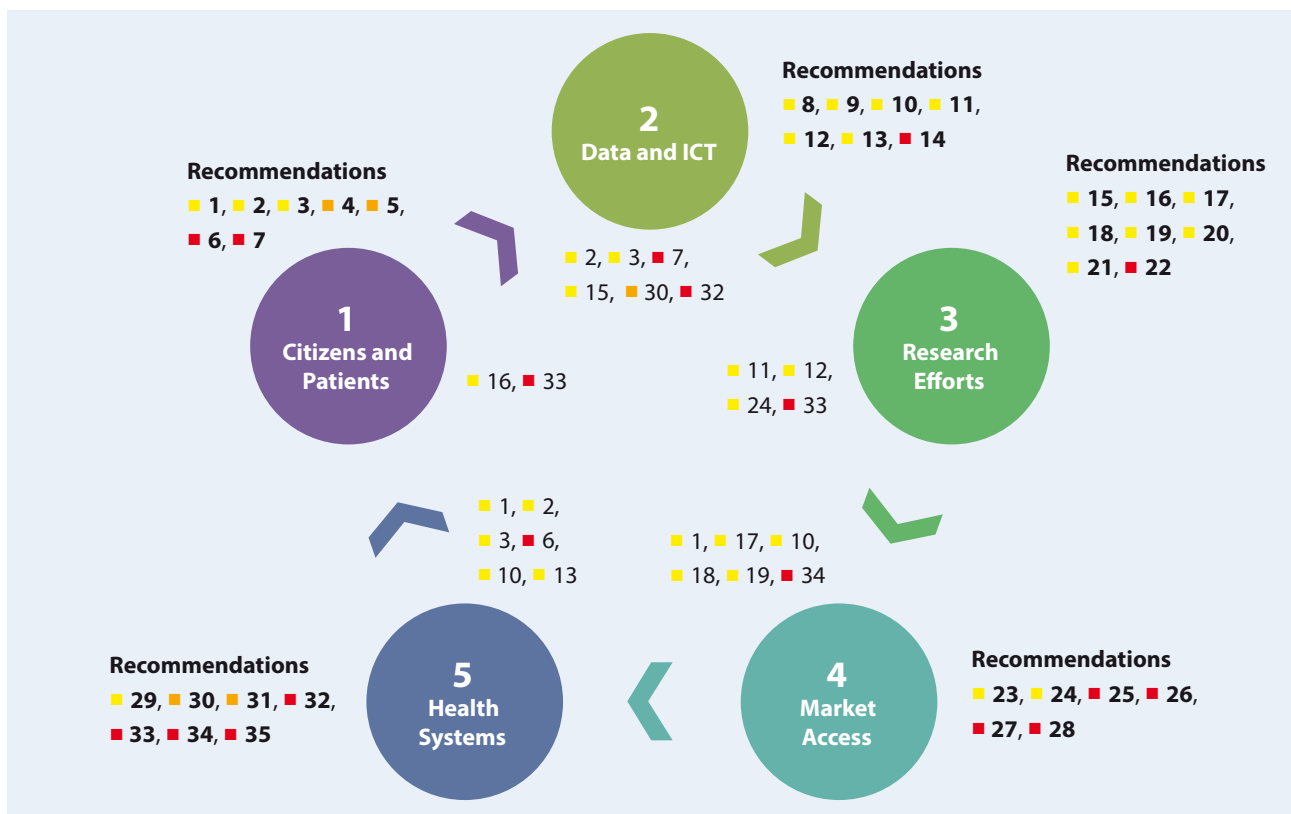


Figure 3 The SRIA recommendations. The 35 recommendations of the five challenges are outside the circle. Some of these recommendations are also related to other challenges, therefore they are shown again within the circle. Furthermore, there are manifold interrelations between the five challenges; these have not been indicated in order to keep the clearness of the figure.

6) Proposed Research Activities to foster Personalised Medicine

Below are a number of suggestions for PM research activities and their expected impact without a prioritisation. These are based on PerMed research recommendations and examples of national measures aimed at the development of PM approaches. In parallel other strategic documents concerning PM implementation and research

activities are published or in preparation, among others the Horizon 2020 work group 'Personalized medicine, mechanisms, systems medicine, biomarkers and diagnostics' (Annex B, 19), the EAPM Research Road Map (in preparation) or the CASyM Road Map 'Implementation of Systems Medicine across Europe (Annex C, 3).

ACTION PROPOSED	EXPECTED IMPACT
Research on the assessment of PM in comparison with current models, e.g. in terms of 'demonstrators' to prove the effectiveness and sustainability of such approaches within health systems.	Information for decision makers, providers and the public to support the implementation of promising PM approaches.
Research on economic aspects at an early stage of innovative PM approaches.	Assessments of whether PM approaches already at an early stage of development are economically appropriate. New tools for the economic assessment of PM.
Collaboration of funding organisations with healthcare providers to identify diseases or group of diseases as a paradigm for PM and fund research on relevant health economics related to PM, e.g. for mental disorders and intellectual deficit.	Demonstrator project for the added-value of PM – improvement of diagnosis and decrease of costs by the use of high throughput technologies compared to conventional approaches.
Feasibility studies on health data cooperatives (HDCs) with an assessment of ethical, legal and social implications comparing different European health systems.	Sound and rational basis for decision-makers in health policy and providers.
Interdisciplinary research on ethical, legal and social aspects of PM.	Generating empirical data to discuss and decide about ethical, legal and social aspects of PM. Basis for the incorporation of such results in the systematic early dialogue on research and PM implementation.
Research on the adequacy of current regulatory pathways and development of new regulatory and legal frameworks for PM/healthcare.	Adapted regulations and standards to support innovation as well as fast and safe access to PM approaches.
Research to investigate different trial designs and their results; whether they have been successful in addressing the question they were designed to answer, whether they have been used for marketing authorisation purposes and if they have been successful in the applications.	Such an investigation would inform the regulatory process and the drug development process.
Research on tools for more personalised healthcare and rehabilitation.	Paving the way for providers to implement standardised, high quality and cost-effective healthcare and rehabilitation.

