The Strategic Research & Innovation Agenda (SRIA) for Personalised Medicine (PM)

April 2023

EP PerMed
European Partnership
for **Personalised Medicine**

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1. SRIA Background and Development

This Strategic Research and Innovation Agenda (**SRIA**) for personalised medicine (PM) will support a wide range of stakeholders and experts to further develop programs, activities, and research towards PM and care, as well as prevention. In line with this mission, its main intention is the support of the planned new European Partnership for Personalised Medicine (**EP PerMed**). The SRIA for PM will support the development of the foreseen seven Joint Transnational Calls (**JTCs**), networking calls as well as other activities, cooperation and events foreseen to be part of the future Partnership for personalised medicine.

In this document we mainly use the definition adopted by the European Council Conclusion on personalised medicine for patients (2015/C 421/03). It states "[…] that it is widely understood that personalised medicine refers to a medical model using characterisation of individuals' phenotypes and *genotypes (e.g. molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention*."

The structures and content of the document is based on the drafting group (dg) member's knowledge, existing strategic documents, and other available information. But more importantly the document is based on several activities and events organised with the support of the European Commission (**EC**), the International Consortium for Personalised Medicine (**ICPerMed**), and connected consortia like the European Research Area Network for Personalised Medicine (**ERA PerMed**).

Among these activities were **interviews** with over 70 experts (see chapter 8.1.6) and stakeholders related to PM and identified by the SRIA drafting group (dg) members, see acknowledgment. The interviews were performed along pre-defined guiding questions with the intention to firstly gather general ideas, recommendations, and information related to PM. Secondly, to identify so called "**Triplets of Action**, *short **ToA***" defining certain challenges, objectives, and the expected outcome of actions to foster PM research and the implementation of innovative PM approaches (see Fig. 1). These ToAs are the core element of this strategic document. They are presented along the main areas crucial for an effective development of PM: Interdisciplinary research efforts, successful innovation and finally, implementation of PM approaches into healthcare systems. Further ToAs were identified for overarching activities essential for PM development and implementation. *Notice that although the ToAs are placed in specific chapters of this document, many of them are relevant for several chapters. Full texts of the ToAs are placed in the Annex.*

Number and title of ToA

Challenge	Here the specific challenge is briefly described
Objective	Here the needed actions to achieve the outcome is described
Outcome	Here the expected outcome is described

***Fig. 1** Overall structure of the so-called "Triplets of Action" (ToA)*

An online **consultation** with the first set of 47 ToAs identified took place from November 21st until December 31st, 2022. The results were analysed and published as a **report** on the ICPerMed, and the ERA PerMed webpage in March 2023. In parallel, the drafting group utilised the findings and suggestions to further refine the SRIA.

Together with ICPerMed, an expert **workshop** was arranged in Pamplona on January 17 and 18, 2023. This event was dedicated to topics and areas crucial for the development and implementation of PM approaches based on interdisciplinary research achievements. This event and the discussions have been a significant contribution to this document. Additionally, the outcome of this event will be published by ICPerMed in a **report** on its website.

In this 1st version of the SRIA, we present in total of 57 ToAs and other valuable recommendations and conclusions to enable the future development, adaption and adaption of PM approaches for the benefit of patients and sustainable healthcare systems. The SRIA for PM is a living document that with be updated according to latest advances and crucial developments of relevance for maximising the benefits of PM approaches.

In April 2023, this 1st SRIA for PM was published on the webpages of ICPerMed and ERA PerMed.

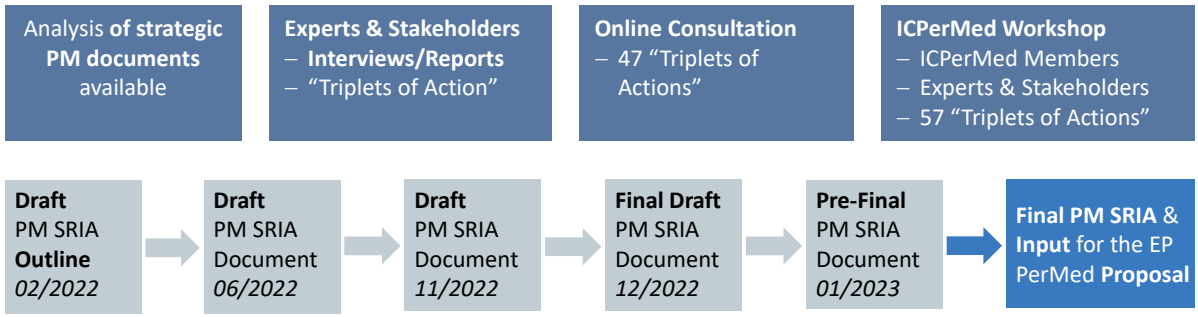

Figure 2: *Process for developing the SRIA for PM (2023)*

2. Introduction

The concept of personalised medicine (PM) has been developed and established over the last 10 years. In the first period, genetic information of patients and its analysis could support the research for tailored diagnosis and treatment for certain diseases, of that mainly cancer and rare diseases treatment benefited. Today, the field of PM has advanced rapidly and the range of technologies, methodologies and information utilised is much broader supporting improved diagnostics and tailormade treatments and prevention strategies.

In the last decade, an impressive number of scientific achievements on the identification and development of precision or PM approaches has been published worldwide. In addition, numerous strategic documents and initiatives devoted to analysis and optimisation of the PM framework and settings have been published and established.

To further support PM developments, the European Commission (EC) and the Member States (MS), including several regions, joined forces in the development of this Strategic Research and Innovation Agenda (SRIA). This process was highly triggered by the plan of the EU to set up a European Partnership for Personalised Medicine (EP PerMed). Thus, a SRIA drafting group (dg) was established to prepare goals and activities for a European Partnership (draft proposal) as well as a SRIA. These activities were strongly supported by the International Consortium for Personalised Medicine and related EU-funded coordination and support actions as well as the ERA PerMed (ERA-Net co-fund for Personalised Medicine, 2017-2023) and national initiatives.

To foster PM, not only interdisciplinary and reproducible research efforts are needed but also successful and rapid innovation steps in cooperation with the private sector are crucial to ensure equal access. Finally, the requirements and frameworks for the implementation of PM approaches into sustainable health systems have to be in the focus of such an agenda. Therefore, the structure of this SRIA, its ToAs, and recommendations is starting with the various research disciplines (chapter 3.1), continuing with the innovation system (chapter 3.2) and finally leading to the PM implementation setting within the diverse health systems and overarching challenges (chapter 3.2).

EP PerMed
European Partnership
for **Personalised Medicine**

Figure 3: *The EP PerMed Logo suggestion is reflecting the PM value continuum of research (blue), Innovation (yellow) and healthcare system implementation (green, see also Fig. 4 below).*

An overview of this PM "**value continuum**" including key players and overarching aspects is sketched in Fig. 4, which is also the guiding principle of the structure of this document. Furthermore, the logo suggestion for EP PerMed is also reflecting this view:

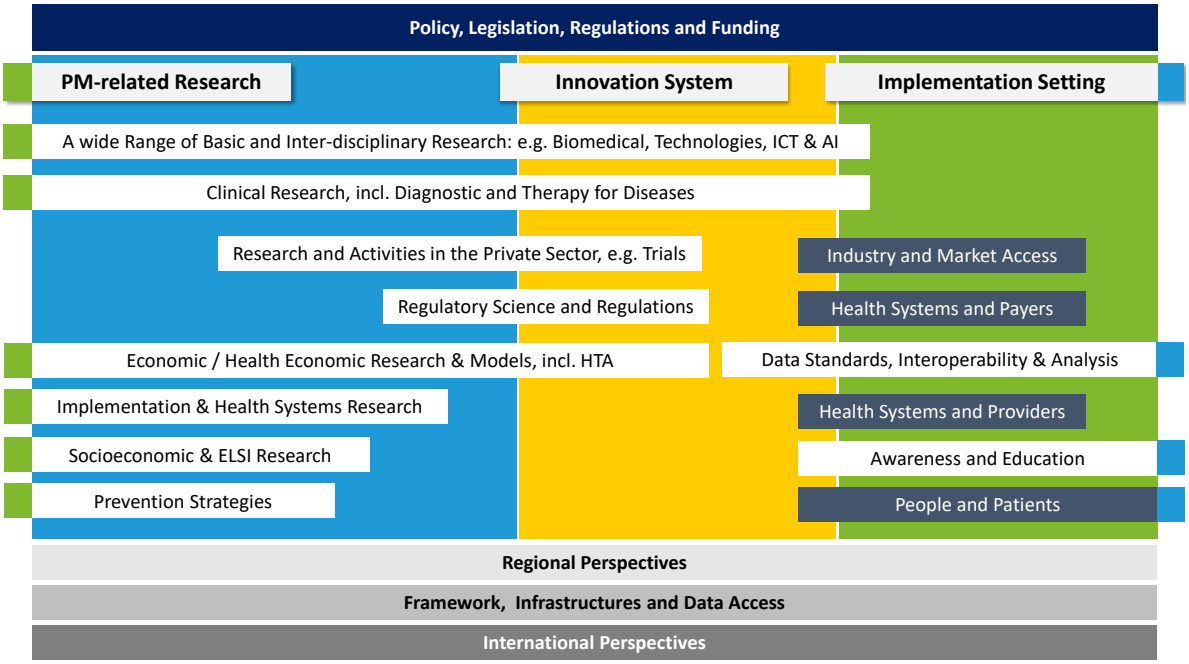

Figure 4: *Overview of the identified needs for maximising the benefits of personalised medicine approaches. This includes, personalised medicine related research (chapter 3.1), innovation (chapter 3.2) and health system implementation (chapter 3.3) as a PM value continuum.*

This includes overlapping major steps and activities of which some span over several areas and sectors. The whole setting is controlled and supported by policy via legislation, regulations as well as funding framework and decisions. Further overarching aspects are the regional perspective (chapter 4.1); frameworks, infrastructures and Data Access (chapter 4.2) as well as the international perspective (chapter 4.3).

The Vision of EP PerMed

The vision of the European Partnership for Personalised Medicine is to improve health outcomes within sustainable healthcare systems through research, development, innovation and implementation of personalised medicine approaches for the benefit of patients, citizens, and society.

3. Research and innovation activities for PM

Research and innovation are at the core of PM. The concept of PM originally arose from genetic research within cancer more than 20 years ago, where the idea, that knowledge of the individual patient's genetic makeup could be translated into more personalised treatments of the patient was conceived. The concept has since evolved tremendously and considers besides genomics, other health data, environmental exposure, and lifestyle information. It is now evident that significant efforts are needed to translate research findings into PM-approaches that can be implemented in the healthcare system to the benefit of patients, citizens, and society. It requires the involvement of all key stakeholders along the full value chain.

Overall, the system must be considered as a "System of Health" (see Fig. 5) where results from one element feed into next step, but also feedback to previous steps in the value chain, forming a cycle of knowledge and insights that flows in both directions. To make such a system possible, it is essential that patients are involved at all stages in the process. Patients shall be the sole owner of their personal data and are the key stakeholders and contributors.

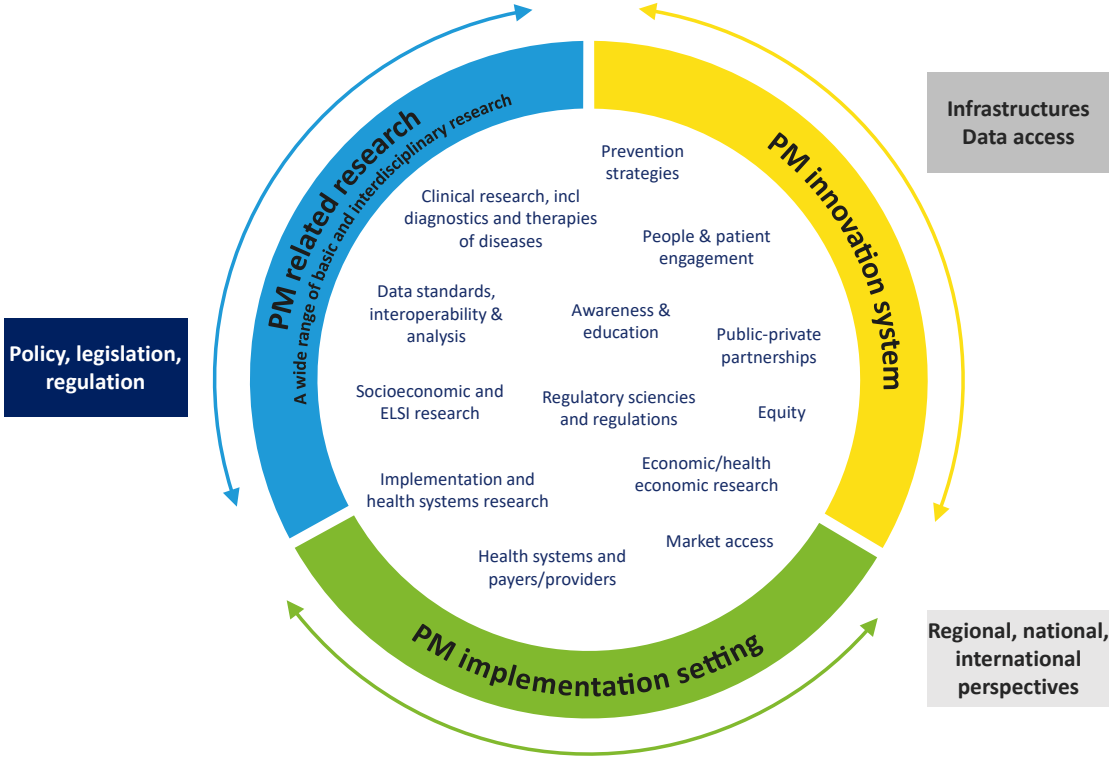

Figure 5: *The Personalised Medicine "System of Health"*

Many of the current most important bottlenecks in the development and implementation of PM are linked to cross-cutting aspects of the PM System of Health. An important example is data generation and access, which are needed for both research and implementation. Access to data in a broader sense is today hampered both by inadequate policy and legal frameworks as well as by a lack of agreed data standards. The first issue needs to be solved by legislators and decision makers whereas the second issue must be solved by science and technology – but all involved parties must work together to solve the problems.