ACTION PROPOSED	EXPECTED IMPACT
Establishing an open data integration platform for PM.	Already existing software applications and tools have to be integrated into a security framework. The challenge is to bring together multiple applications and multiple data standards to allow a dataflow in a meaningful and secure way.
Reclassification of diseases at the molecular level for optimisation of therapeutic strategies.	Development of new and more effective diagnostic and treatment tools.
Modelling of health and diseases by interdisciplinary research projects, for example via systems medicine and in silico modelling/simulation approaches.	The aim is the representation of health and disease based on the simultaneous consideration of clinical, biological, imaging, cognitive and behavioural data. Revelation of the characteristics of the cause of the disease and the patient's personal constitution.
Support clinical validation of pharmacogenomics approaches that integrate age and gender considerations into genetically divergent populations.	The findings will accelerate the translation from basic research biomarker development to their efficient implementation, optimise therapies, thereby reducing inappropriate drug use, and reduce adverse drugs events. The development of equitable PM approaches for all patients, including woman, the elderly, children and overlooked populations, will be promoted.
Research on phenotype–genotype correlations on existing data and specifically established cohorts.	Optimal use of national resources for established cohorts; better prediction of clinical outcome in trials.
Correlation studies of phenotypic evolution of diseases in subgroups or individuals within longitudinal cohorts, for example in terms of poly-pathologies, socio-economic inequalities and access to care.	Evidence on the impact of the environment on the evolution of diseases. Support for decision makers and providers to set up public health measures for disease prevention and improvement of the performance of health systems.
Develop inexpensive and rapid test systems to produce a short development cycle for diagnosis and therapy, e.g. 'living test tubes'.	A better understanding of disease mechanisms related to genetic variants and the design of biopharmaceutical compounds, biologics, and medical devices with the desired biological effect. Further improvement of stratification of patients for clinical trials.

ACTION PROPOSED	EXPECTED IMPACT
Studies of genomic variants in European and non-European populations.	Stratification of patients into homogenous groups thereby increasing validity of clinical trials. Earlier diagnostic markers would support the assessment of prognosis, monitoring and identification of the most effective treatment for a given group of patients.
Development and validation of precision tools and tests for accurate PM oriented diagnosis.	Tests and other tools for optimised and cost-effective diagnosis and treatment.
Research to monitor long term treatments.	Optimised long-term treatments, e.g. in terms of toxicity.
Optimise individual drug therapies and poly-pharmacy especially in the case of multi-morbidity.	More specific and effective drug therapies particularly for the multi-morbid and elderly. Reduction of drugs prescribed, side-effects and costs through fewer and more specific therapies.
Multi-parametric assessment of the responsiveness to preventive or therapeutic vaccines by subgroups or individuals.	Elaboration and validation of predictive tools to implement PM in vaccination.
Research on drug interaction (drug–drug and drug–gene).	Optimised therapies with minimised side-effects.
Clinical validation of candidate biomarkers for PM.	Increasing the number of well validated and robust biomarkers with proven stratification potential ready for clinical routine.

Furthermore, all research activities have to be supported by adapted frameworks in Europe as well as at the national level in terms of health systems, insurers, providers, and regulatory bodies. Additionally the responsible authorities need to put in place appropriate regulatory frameworks, recognise and overcome the normative and ethical challenges and, crucially, ensure that the patients' and citizens' needs and interests are implemented (see also Challenges 1, 2, 4 and 5).

7) A glimpse into the future

The implementation of PM is a major objective in Europe and beyond. A substantial amount of research has been done already that has led to many innovative findings. However, evidence for real benefits to national health systems remains scarce. Results must now be consolidated and pilot studies conducted so that PM can be implemented into everyday healthcare. This is an on-going process in Europe as well as in each Member State, demonstrated for example by the recent EC call for 'Piloting personalised medicine in health and care systems'. Also the European Institute of Innovation and Technology on Health ([EIT Health](https://www.eit-health.eu)) will surely add to the development of PM as it is leveraging the expertise of more than 140 leading organizations spanning key areas of healthcare such as pharma, medTech, payers, research institutions and universities (<https://www.eit-health.eu>).

In parallel several national strategic programmes have been set up or are in preparation (e.g. [Canada](#), France, [Germany](#), [United Kingdom](#) and [United States](#)) and/or specific funding measures on PM have been published or are being prepared (e.g. [Finland](#), France, Ireland, [Luxembourg](#), [Netherlands](#) and [Spain](#)).

Facing and overcoming the challenges listed in this SRIA will significantly contribute to global research and innovation as well as to personal health and care. In the global context Europe has the potential to be a world centre for research and development and to take a global lead in the implementation of personalised prevention, diagnosis and therapy. This calls for appropriate governance strategies at the European level as it challenges the way in which healthcare systems worldwide are currently set up.

To promote optimal PM implementation for the benefit of the citizens of Europe and beyond, details of national strategic initiatives, research activities and best practices along the entire value chain have to be exchanged and, where feasible, reasonably aligned. This can be achieved

through adequately funded and governed European transnational research.

Unfortunately independent international communication platforms – especially for funders, policy makers and healthcare providers – are scarce. Given that stakeholders originate from highly diverse fields and in some cases lack a strong tradition of collaboration, new networking structures need to be built. Thus transnational European research consortia might be the nucleus for an International Alliance for Personalised Medicine. Such an alliance, maybe on the basis of a coordination and support action (CSA) for PM, could include other countries at the forefront of innovative and extensive research funding, such as the US, Japan or Canada. In addition, it will be crucial to also include developing countries facing a rapid increase in the incidence of chronic diseases, as is the case, for example, for diabetes in Mexico, India and Brazil. Besides giving access to new perspectives, approaches and research opportunities this could also open new business opportunities for these countries as well as for Europe.

Such transnational collaborative research actions that implement at least some of the recommendations identified by this SRIA would undoubtedly add value. One suitable instrument in the European context could be an ERA-Net Cofund on PM with training and outreach modules as well as support for cross-sectional projects. Such a cross-border research funding scheme would be synergetic and complementary to on-going ERA-NETs (for example ERA-Nets such as [E-Rare](#), [TRANSCAN](#) or [ERA-CoSysMed](#)) and international research consortia (e.g. [IRDiRC](#), [ICGC](#) or [iHEC](#)), and could collaborate closely with existing European platforms and research structures such as the ESFRIs. Such European initiatives could be a good starting point for further international activities which would generate enough impact to enable the implementation of PM routinely in the clinic and in health as a whole.

8) Authors and Experts consulted

A. Authors

(PerMed partners and Round Table participants)

Aguirre Maria, Basque Ministry of Health, Spain | Alon Irit, Chief Scientist Office, Israeli Ministry Of Health, Israel | Baanante Ignacio, National Institute of Health Carlos III, Spain | Ballensiefen Wolfgang, Project Management Agency, Part of the German Aerospace Center, Germany | Benzimra Emmanuelle, European Personalized Medicine Association, Luxembourg | Berling Christine, The French National Cancer Institute, France | Brand Angela, University of Maastricht, The Netherlands | Brand Helmut, University of Maastricht, The Netherlands and International Forum Gastein, Austria | Buonaguro Luigi, Ministry of Health and National Cancer Institute, Italy | Busshoff Ulrike, Project Management Agency, Part of the German Aerospace Center, Germany | Cesario Alfredo, Ministry of Health, Italy | Claude-Marie Marx, Fonds National de la Recherche, Luxembourg | De Andres Medina Rafael, National Institute of Health Carlos III, Spain | Gabaldi Paola, Ministry of Health, Italy | Garel Pascal, The European Hospital and Healthcare Federation, Belgium | Grognet Jean-Marc, French Alternative Energies and Atomic Energy Commission, Life Science Division, France | Guglielmi Gaetano, Ministry of Health, Italy | Gutiérrez-Ibarluzea Iñaki, Basque Office for Health Technology Assessment, Spain | Hackenitz Erica, The Netherlands Organisation for Health Research and Development, The Netherlands | Hadlington Simon, SRIA editorial, Scientific Writer, United Kingdom | Horgan Denis, European Alliance on Personalized Medicine, Belgium | Israeli Avi, Chief Scientist Office, Israeli Ministry of Health, Israel | Jungwirth Rebecca, Hoffmann-La Roche Ltd, Switzerland | Kuhlmann Katja, Project Management Agency, Part of the German Aerospace Center, Germany | Lange Bodo, Alacris Theranostics GmbH, Germany | Lasko Paul, Canadian Institutes of Health Research, Institute of Genetics, Canada | Leyens Lada, University of Maastricht,

The Netherlands | Martin Natalia, The French National Research Agency, France | Michel Klaus-Peter, Federal Ministry of Education and Research, Germany | Mitreiter Richard, Project Management Agency, Part of the German Aerospace Center, Germany | Morrow Anne, Canadian Institutes of Health Research, Institute of Cancer Research, Canada | Nopitsch-Mai Cornelia, Federal Institute for Drugs and Medical Devices, Germany | Nowak Frédérique, The French National Cancer Institute, France | Philippe Isabelle, French Alternative Energies and Atomic Energy Commission, Life Science Division, France | Plum Achim, Siemens AG Austria, Austria | Preuss Ute, Project Management Agency, Part of the German Aerospace Center, Germany | Richer Etienne, Canadian Institutes of Health Research, Institute of Genetics, Canada | Robbins Stephen, Canadian Institutes of Health Research, Institute of Cancer Research, Canada | Siest Gerard, European Society of Pharmacogenomics and Personalised Therapy, France | Steinhäusen Kristin, European Science Foundation, France | Stingl Julia, Federal Institute for Drugs and Medical Devices, Germany | Vurio Eero, University of Helsinki, Biocenter Finland, Finland | Walsh Desmond, Medical Research Council, United Kingdom | Weller Andreas, Project Management Agency, Part of the German Aerospace Center, Germany

B. Experts consulted by PerMed

(interviews and reviewing the SRIA)