Overall, this means that there are several important areas in the value chain which needs to be developed in a concerted way, including pre-clinical research, diagnostics, biomarkers technologies, clinical strategies, regulatory frameworks, market access processes, health economic models, technological infrastructures, healthcare processes etc. Many enablers are required in this process and at different steps. This could also be described in form of Technology Readiness Levels (TRLs, Table 1 and more detailed table in the Annex for medical devices), e.g. safe and secure health data utilisation, digitalisation, artificial intelligence (AI), public-private partnerships, education & training, involvement of patient and citizens. The development of all these areas is complex and requires involvement of all relevant key stakeholders.

It is very important to consider overarching topics such as regional (between different European regions, but also internationally) and national differences (e.g. between the European countries) and to have equity in mind. Therefore, it is essential that the areas are prioritised and addressed according to potential, framework conditions, urgency, and implementation duration in the annual work programmes of EP PerMed. The foreseen Partnership can contribute to all areas through a range of activities, e.g. organisation of joint funding (research or innovation projects or demonstration pilots), organisation of trainings, dedicated communication and dissemination activities, and joint reflections that are translated into strategic developments.

The SRIA was developed to address challenges that need to be tackled to further develop and maximise the impact of PM. The ToAs identify specific objectives and actions that will contribute to realise the outcomes needed to address different challenges. In the subsequent chapters on research, innovation, and implementation, specific needs will be described in more detail via the ToAs. The ToAs are intended to guide the annual work programmes of EP PerMed. In this process, it is essential that the overall PM System of Health towards effective implementation of PM is always kept in mind to ensure all necessary links.

To allow easy reading of this SRIA document, the ToAs that contribute to multiple topics fields (e.g. biomedical research, ELSI research, health economic research, etc.) are each sorted to a dedicated sub-chapter and then references, if relevant, for other subchapters. Having the PM System of Health concept in mind, some ToAs might be of equal importance for more than one topic and those cases are highlighted in the respective sub-chapter descriptions.

3.1. Personalised medicine related research

To keep Europe at the forefront of PM research and innovation, and to maximise the impact of health research in Europe, different activities along the whole value chain are needed. The focus of this sub-chapter is on PM related research which is a major corner stone of the PM System of Health. The aim is to intensify research for PM to increase our knowledge and understanding of disease mechanisms and the status of health and disease over the course of a lifespan in a systemic way. This will lead to new insights and novel research results in PM, will identify new targets for PM approaches for prevention, diagnosis, prognosis, and treatment of disease, and will lead to new evidence regarding their clinical impact (see Fig 6).

All these activities will support Europe's strategy to stay in forefront of research and innovation and foster, simultaneously, synergies between European regions and countries as well as international collaboration.

Figure 6: *Overview of the main research areas relevant for PM.*

In general, the research that needs to be conducted aims to find the right individual preventive or therapeutic approach for the right person at the right time. The data-driven and systemic PM-approaches are aiming at determining the predisposition to disease, to lead to early diagnosis, decrease in adverse drug reactions, efficient and cost-effective treatments, and to deliver timely and targeted prevention. Altogether, in the long term, this will result in quality-of-life improvement for citizens and patients, in reduction of general morbidity in the population and in cost savings seen from a macro-economic perspective.

Research, e.g. supported by the EP PerMed, needs to be collaborative, interdisciplinary and across borders to maximise synergies. The priority setting of the SRIA has been driven by the major challenges and needs. The implementation of the research agenda will lead to a considerable project portfolio, to new research results and an increased knowledge base, to publications, new intellectual property, position papers, and new clinical guidelines and medical recommendations. It will provide the basis for the translation of research results into clinical practice. The main drivers of PM research shall remain to create value for citizens and patients, to ensure equity in access to personalised innovations, and to consider affordability for healthcare systems.

In the context of PM research, the principles of “Ethical, Legal and Social Implications” (ELSI) are essential and need to be further explored by research and applied by all stakeholders. ELSI related ToAs are placed in chapter 3.3 but is essential to be supported through research activities as well.

3.1.1. Pre-clinical research

Basic principles of molecular or disease mechanisms identified through research lay the foundation for PM. An example of the importance of fundamental research and understanding of underlying mechanisms is the development of personalised regenerative medicine strategies, which has benefited largely from stem cell research. Genetic modification of stem cells allows for adjusting of phenotypes and expression profiles, thereby improving properties such as growth factors and cytokine expression. This in turn can optimise and personalise therapeutic strategies.

ToA-01	**New targets for Personalised therapies making use of an improved understanding of disease mechanism**
ToA-02	**Metabolic profiling**
ToA-03	**Clinically relevant experimental models**
ToA-04	**Robust and reproducible preclinical studies**

3.1.2. Advanced therapies / Advanced therapy medicinal products (ATMPs) / Devices

Advanced therapies refer to new medical products that use gene therapy, cell therapy, and tissue engineering. Usually, they are designed for individual patients based on their individual molecular profile and are therefore regarded as PM approaches.

So far, these approaches are still primarily investigated in the fundamental and translational research arena but do have a great potential for the improvement of diagnostics and treatment.

For example, organs-on-chips with the potential to exhibit tissue- and organ-level functions have so far not been implemented in personalised treatment decisions. These could offer a promising avenue for PM as several attributes of organs-on-chips can be personalised to the individual.

Another example are organoids, which have great potential for individualised drug screening and therefore optimised therapy. This technology also faces certain challenges as culture conditions are not standardised and the cultures require a matrix that causes variability in each batch composition. Moreover, pure tumour organoids are especially difficult to create. Hence, there is still a lot of research to be continued in the field of organoids.

The emerging 3D-bioprinting strategies involves the establishment of a three-dimensional object in a layer upon layer manner using various computer software. 3D-bioprinting enables rapid customisation of personalised devices, drugs, and applications, achieving the ability to restore the tissue functionality. From a pharmaceutical point of view, 3D-printing can be used to construct a wide variety of pharmaceutical dosage forms varying in shape, release profile, and drug combination.

The development of nanotechnology and nanomedicine have resulted in novel approaches to designing more specific pharmaceutical formulations. One relevant topic is the extracellular vesicles or exosomes. Owing to their function as delivery vehicles, exosomes can cross biological barriers, improving the drug delivery, and they also represent a new method of diagnosis owing to their ability to concentrate and preserve biomarkers.

Cell-based therapy is a further example of a very specific PM approach. Currently, cellular approaches are only little in use in the field of cancer research (CAR-T cells). Further research from basic to translational research is needed to explore cellular-based therapies in oncology as well as in other areas.

Gene-based therapies has shown great promise in rare diseases and has the potential of optimising treatments for individuals where biological defects are caused by aberrant genes. Development of gene therapy into areas outside the field of rare diseases is needed.

ToA-05	**Single-cell technologies in combination with AI and ML for PM**
ToA-06	**Early considerations of security, efficacy, and evidence for advanced therapies (ATMPs)**
ToA-07	**New treatment modalities for PM**
ToA-08	**Medical devices and in-vitro diagnostics to support PM innovations**

3.1.3. Collaborative research

Integrating research knowledge into clinical research is often challenging. A two-way interaction between pre-clinical research and clinical researchers, including the patient and citizen perspectives, would improve the understanding of why certain therapeutic strategies are successful, increase their acceptance and adherence of patience, and in the same time help validating hypotheses of basic principles with the needed (health) information (data) available; thanks to informed and actively participating citizens and patients. A solid collaborative system would also improve efficiency.

ToA-09	**A collaborative approach between pre-clinical and clinical research**
ToA-10	**Active involvement of patients in PM research**

3.1.4. Identification and validation of biomarkers

Biomarkers contribute to the diagnosis and prognosis of diseases, better stratification of patient groups, and represent targets for new therapeutics and drugs. The identification and validation of biomarkers is still a challenge.

Functional studies are needed to better characterise biomarkers and to understand their role in physiology and pathology. In addition, pre-clinical (with human biological samples) and clinical validation studies will be needed to increase the available biomarkers for the various applications mentioned. Approaches from molecular PM assist in identifying individual biomarkers, including genetic, phenotypic, imaging, and behavioural techniques which, in turn allows for precisely targeting therapy.

ToA-11	**More biomarker evidence for PM**
ToA-12	**Combination Treatments**
ToA-13	**Broader biomarker approaches to enable more informed health decisions**
ToA-14	**Validity and Prognostic Value of a Polygenic Risk Scores**

3.1.5. Informatics and data research for PM approaches

Health, medical and real-world (health) data are often unstructured, poorly annotated, and not well characterised. It is still a challenge to transfer unstructured data into well-defined medical cohorts that provide a valuable asset for PM research and care. Therefore, there is the need for setting up large-scale projects that establish these cohorts in an interdisciplinary way. Structured and secure data resources should be closely linked to already existing health research infrastructures and then be made accessible for the re-use of data. An overarching aim should be the connection of research and

medical/health data and to make them accessible, and to establish a two-way data sharing process between research and clinical data.

Large-scale observational studies would benefit from interoperability with real-world data at national and international levels, which allows epidemiological issues to be addressed.

Integrating and analysing different data sets is a prerequisite for maximising the benefits of PM approaches as well as supporting research. However, a key challenge is the interoperability between different data sources. This requires an interdisciplinary approach including health providers, insurances, IT experts, bioinformatics, researchers, data scientists & engineers, and policy makers and is essential for various reasons such as IT solutions, pseudonymisation of data and data protection.

Various methods and algorithms have been created, or are being developed, to deal with large-scale molecular, health clinical and lifestyle data in order to obtain meaningful predictive or diagnostic patterns or recommendations for individual treatments.

State-of-the-art data science with techniques from artificial intelligence are invaluable for identifying marker signatures. For example, the approach of multivariate stratification algorithms is becoming meaningful for the difficult undertaking of marker identification.

Machine learning has become increasingly important when dealing with big data, however, various issues can arise. At present, prediction performance of algorithms is still insufficient to a certain extent when it comes to clinical practice.

ToA-15	**Medical cohorts for collecting high-quality health and molecular data**
ToA-16	**Standardisation framework for data integration and data-driven in silico models for personalised medicine**

3.1.6. Clinical research

In order for PM approaches to be validated and implemented in clinical settings, clinical trials are crucial. Therefore, a specific focus should be placed on adaptive-, umbrella- and basket-trials. Regarding umbrella- and basket-trials, these designs are recommended to apply randomisation of participants to experimental treatments or an active comparator, as this is presently not common practice.

Research on companion diagnostics and monitoring is imperative for developing better-defined endpoints. A more precise selection of clinical endpoints and improved technical monitoring devices, such as mobile health applications and wearable sensors, will ultimately lead to prediction models that are more suitable for clinical practice.

As the field of PM is highly complex, new clinical study designs are being researched. For example, clinical trials in which phase 1-expansion cohorts replace phase 2 testing are being explored. However, various research gaps in clinical trial research exist, such as the lack of standardised terminology for trial designs and need for application of new clinical study designs to fields other than oncology.

ToA-17	**PM clinical research in a wide variety of disease indications**
ToA-18	**Inclusive clinical PM research that avoids bias**
ToA-19	**Online recruitment strategies to support PM clinical research**

3.1.7. Research on personal preventive medicine

Research on personal prevention is an essential part of PM to achieve the development of individual risk-assessment methods, by, for example, utilising big data. Analysing such (big) data can be done with several available techniques including data mining, predictive modelling, and machine learning. Thereby, individual risk assessments can be conducted with models that include genetic susceptibility, environmental exposures, and lifestyle factors, and which are the key to personalised prevention.

Preventive interventions require well-defined risk classification so that personalised preventive strategies and specific treatments can be applied to cohorts with a documented increased disease risk, and not to the general population as a whole. Further development of these strategies in an efficient and timely manner requires investment in the discovery and validation of surrogate biomarkers with both prognostic and predictive value to detect and monitor the efficacy of interventions in clinical trials and beyond.

It is crucial to leverage advances in devices that store personal data, including mobile health apps and wearable sensors, to improved accessibility of personal preventive measures. This allows evaluating influences on individual health in real-time.

ToA-20	**Proof of concept for personalised prevention strategies**
ToA-21	**Development of personalised preventive medicine strategies and therapies**

3.1.8. Implementation and health outcomes research

Successful implementation in healthcare of PM-based solutions is complex for several reasons: the PM solutions are often new, e.g. based on new technologies, and the many stakeholders must be involved to ensure implementation (see also chapter 3.2). Currently, PM implementations have been successful mainly in smaller regions where there are closer links between the necessary stakeholders, whereas translation to for example national scale has turned out to be difficult. In-depth research is needed to clarify the factors that determine successful PM implementation and thereby to provide guidance for future implementation efforts.

ToA-22	**Implementation Research in PM**
ToA-23	**Health and patient-centred outcomes research in PM**

3.2. The innovation system and PM

An effective innovation system should ensure translation of research outcomes into new applications and treatment options based on PM. Incentives to stimulate absorption and uptake of innovative PM-based approaches will support the implementation of PM in the healthcare systems. The innovation system should focus on the entire value chain, and include the enablers and key stakeholders to promote and achieve implementation of PM. It is in this phase that all key aspects are brought together to enable realisation and implementation of PM in healthcare systems for the benefit of patients, citizens, and society.