Anhoury Pierre, Accenture Life Sciences Europe, Africa, Middle East and Latin America, France | Artiguenave François, French Alternative Energies and Atomic Energy Commission, Life Science Division, France | Balling Rudy, Luxembourg Centre for Systems Biomedicine, Luxembourg | Banken Reiner, Institut National d'Excellence en Santé et en Services Sociaux, Canada | Benhabiles Nora, French Alternative Energies and Atomic

Energy Commission, Life Science Division, France | Berns Anton, Netherlands Cancer Institute, The Netherlands | Bertero Michela, Center for Genomic Regulation, Spain | Blomberg Niklas, Director of ELIXIR and AstraZeneca R&D Mölndal, Sweden | Bungener Martine, Centre de Recherche Médecine, Sciences, Santé, France | Cambon-Thomsen Anne, University Toulouse III, France | Campo Elías, University of Barcelona, Spain | Chlebus Magda, European Federation of Pharmaceutical Industries and Associations, Belgium | Dauben Hans-Peter, German Institute of Medical Documentation and Information, Germany | De Boer Pim, HuMedSci Consultancy, The Netherlands | Del Barrio Seoane Jaime, Instituto Roche, Spain | Deleuze Jean François, Centre National de Génotypage, France | Denèfle Patrice P., Roche Institute of Research & Translational Medicine, France | Fode Peder, Danish Council for Strategic Research, Denmark | Fraga Mario Fernandez, University of Oviedo | Geissler Jan, European Patients' Academy on Therapeutic Innovation, Belgium | Hafen Ernst, ETH Zurich, Switzerland | Hudson Tom, Ontario Institute for Cancer Research, Canada | Huntsman David, University of British Columbia, Canada | Kinkorová Judita, Technology Centre ASCR, Czech Republic | Kirschner Marc, CASyM coordinator, Forschungszentrum Jülich GmbH, Germany | Lange Stefan, Institute for Quality and Efficiency in Healthcare, Germany | Larue Cathe-

rine, Integrated Biobank of Luxembourg, Luxembourg | Lauterberg Jörg, Institute for Quality and Efficiency in Healthcare, Germany | Lee David K., Health Canada, Canada | Lodbrok Olaf, Health Analytics EMEA/LA ELSEVIER, Germany | MacKenzie Alex, Children Hospital of Eastern Ontario, Canada | Marlow Mirella, National Institute and Care Excellence, United Kingdom | Mavris Maria, EURORDIS Rare diseases Europe, Belgium | Meade Nick, Genetic Alliance UK, United Kingdom | Ozbek Ugur, Istanbul University, Turkey | Papaluca Amati Marisa, European Medicines Agency, United Kingdom | Pazzagli Mario, University of Florence, Italy | Prasad Krishna, Medicines and Healthcare Products Regulatory Agency, United Kingdom | Redekop Ken, Erasmus Universiteit Rotterdam, The Netherlands | Rütther Alric, Institute for Quality and Efficiency in Healthcare, Germany | Serrano Luis, Centre for Genomic Regulation, Spain | Stupka Elia, San Raffaele Scientific Institute, Italy | Sudbrak Ralf, Max Planck Institute for Molecular Genetics, Germany | Tabuteau Didier, Chaire Santé de l'Institut d'Études Politiques, France | Thürmann Petra, University Witten/Herdecke, Germany | Valencia Alfonso, Spanish National Cancer Research Centre, Spain | Van Schaik Ron, Erasmus MC Rotterdam, The Netherlands | Von Kalle Christof, National Center for Tumor Diseases Heidelberg, Germany | Zatloukal Kurt, Medical University Graz, Switzerland

C. Lectures at PerMed workshops

- PerMed workshop Berlin, March 2014: <http://www.permed2020.eu/1408.php>
- European Health Forum Gastein (EHFG), October 2014: <http://www.permed2020.eu/1420.php>
- **Banken** Reiner, Institut National d'Excellence en Santé et en Services Sociaux, Canada: [Health Technology Assessment for adding Value to Innovation](#), Berlin March 2014
- **Boorsma** André, Netherlands Organisation for Applied Scientific Research, The Netherlands: [Best Practice Example – Nutrition](#), EHFG Forum 4, October 2014
- **Brand** Helmut, University of Maastricht, The Netherlands: [Personalised Medicine for the European Citizens](#), Berlin March 2014
- **Ehmann** Falk, European Medicines Agency, United Kingdom: [Early Dialogue and Regulatory Aspects](#), EHFG Forum 4, October 2014
- **Hajnal** Ferenc, University of Budapest and European Union of General Practitioners, Hungary: [The General Practitioner's Perspective](#), EHFG Forum 4, October 2014
- **Immonen-Charalambous** Kaisa, European Patients' Forum, Belgium: [Citizens' Perspective and Needs](#), EHFG Forum 4, October 2014
- **Klein** Christoph, University Munich, Germany: [Best Practice Example – Rare Diseases](#), EHFG Forum 4, October 2014
- **Meulien** Pierre, Genome Canada, Canada: [Towards Implementing Personalized Medicine in Canada](#), Berlin March 2014
- **Norstedt** Irene, Unit Innovative and Personalised Medicine, Research & Innovation DG, European Commission, Belgium: [Personalised Medicine: an EU Perspective](#), Berlin March 2014
- **Andreu** Antonio L., Instituto de Salud Carlos III, Spain: [A Hospital's Perspective](#), EHFG Forum 4, October 2014
- **Vayena** Effy, University of Zurich, Switzerland: [Legal and Ethical Aspect](#), EHFG Forum 4, October 2014

Summaries of the four Session Presentations at the Workshop I in Berlin, March 2014, <http://www.permed2020.eu/1408.php>:

1. [Basic Research and New technologies](#)
2. [Translational Research](#)
3. [Regulation, Reimbursement & Market Access](#)
4. [Health \(care\) Systems and Personalised Medicine](#)

9) Annexes





Annex A: PerMed Recommendations




All recommendations have been colour-coded according to the activities referred to, which are grouped into three broad areas. However, many recommendations do have a share in two or sometimes all three types of activity (see also figure 3 in chapter 5). In these cases, the recommendation has been assigned to the activity deemed to have the major share.