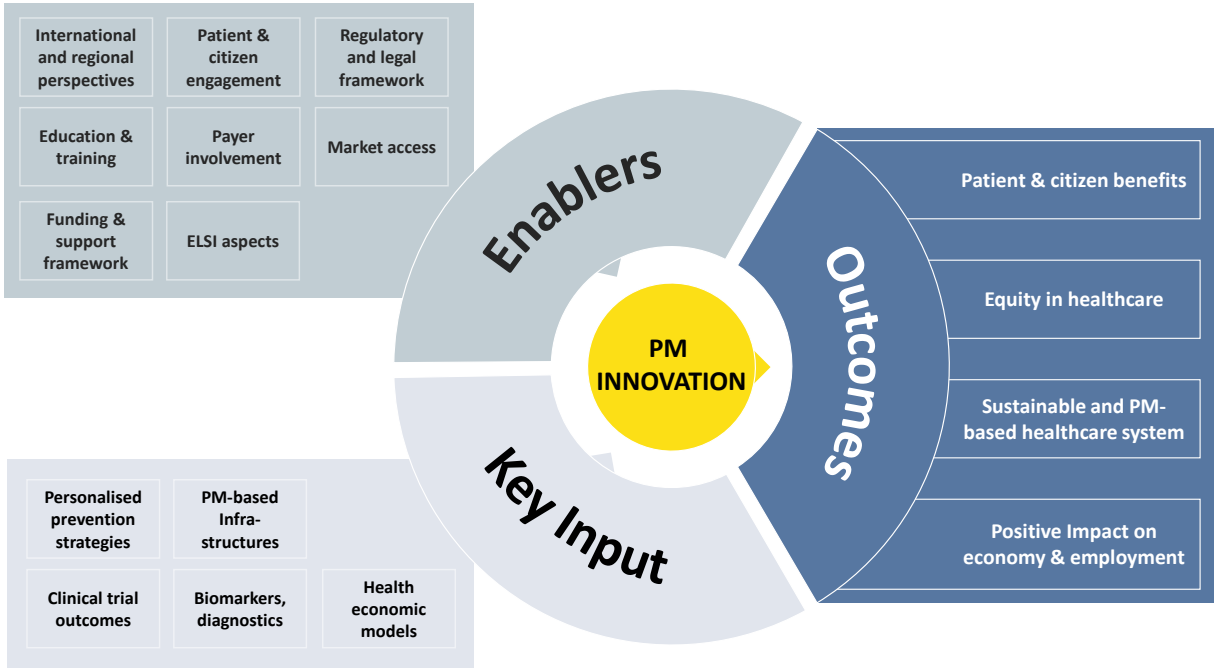

Figure 7: *Contribution of research and innovation activities, as well as policy frameworks to the overall outcome.*

In addition, PM should not only provide better treatment options for patients, but also be of benefit for the general society. Healthcare systems embracing PM-based options should contribute to:

- More efficient and effective treatment options and hence more successful and satisfactory experience of care for patients, healthcare professionals, and relatives.
- Ensuring inclusiveness and health equity for all and lower barriers to healthcare, leaving no one behind.
- Improving the overall health of the community with stronger focus on personalised prevention efforts and through access to better and more effective treatments.
- Providing sustainable healthcare models, including a focus on prevention.

To further the implementation of PM in healthcare environments, it was clearly confirmed by experts and public consultations that focused efforts are needed with respect to:

- Communication and cooperation between public and private partners.
- Health economic aspects, including overarching economical aspects of PM approaches.
- Regulatory aspects of PM.
- Market access of PM approaches

Most of these areas must be addressed already in the research phase, but the challenges and needs for each area shifts when moving forward from research towards innovation and implementation. It is also important to realise that innovation and implementation feeds back to research, thus the PM System of Health described earlier must continuously be kept in mind.

3.2.1. Communication and cooperation between public and private partners

For PM-based approaches to reach implementation in health care, cooperation between public and private partners (PPPs) are highly needed. On the public side this includes academic institutions, hospitals, and other public research institutions, whereas on the private side it includes both small and medium size companies as well as pharmaceutical industry. PPPs are important actors, driving research innovations. In particular, to translate research results and establish necessary clinical trials, major competences with respect to regulatory approvals and market access are residing very much within the pharmaceutical industry. Combination of competencies between all players in the field is therefore the best guarantee that PM-based approaches will be developed and matured to enter healthcare.

Furthermore, although a lot of new insights are being developed in the academic environment, academic institutions and medical hospitals do not have the capacity to promote no-profit studies on personalised PM. Hence, there is a significant risk that several of potential innovative PM-approaches never make it to society.

Another challenge is the manufacturing of PM medication, which is often complex and costly. Thus, delivering e.g., a one-time treatment for a rare disease can be at very high manufacturing costs, while these therapies are coming to the market with a tremendous value for the healthcare system and society. The innovation system should therefore provide options for novel health economic and investment models for PM-based treatments and approaches, where both public and private players will benefit. In addition, new reimbursement models for healthcare systems may be envisioned to tackle PM-related costs when contributing to preventive health management and more effective interventions, avoiding enduring treatment of chronic conditions.

In terms of funding, fragmentation and separation of mandate is a challenge. Funding is provided by different funding bodies and there is a lack of continuum across the various levels (regional, national, EU, beyond EU) and mandate between societal sectors (health care, innovation, research and infrastructures etc.) as well as the unawareness of already existing tools, expertise, and good-practice examples. In short, using more efficiently synergies, cost- and resource efficiency should be a major focus to defragment funding, lower administrative burden, and allow sustaining/implementing.

ToA-24 Early cooperation between public research and the private sector

ToA-25 Improved Intellectual Property (IP) regulations for PM-based approaches

3.2.2. Health economic aspects of PM

Health technology assessment (HTA) provides objective arguments to adopt new clinical guidelines. It is based on systematic analyses of new interventions and technologies to assess the impact on health and on healthcare systems. The impact of PM-based interventions has transformative capacity and new cost-effectiveness models may be needed to underpin the added value of PM-based innovations. It is here important to ensure that cost-effective analysis should model entire patient pathways and include the long-term health benefits as well as non-health benefit. Aspects relating to health economic/technology assessments should be considered already at the early research stage to guide the research projects towards an outcome that not only provides benefit for patients, but also is feasible within a sustainable healthcare system.

Another issue concerns the reimbursement systems with its reimbursement and value-based models. PM is inducing and requiring a paradigm shift of the ‘traditional’ pharmaceutical model. In the current setting the pharma industry favours the block buster model and promotes therapies that are "fit for all". PM is in contrast offering targeted therapies on a personalised design. The profit margins are

therefore different and the interventions often costlier. New financing models are therefore needed to ensure a sustainable business environment for both the healthcare system as well as for the pharma industry. The ToAs in this section are expected to support the development of such new cost-effectiveness and reimbursement models. These models will support the adoption and implementation of PM-based approaches in healthcare systems.

ToA-26 Expanded knowledge on value for PM

ToA-27 Adapted payment models for PM

ToA-28 Value based reimbursement models for PM

ToA-29 Incentives for enterprises supporting research and development

3.2.3. Regulatory aspects of PM

Regulatory science for emerging therapies and technologies must be taken into consideration early in the process of development of innovative diagnostics, drugs, and other medicinal products. Regulatory science ranges from compelling principles for discovery and non-clinical data models, to simple but clever design tweaks for clinical trials that deliver extra information at no extra cost for the developers. It also provides methodologies for clinical prediction models that inform different questions from stakeholders, from health professionals discussing with patients, to medicine regulators and to HTA. This must be done via collaborations between regulators and academia. Such type of actions should also include dissemination and training programmes and activities.