The colour-coding is as follows:








-  Recommendations on biomedical, health-related ICT and health research
-  Recommendations on humanities and social sciences research
-  Recommendations to improve the framework for implementing PM (e.g. economic, organisational, regulatory, ethical, legal and social)

Challenge 1 – Developing Awareness and Empowerment

-  1. Provide further evidence for the benefit delivered by PM to health systems.
-  2. Develop and promote models for individual responsibility, ownership and sharing of personal health data.
-  3. Develop mobile health applications to maximise engagement of patients with their treatment pathways and track the safety and effectiveness of these interventions.
-  4. Understand how the changes related to PM will impact public health and ensure they translate directly to benefits for individual citizens and society.

-  5. Improve communication and education strategies to increase patient health literacy.
-  6. Incorporate patient participation in the healthcare system and increase the patient's role in all phases of research and development.
-  7. Develop common principles and legal frameworks that enable sharing of patient-level data for research in a way that is ethical and acceptable to patients and the public.

Challenge 2 – Integrating Big Data and ICT Solutions

-  8. Promote strategies to make sense of 'big data'.
-  9. Develop and encourage the fast uptake of technologies for data capture, storage, management and processing.
-  10. Promote the development of high quality sustainable databases including clinical, health and well-being information.
-  11. Support translational research infrastructures and enforce data harmonisation fostered by specific ICT infrastructures designed to the health data.
-  12. Support analytical methods and modelling approaches to develop new disease models, e.g. 'Computerised Twins' or a 'Virtual Patient'.
-  13. Develop new decision support tools and methodologies of ICT to analyse and interpret data in order to support physicians in their decision-making process.
-  14. Create a European 'big data' framework and adapt legislation.

Challenge 3 – Translating Basic to Clinical Research and Beyond

- 15. Develop methods to better integrate and evaluate the information provided by genomic, epigenetic, transcriptomic, proteomic, metabolomic and microbiome analyses.
- 16. Support research in preclinical models to validate hypotheses resulting from molecular analyses of patient samples and treatment outcomes.
- 17. Promote collaborative pre-competitive and trans-disciplinary research in all disease areas to gain trustworthy and objective information.
- 18. Instigate a European-wide biomarker evaluation and validation process.
- 19. Promote longitudinal studies in the areas of PM.
- 20. Support development of new clinical trial designs and promote integration with concomitant preclinical testing.
- 21. Re-classify diseases at the molecular level.
- 22. Develop suitable funding models to enable cross-sector working in PM research.

Challenge 4 – Bringing Innovation to the Market

- 23. Formalise a risk-based approach for the evaluation of PM.
- 24. Optimise individual drug therapies and poly-pharmacy especially in the case of multi-morbidity.
- 25. Support research on an adequate regulatory and legal framework for PM.

- 26. Encourage a systematic early dialogue between innovators, patients and decision-makers throughout all regulatory steps to provide guidance and clarity.
- 27. Facilitate partnerships and innovation networks to encourage cross-disciplinary and cross-border collaboration in research and development using an 'Open Innovation' approach.
- 28. Provide support and guidance for companies to enter the market for PM with sustainable business cases.

Challenge 5 – Shaping Sustainable Healthcare

- 29. Support health economics research of PM to support decision makers.
- 30. Develop prospective surveillance systems for personal health data that facilitate accurate and on-going assessment of highly dynamic health information across the life course.
- 31. Develop training programmes on PM for health professionals.
- 32. Encourage a citizen-driven framework for the adoption of electronic health records.
- 33. Promote engagement and close collaboration between patients, stakeholders and healthcare actors across sciences, sectors and borders.
- 34. Develop a framework for pricing and reimbursement for PM that ensures equitable access for all patients – regardless of economic or geographic status – and is sustainable for health systems.
- 35. Develop an optimised overall healthcare financing strategy.

Annex B: Strategic Reports on Personalised Medicine

1. European Commission. Use of '-omics' technologies in the development of personalised medicine. Brussels: European Commission, 2013.
2. Technology Strategy Board. Stratified Medicines in the UK, Vision and Roadmap. Swindon: Technology Strategy Board, October 2011.
3. BMBF. Personalised Medicine – Action Plan, a new approach in research and healthcare. Germany: Federal Ministry of Education and Research (BMBF), February 2013.
4. Claeys A, Vialatte J-S. Advances in genetics: towards a Precision Medicine? Technological, social and ethical scientific issues of personalised medicine. [Les progrès de la génétique : vers une médecine de précision? Les enjeux scientifiques, technologiques, sociaux et éthiques de la médecine personnalisée], January 2014. Available at: <http://www.ladocumentationfrancaise.fr/rapports-publics/144000117/>
5. Testori Coggi P. A European view on the future of personalised medicine in the EU. Eur J Public Health 2011; 21(1):6–7. doi: 10.1093/eurpub/ckq202
6. European Commission. Europe 2020, the Digital Agenda, the Innovation Union and Horizon 2020. Available at: <http://ec.europa.eu>
7. European Science Foundation. Forward Looks. Personalised Medicine for the European Citizen. Towards more precise medicine for the diagnosis, treatment and prevention of disease (iPM), 2012.
8. EAPM. Innovation and Patient Access to Personalised Medicine, 2013. Available at: <http://euapm.eu/wp-content/uploads/2012/07/EAPM-REPORT-on-Innovation-and-Patient-Access-to-Personalised-Medicine.pdf>
9. Ruxandra Draghia-Akli, "Enabling personalized medicine in Europe: a look at the European Commission's funding activities in the field of personalized medicine research", Future Medicine, *Personalized Medicine* (2012) 9(2), 151–155
10. Brand A, Lal JA. European Best Practice Guidelines for Quality Assurance, Provision and use of Genome-based Information Technologies: the 2012 Declaration of Rome. Drug Metabolism and Drug Interaction Studies 2012; 27(3): 177–82.
11. European Medicines Agency. Pilot project on Adaptive Licensing. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500163409.pdf
12. iNNOVAHEALTH. Building on Open Innovation ecosystem in Europe for Healthcare, October 2012. Available at: <http://www.enterpriseisrael.org.il/wp-content/uploads/2013/04/Innovahealth-Report.pdf>
13. European Commission. Staff Working Document on Personalised Medicine, http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf
14. Life and health sciences horizon panel. A report on business opportunities in Personalised Medicine in Northern Ireland by the Northern Ireland Science Industry Panel of the Department of Enterprise, Trade and Investment. <http://archive-org.com/page/1417720/2013-02-17/http://www.matrix-ni.org/e-mail-sign-up/4571127613>
15. Nuffield Council of Bioethics. Report on the ethics of personalised medicine: "Medical profiling and online medicine: the ethics of 'personalised healthcare' in a consumer age". <http://nuffieldbioethics.org/wp-content/uploads/2014/07/Personalised-health-care-short-guide-for-web.pdf>
16. Stratified Medicine Innovation Platform. Vision and Roadmap, <https://connect.innovateuk.org/documents/2843120/3724280/Stratified+Medicines+Roadmap.pdf/fbb39848-282e-4619-a960-51e3a16ab893>
17. "Towards a balanced value business model for personalized medicine: an outlook", C. Koelsch, J. Przewrocka and P. Keeling; Pharmacogenomics (2013), 14(1), 89–102.
18. World Health Organization. Priority Medicine for Europe and the World Update Report, 2013, www.who.int/medicines/areas/priority_medicines/en/
19. European Commission. Advice for 2016/2017 of the Horizon 2020 Advisory Group for Societal Challenge 1, "Health, Demographic Change and Wellbeing", July 2014: <http://ec.europa.eu/transparency/regexpert/index.cfm?do=groupDetail.groupDetail&groupID=2942>

20. PerMed article: Lada Leyens, Erica Hackenitz, Denis Horgan, Etienne Richer, Angela Brand, Ulrike Bußhoff and Wolfgang Ballensiefen on behalf of the PerMed consortium: CSA PerMed: Europe's Commitment to Personalised Medicine; EuroHealth incorporating Euro Observer Vol.20, No.3, 2014: [http://www.per-med2020.eu/media/EuroHealth_PerMed\(1\).pdf](http://www.per-med2020.eu/media/EuroHealth_PerMed(1).pdf)
21. PerMed article: Horgan D, Jansen M, Leyens L, Lal JA, Sudbrak R, Hackenitz E, et al. An index of barriers for the implementation of personalised medicine and pharmacogenomics in Europe. Public Health Genomics 2014;17:287–98. An Index of Barriers for the Implementation of Personalised Medicine and Pharmacogenomics in Europe; Public Health Genomics 2014; 17: 287–298: http://www.permed2020.eu/media/PHGJ_Barriers_PM_in_Europe.pdf
22. Leyens L, Horgan D, Lal JA, Steinhausen K, Satya-moorthy K, Brand A. Working towards personalization in medicine: main obstacles to reaching this vision from today's perspective. Pers Med 2014;11:641–9.