Development of appropriate regulatory strategies needs to be part of the development of new PM-based treatments to ensure they make it to society / patients. The current regulatory requirements are often perceived as not accommodating to PM developments, e.g. due to lack of robust scientific approaches worked out for very small patient groups, or under-use of existing flexibilities and opportunities by developers. Thus, multi-disciplinary work is needed for defining and clarifying approaches that generate a level of safety and efficacy data that is appropriate for all decision-makers (researchers, regulators, health professionals, patients, HTA), and this should allow the pharma industry to engage in innovations.

Therefore, it is important to have an open and constant dialogue with European Medicine Agency (EMA), between EMA and the national competent regulatory authorities, and between regulators and academia to overcome some of the bottlenecks.

ToA-30 Early consideration of regulatory frameworks and authorities

ToA-31 Keep the regulatory framework up to date with innovation

ToA-32 Clinical trial design adapted to smaller patient groups

3.2.4. Market access of PM

New PM-based treatments are today reaching the patients mainly via two routes: either via the traditional market access process, which is driven commercially by a pharmaceutical company, or via research hospitals, where the efforts are driven mainly by experimental medicine efforts, for example within cancer. In some cases, very special setups have been made within rare diseases (often privately funded) to allow patients access to the treatment.

In the future PM-based healthcare systems new models for market access are needed to ensure a broader market access framework. These models must include access to biomarkers and diagnostics as well.

ToA-33 Improved market access for companion diagnostics

3.3. The PM implementation setting

A dedicated set of measures is needed to ensure the adoption of PM-based approaches by patients and citizens and its uptake into healthcare systems. Many stakeholders are involved (see Fig. 7), therefore this needs a supportive regulatory framework and appropriate investments and most importantly, it needs an environment that is eager to test and integrate innovative approaches. It needs awareness of PM by the healthcare professionals, by patients and citizens, as well as by decision and policy makers. Healthcare providers need to be able to invest time and efforts to co-create, adapt and adopt new knowledge, innovations and solutions. The testing in pilot and demonstration studies is a very important step in the feedback loop of PM to further improve new knowledge, methods, solutions, technologies and innovations.

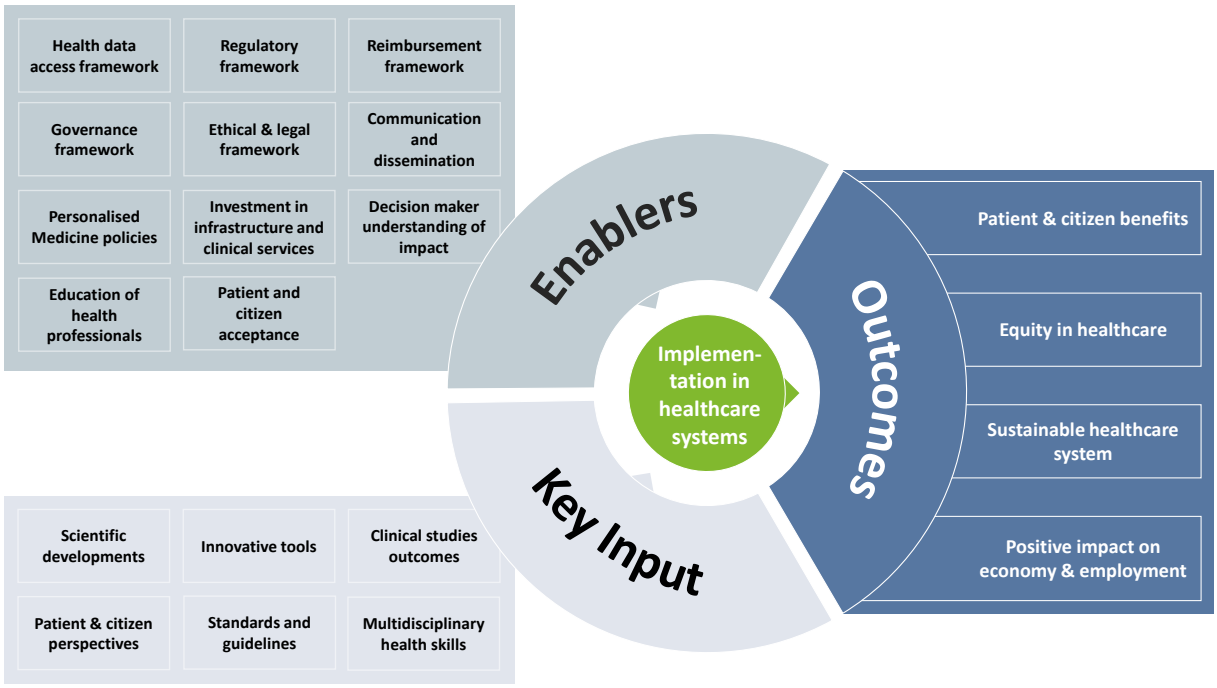

Figure 8: *Contribution of research and innovation activities, as well as policy frameworks to the overall outcome.*

It is essential that the architects of the future System of Health are aware of what the requirements are within the healthcare systems and society at large to fully implement PM-based approaches, both in terms of healthcare infrastructures, data systems, long-term investment plans, legal frameworks, communications and dissemination. Since the development of more personalised approaches, it has been mainly a bottom-up process, there is a high need to inform the architects about these requirements.

A very important aspect concerns ethical, legal, and societal issues (ELSI). Since PM requires full involvement of patients and citizens at all levels, a framework which ensures the safety and privacy of

e.g. biomedical and healthcare data, and at the same time allows the use of these data for both research, therapy, and prevention purposes, is needed.

ToA-34	**Test beds in hospitals**
ToA-35	**Accessibility and knowledge of genomic tools for healthcare professionals**
ToA-36	**Use of pharmacogenomics and pharmaco-metabolomics in standard healthcare**
ToA-37	**Establishment of chronic disease management along with PM**
ToA-38	**Develop and implement NGS testing**
ToA-39	**Efficiency and value of PM approaches consider the full healthcare chain**
ToA-40	**Establishment of Learning Healthcare Systems (LHS)**
ToA-41	**Establishment of decision support systems facilitating PM**
ToA-42	**Patient-centred care pathways**

3.3.1. Access to real-world and clinical/healthcare data for PM

Secure access to and utilisation of high quality, structured and well annotated health data is a prerequisite for PM-based research, for optimal treatment of patients, and for personalised prevention efforts. Collected in the context of routine healthcare through Electronic Health Records (EHR), through wearable and mobile devices, e-health services and other technology-based data sources, Real-World Data (RWD) can thoroughly characterise the health status of an individual. As such, it provides a wealth of information beyond traditional clinical trial settings and is increasingly more important for healthcare.

It is crucial that healthcare systems establish the infrastructure and provide resources for high quality data collection from patients and citizens. It is also crucial to ensure that the concept of FAIR (Findable, Accessible, Interoperable, Reusable) data is followed in the implementation phase.