Annex C: Further References

1. Brand A, Lal JA; Public Health Genomics European Network. European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies: the 2012 Declaration of Rome. Drug Metabol Drug Interact. 2012;27(3):177–82.
2. CALLIOPE EU eHealth Interoperability Roadmap. Available in: [http://www.ehgi.eu/Download/European%20eHealth%20Interoperability%20Roadmap%20\[CALLIOPE%20-%20published%20by%20DG%20INFSO\].pdf](http://www.ehgi.eu/Download/European%20eHealth%20Interoperability%20Roadmap%20[CALLIOPE%20-%20published%20by%20DG%20INFSO].pdf)
3. CASyM Roadmap: "Implementation of Systems Medicine across Europe": https://www.casym.eu/lw_resource/datapool/items/item_328/roadmap_1.0.pdf
4. Chute CG et al. Some experiences and opportunities for big data in translational research. Genet Med. 2013 Oct;15(10):802–9.
5. Commission Recommendation of 2 July 2008 on cross-border interoperability of electronic health record systems (notified under document number C(2008) 3282).
6. Directive on patients' rights in cross-border healthcare (2011/24/EU) and Overview of the national laws on electronic health records in the EU Member States and their interaction with the provision of cross-border eHealth services Final report and recommendations Type Contract 2013 63 02. Available in: http://ec.europa.eu/health/ehealth/docs/laws_report_recommendations_en.pdf
7. Dranitsaris G, et al. What is a new drug worth? An innovative model for performance-based pricing. Eur J Cancer Care (Engl). 2014 Sep 25.
8. Godman B, et al. Personalizing healthcare: feasibility and future implications. BMC Med. 2013 Aug 13;11:179.
9. Goldman M. The innovative medicines initiative: a European response to the innovation challenge. Clin Pharmacol Ther. 2012 Mar;91(3):418–25.
10. Golubnitschaja O et al. Position paper of the EPMA and EFLM: a global vision of the consolidated promotion of an integrative medical approach to advance healthcare. EPMA J. 2013 May 10;4(1):12.
11. Haycox A, et al. Through a glass darkly: economics and personalised medicine. Pharmacoeconomics. 2014 Nov;32(11):1055–61.
12. Henshall C, Schuller T; HTAi Policy Forum. Health technology assessment, value-based decision making, and innovation. Int J Technol Assess Healthcare. 2013 Oct;29(4):353–9.
13. Hutton J, Trueman P, Henshall C. Coverage with evidence development: an examination of conceptual and policy issues. Int J Technol Assess Healthcare. 2007 Fall;23(4):425–32.
14. Klemp M, Frønsdal KB, Facey K; HTAi Policy Forum. What principles should govern the use of managed entry agreements? Int J Technol Assess Healthcare. 2011 Jan;27(1):77–83.
15. Leopold C, et al. Personalised medicine as a challenge for public pricing and reimbursement authorities – A survey among 27 European countries on the example of trastuzumab. Health Policy. 2013 Dec;113(3):313–22.

16. Merelli I et al. Managing, analysing, and integrating big data in medical bioinformatics: open problems and future perspectives. *Biomed Res Int*. 2014; 2014:134023.
17. Raftery J. Value based pricing: can it work? *BMJ*. 2013 Oct 11;347:f5941.
18. Rosenkötter N, Vondeling H, Blancquaert I, Mekel OC, Kristensen FB, Brand A. The contribution of health technology assessment, health needs assessment, and health impact assessment to the assessment and translation of technologies in the field of public health genomics. *Public Health Genomics*. 2011;14(1):43–52.
19. Said M, Zerhouni E. The role of public-private partnerships in addressing the biomedical innovation challenge. *Nat Rev Drug Discov*. 2014 Nov;13(11):789–90.
20. Singer E. Personalized medicine prompts push to redesign clinical trials by, *Nature Medicine* 11, 462 (2005): <http://www.nature.com/nm/journal/v11/n5/full/nm0505-462a.html>
21. Teutsch SM et al. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med*. 2009 Jan;11(1):3–14.
22. The European eHealth Governance Initiative (ehgi): <http://www.ehgi.eu/Pages/default.aspx?articleID=1>
23. United Nations (Draft resolution (A/67/L.36) Global health and foreign policy 2012. Available in: http://www.un.org/ga/search/view_doc.asp?symbol=A/67/L.36&referer=http://www.un.org/en/ga/info/draft/index.shtml&Lang=E)
24. Ferrario A. and Kanavos P.: Managed entry agreements for pharmaceuticals: The European experience: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/mea_report_en.pdf
25. Garrison L. and Carlson J.: Performance-Based Risk-Sharing Arrangements for Drugs and other Medical Products: https://depts.washington.edu/pbrs/PBRS_slides.pdf
26. Coulton L. et al.: Risk-sharing Schemes Worldwide: A Landscape Analysis of Health Outcomes based Reimbursement Agreements: http://www.ispor.org/research_pdfs/35/pdffiles/PHP15.pdf
27. Good C.B.: Pharmaceutical Risk Sharing Agreements: http://www.amsus.org/wp-content/uploads/2014/05/RxRiskSharingAgreements_Good1.pdf
28. Malentacchia F. et al., Is laboratory medicine ready for the era of personalized medicine? A survey addressed to laboratory directors of hospitals/academic schools of medicine in Europe. <http://www.efcclm.org/files/efcc/2.16%20CCLM-2015-Malentacchi.pdf>