ToA-43	**Data collection by healthcare professionals for PM**
ToA-44	**Availability and accessibility of real-world data and real-world evidence**
ToA-45	**Feedback loops from clinical application and patients experiences to R&I**

3.3.2. Communication, training and education related to implementation of PM approaches

To develop PM communications is a major aspect. It will create awareness and understanding among the public at large and in this way, it may create a demand for access to the most advanced and efficacious interventions and approaches.

Access to innovative interventions is a major issue in the healthcare environment. Communication efforts will ensure the information flow to healthcare professionals. At the same time the dialogue should be open to capture the innovation needs from the healthcare community and from patients, to be addressed in innovation trajectories designed by innovators.

The engagement of patients and citizens must also be addressed. Patient perspectives play an increasing role in research, both because access to patient data is crucial, but also because research strategies need to change to include patient perspectives, which often are less focused on curative

aspects and more on life quality aspects. The citizen perspective will become very important when considering preventive strategies including personal prevention.

A key aspect is related to establishment of trust with the patients and citizens, particularly in relation to the use of their data. Communication, training, and education is the only way forward to establish such trust.

ToA-46 Create evidence and communicate PM success stories

ToA-47 Improved awareness for patients and citizens for PM

ToA-48 Training and education of people and patients

ToA-49 Training and Education of healthcare professionals

3.3.3. ELSI related aspects for PM

Research on and implementation of PM might lead to negative societal attitudes. For instance, there is a risk of racial stigmatisation based on genetic information, discrimination based on gender and age, and misuse of person-specific data when handled unethically or in case of data security breaches. PM might not be accessible to individuals from a low socio-economic background or from rural areas. PM could therefore lead to discrimination.

To prevent the development of such negative societal impacts, research programmes are needed on how to best involve citizens, patients and stakeholders in the whole research, innovation, and implementation process. Developing methods for pseudonymisation and anonymisation should be given top priority.

Focus shall be given to equity aspects. The terms “equity within societies” and “equity across societies” should be distinguished, as the debates as well as risks and measures surrounding those topics are very different. Within societies, it is primarily a discussion of equal and fair access for all, while in the global context several other issues including the participation in research, rights of control and ownership of data, and access to the benefits of PM are being addressed.

ToA-50 Interdisciplinary PM research projects co-developed with experts in social sciences

4. Overarching activities supported for PM

Besides investing in R&I through funding provided by the Partnership, the EP PerMed will be one major platform bringing together a diverse set of stakeholders involved in PM development and implementation as well as the end users, including health professionals, patients, and citizens. The Partnership will contribute by fostering strategic discussions, development, alignment, and the development of close synergies between the different stakeholders (actors on European regional or national policy level and of different sectors).

Addressing global health challenges and achieving overall access to PM in specifically is only possible by building and strengthening cooperation on all levels: European regions, national level, transregional/-national level, and international level. Collaboration needs to be developed between scientists, decision/policy makers, the private sector (smaller biotech and industry), health professional and the civil society as well as existing infrastructures and those being developed in future.

The activities described in this chapter support different ToAs presented but also other already mentioned in chapter 3 and therewith contribute to PM development and implementation.

4.1. Regional perspectives of PM

Regions often reflect the culture, identity, and common interests of a population better and are often powerhouses for innovation. To drive the transition towards PM and health in Europe, regions are therefore important partners. Such transition will contribute to the sustainability of healthcare systems and better wellbeing for the citizens. Regional authorities and stakeholders have joined the race to deliver personalised care and are driving toward what could be termed as the next personalised healthcare. Their role as a key stakeholder in PM is pivotal. Therefore, PM is an investment priority by numerous European Regions as shown for example by the Regions4PerMed article “The evolution of personalised healthcare and the pivotal role of European regions in its implementation”, in 2021. This coordination and support action (CSA) Regions4PerMed received funding from the European Union’s Horizon 2020 research and innovation program for 4 years. Also, a survey was established to have clear view on PM policies in European regions and the respective SAPHIRe survey is still open. SAPHIRe has been a 3,5-year coordination and support action funded by the European Commission (2019-2022) and was aiming at securing the adoption of personalised health in regions.

Almost all regions in Europe took up health and often specifically refer to precision and preventive medicine in their regional smart specialisation strategies (RIS3). The RIS3 strategies are an important aspect to address the regional structural funds.

Regional development and inclusiveness are addressed under the Cohesion Policy and the European Structural and Investment Funds (ESIF) is the largest investment policy of the EU. Investments through the ESI Funds are jointly managed by the EU and EU Member States via shared management, in accordance with the principle of subsidiarity. To spend the ESIF allocated budget, partnership agreements are drawn up between the EU and individual EU Member States. These agreements outline the national authorities' plan, including its strategic goals and investment priorities on how they will use the funding from the ESIF.

Once the partnership agreements have been adopted, the EU and the national authorities agree on Operational Plans (OPs), which set out the priorities for each Member State, region, or policy area. It is on this basis that the EU countries administer the funds on a decentralised basis. As part of the regional innovation strategies, the establishment of regional high-tech innovation clusters to increase

'regional competitiveness' was encouraged since a long time. Regional innovation clusters represent the regional actors and through interregional collaboration added value is created by combining complementary assets. The cross-border interregional interactions are important to improve the regional innovation capacity.

The regional innovation capacities and focus on health indicate it is important to align and integrate regional actors in EP PerMed to accelerate innovation and adoption of innovations in the health care settings and society.

Even though some regions have limited innovation capacity, there are often strong regional actors that may contribute to the development of PM. Such regional actors may be university hospitals, or other expertise centres specializing in AI and other technologies that may further the development of PM. It is important to combine and align all European expertise in an inclusive manner. It will ensure that knowledge and innovations developed will be common assets that are accessible to all Europeans.

To ensure regional commitment, joining forces with the Vanguard Initiative may be considered. The Vanguard Initiative is an ASBL in which several regions joined to boost innovation in their regions in specific identified pilots. The pilot on Smart Health has PM as major focus domain. Integration of the Vanguard Initiative in the EP PerMed Partnership would open the Partnership for all regions willing to participate and align the RIS3 strategies and hence open the opportunity to access the structural funds and regional innovation funds to contribute to the development of PM and support innovations and implementation based on PM advances. Aspects proposed to be considered in this section:

- Innovative potential to foster innovation in and via European regions.
- Adaptions of infrastructure and economic settings for PM on regional level.
- Adaptions of academic settings for PM on regional level.
- Transregional and transnational cooperation of regions about PM

ToA-51	**PM innovations in a regional environment**
ToA-52	**Network of regional innovation hubs**
ToA-53	**Aligning regional funds for PM**

4.2. Framework, Infrastructures, and data access for PM

To provide equal access to therapies and prevention measures based on PM approaches, adequate PM-supporting frameworks must be developed and articulated following the process of translating research into practice. The most significant frameworks and approaches that have been proposed to support personalised medicine include:

The "omics" technologies (genomics, proteomics, and metabolomics to identify genetic, protein, and metabolic markers) to tailor medical treatment to the patient's needs; Electronic health records (EHR) to store and manage patient data, including genetic information, to support decision-making in personalised medicine (ToA-44); Clinical decision support systems (CDSS) to analyse patient data and provide recommendations for diagnosis and treatment; providing information on the potential risks and benefits of different treatment options for a particular patient; Clinical trial databases to identify treatment options for a particular patient, based on their genetic profile or other factors; Public health systems to collect population-level data on disease prevalence and treatment outcomes (ToA-15; ToA-43); Healthcare delivery systems designed to support PM by incorporating other tools to tailor treatment to the individual needs of patients.