Annex D: References and Links

- Amgen: http://www.amgen.com/pdfs/misc/vpk_biomarker_diagnostics.pdf
- BBMRI-ERIC: www.bbmri-eric.eu
- CASyM: <https://www.casym.eu/>
- EAPM: <http://euapm.eu/>
- EATRIS: www.eatris.eu/about/organisation.html
- EBE: <http://www.ebe-biopharma.eu/>
- EC: http://ec.europa.eu/health/human-use/personalised-medicine/index_en.htm
- EC: http://ec.europa.eu/research/health/policy-issues-personalised-medicine_en.html
- EC: http://ec.europa.eu/research/health/policy-issues-pm-conferences-workshops_en.html
- ECRIN: www.ecrin.org
- EDCA: www.edc-alliance.eu/
- EDMA: <http://www.edma-ivd.be/index.php?page=About-Us>
- EFLM: [European Federation of Clinical Chemistry and Laboratory Medicine](http://www.efpia.eu)
- Efpia: www.efpia.eu/topics/innovation/personalised-medicines
- EHR4CR: www.ehr4cr.eu
- EIT Health: <https://www.eit-health.eu/>
- ELIXIR: www.elixir-europe.org
- EMA: www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000347.jsp&mid=WC0b01ac05800baeda
- EPAMED: www.epemed.org/online/www/content2/104/1577/ENG/index.html#ribbon
- EPMA: www.epmanet.eu/
- E-RARE: www.erare.eu/
- ESF: www.esf.org/uploads/media/Personalised_Medicine.pdf
- ESFRI: http://ec.europa.eu/research/infrastructures/index_en.cfm?pg=esfri
- ESPT: <http://www.esptnet.eu/S1/Home>
- EUAPM: <http://euapm.eu/>
- Eucomed: <http://www.eucomed.be/about-us>
- EUDAT: www.eudat.eu
- EU-Openscreen: www.eu-openscreen.eu
- EuroBioForum: www.eurobioforum.eu/10/home/
- Euro-Biolmaging: www.eurobioimaging.eu
- EuropaBio: <http://www.europabio.org/about-europabio>
- FDA: www.fda.gov/ScienceResearch/SpecialTopics/PersonalisedMedicine/ucm372544.htm
- FDA: www.Personalisedmedicinebulletin.com/category/fda-guidelines/
- HealthTIES: <http://vrr.healthties.eu/>
- http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf
- <http://jama.jamanetwork.com/article.aspx?articleid=1691756>
- ICGC: <https://icgc.org>
- IFCC: [International Federation of Clinical Chemistry and Laboratory Medicine](http://www.ifcc.org)
- IMI: www.imi.europa.eu/
- IMI 2: Strategic Research Agenda: www.imi.europa.eu/sites/default/files/uploads/documents/IMI2_SRA_March2014.pdf
- Infrafrontier: <https://www.infrafrontier.eu>
- Instruct: <https://www.structuralbiology.eu>
- IRDiRC: www.irdirc.org
- NeIC: <http://neic.nordforsk.org/>
- NIH: <http://ghr.nlm.nih.gov/handbook/genomicresearch/pharmacogenomics>
- PerMed Forum 4 at the European Health Forum Gastein, October 2014: <http://www.permed2020.eu/1420.php>
- PerMed Workshop I in Berlin, March 2014: <http://www.permed2020.eu/1408.php>
- PerMed: www.permed2020.eu/
- PERSOMED: <http://www.perso-med.eu/>
- PMC: www.Personalisedmedicinecoalition.org
- PMC: www.Personalisedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_case_for_Personalised_medicine.pdf
- p-medicine project: www.p-medicine.eu/
- PREDICT: www.predictconsortium.eu/
- TRANSCAN: <http://www.transcanfp7.eu/transcan/index.php>
- UIC (University of Illinois at Chicago): <http://healthinformatics.uic.edu/infographics/when-healthcare-and-computer-science-collide/>

Annex E: Abbreviations and Acronyms

BBMRI: Biobanking and BioMolecular Resources Research Infrastructure

CASyM: Coordinating Action Systems Medicine

EAPM: European Alliance for Personalised Medicine

EATRIS: European Advanced Translational Research Infrastructure

EBE: European biopharmaceutical enterprises

EC: European Commission

ECRIN: European Clinical Research Infrastructure Network

EDMA: European Diagnostic Manufacturers Association

EHR4CR: Electronic Health Records for Clinical Research

EIT Health: European Institute of Innovation and Technology on Health

ELIXIR: European Life Science Infrastructure for Biological Information

ELSI: Ethical, Legal and Societal Issues

EMA: European Medicines Agency

EPAMED: The European Personalised Medicine Association

ERIC: European Research Infrastructure Consortium

ESFRI: European Strategy Forum for Research Infrastructures

ESPT: European Society of Pharmacogenomics and Personalised Therapy

EU: European Union

Eucomed: represents the medical technology industry in Europe

EU-Openscreen: European Infrastructure of Open Screening Platforms for Chemical Biology

Euro-BioImaging: European Biomedical Imaging Infrastructure

EuropaBio: European Association for Bioindustries

HTA: Health Technology Assessment

ICGC: International Cancer Genome Consortium

ICT: Information and Communication Technology

Infrafrontier: European Infrastructure for Phenotyping and Archiving of Model Organisms

Instruct: An Integrated Structural Biology Infrastructure for Europe

iPS: induced pluripotent stem cells

IPTS: Institute for Prospective Technological Studies

IRDiRC: International Rare Diseases Research Consortium

MEP: Member of European Parliament

MS: Member State/s

NeIC: Nordic e-Infrastructure Collaboration

PM: Personalised Medicine

PMC: Personalised Medicine Coalition

SME: Small and medium-sized Enterprises

VPH: Virtual Physiological Human

WP: Work Package

Imprint

EU Grant



The Coordination and Support Action (CSA) PerMed has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no [602139].

Contact

PerMed coordination:

Wolfgang Ballensiefen and Ulrike Busshoff

E-Mail: Wolfgang.Ballensiefen@dlr.de or

Ulrike.Busshoff@dlr.de

PerMed webpage: <http://www.permed2020.eu>

Publisher

Deutsches Zentrum für Luft- und Raumfahrt e. V.

German Aerospace Center (DLR)

Linder Höhe, 51147 Köln (Cologne) Germany

Links to external websites

This PerMed SRIA contains links to external third-party websites. These links to third-party sites do not imply approval of their contents. Project Management DLR has no influence on the current or future contents of these sites. We therefore accept no liability for the accessibility or contents of such websites and no liability for damages that may arise as a result of the use of such content.

Using the content and citation

If you wish to use some of the written content, please make reference to: The PerMed SRIA: 'Shaping Europe's Vision for Personalised Medicine' (2015).

Date

June 2015