These framework approaches can be based on the results of pilot research projects focused aimed at building up the evidence and evaluating the added value of PM in healthcare systems (ToA-28).

Additionally, there is a need to more fully utilise the data information generated by PM research as well as within the healthcare system, to offer new insights for more tailormade treatments and prevention. The diversity of various data sources, the absence of widely acknowledged standards, and the ethical and legal aspects around the use of personal data are some of the challenges (ToA-30).

To fully increase the predictive potential of PM, there is a clear multidisciplinary need to develop data harmonisation and integration approaches across the several fields (ToA-50).

Under this line, the development of complementarities or synergies between research infrastructures is needed. Not only at the thematic but also at the cross-disciplinary level to increase efficiency, sustainable and long-term integration of services and resources, and prevent unnecessary duplications addressing PM challenges and priorities. The scope is to optimise the functioning of the broad research infrastructures landscape.

There are several key RIs that support the development and implementation of PM such as:

- Biobanks are an important resource for PM research, as they provide a source of high-quality samples (collect, store, and manage) that can be used to study genetic variations and other factors that may influence an individual's response (ToA-55).
- Genomic research centres dedicated to the study of genetics and genomics, and often have state-of-the-art facilities and equipment for DNA sequencing and other genomic analyses. For example, the European Genome-phenome Archive (EGA) which is a data repository. It stores and manages genomics data from research studies, including data from large-scale projects such as the International Cancer Genome Consortium (ICGC) and the B1MG Project. It is operated by the European Bioinformatics Institute (EBI) and is funded by the European Commission.
- Clinical research networks (hospitals, clinics, and other healthcare facilities) that collaborate to conduct clinical trials and other research studies. They provide access to large numbers of patients and allow for the collection of data from diverse populations (ToA-15; ToA-19). Interoperable health data integration as well as standards for data-driven computational modelling are needed for quality PM research approach and implementation.
- Computational advanced infrastructure for the analysis of large amounts of data, such as genomics data. RIs for PM often include high-performance computing systems and specialised software tools for data analysis (ToA-44). For example, the European Molecular Biology Open Software Suite (EMBOSS) with a collection of free, open-source software tools for molecular biology research. It includes tools for DNA and protein sequence analysis, gene prediction, and other tasks that are relevant to PM.
- RIs may also include efforts to improve interoperability and standardisation for data collection, storage, and analysis (ToA-43; ToA-54). The Clinical Research Initiative for Global Health Supporting international collaboration (CRIGH) on clinical research, aims to optimise clinical research programs, develop global standards on clinical research, promote the take-up of innovative methodology and technologies, and encourage international cooperation to respond to global health challenges rapidly and efficiently.

The infrastructure cooperation can lead to increased efficiency, sustainable and long-term integration of services and resources and prevent unnecessary duplications addressing PM challenges and priorities (ToA-52). The scope is to bring RI together to develop tools, services, training, resources, and support for clinical research and related activities in multinational PM studies. In fact, in the European

Alliance of Medical Research Infrastructures, EU-AMRI, the three RI work in parallel providing complementary services to researchers in the field of biomedical sciences and support the development of PM and new treatments.

The interaction among RI is a valuable asset, such as EU Openscreen in screening drug efficacy on patient cells and tissues in a personalised manner, BBMRI in biobanking field that offer quality management services, support with ethical, legal and societal issues, and a number of online tools and software solutions, EATRIS that bring together resources and services for research communities to translate scientific discoveries into benefits for patients, and ECRIN in facilitating multinational clinical research.

One model that can facilitate progress in this complex field can be an infrastructure for consented samples, genetic analysis (WGS, Exome and specific), molecular analysis (proteome, microbiome etc.), and developing relevant diagnostic and prognostic indicators using the structured IT system across labs, all with a dynamic approach (ToA-19).

Other related initiatives are the EMBL-EBI Industry Program [European Molecular Biology Laboratory (EMBL)] to accelerate the translation of genomics research into clinical practice. It includes core facilities and services that support PM, including a genomics platform, a proteomics facility, and a bioinformatics support team. Recently, the BioMedical Informatics Hub (BMH) [from the European Molecular Biology Laboratory (EMBL)] brings together researchers from a range of disciplines to develop new tools and technologies for PM, including machine learning algorithms, data visualisation tools, and decision support systems.

ToA-54 Connected large-scale health databases

ToA-55 PM adapted and focused biobanks and real-world data registries

4.3. International perspectives of PM

As the European Commission outlines: “Most health-related issues have a global nature and require a global solution. The EU alone will not crack the challenge of implementing better healthcare for all. The ability to attract international stakeholders and their resources into EU–led collaborations will help the EU to combine best skills and outcomes and deliver tangible results to patients. International cooperation is therefore not an option but a fundamental and inherent component of health research and innovation.”

The Human Cell Atlas project is an example where worldwide communities develop a shared vision and set of goals regarding the science as well as the technology.

Various international health related initiatives with different focus were formed in the past, are currently running, and are planned for the future (e.g., concerning specific disease fields as rare diseases, infectious diseases, chronic diseases, brain research, cancer; and overarching topics as genomics, microbiome, clinical trials). PM is one of these topics with a clear global dimension and interest for that cross-border and international collaboration is essential to enable the timely delivery of and access to precise diagnostics, therapies, and prevention strategies for all citizens around the world and within each country. It was already demonstrated that for example the genetic background plays a critical role in the efficiency of various diagnostic tests and particularly the efficacy of drugs and treatment combinations.

It has been shown that transnational collaboration is essential to reach the critical mass of data from various sources to develop and train algorithms and models used in PM approaches. This has proven

to be critical in ensuring that the developed approaches are applicable as broadly as possible and not limited to a specific regional (continental, genetical) context, therefore limiting the value of the innovations for the common good (ToA-56 and ToA-57). Tourism, mobility, immigration, migration, forced displacement but also the presence of different ethnic groups/indigenous peoples within one country clearly demonstrates the need for inclusive diagnostics and treatment strategies for all healthcare systems and their concerned population and including diseases largely affecting the local society but also rare diseases, lifestyle and other more regionally located diseases (e.g. neglected tropical diseases but also genetic disorders). The last pandemic has highlighted the strong links between human health and specific environmental health.

Strong global collaboration in PM can support tackling of global health challenges such as pandemics but also advance diagnostics, treatment strategies and preventive approaches for non-communicable diseases (NCDs) and other medical needs (e.g. trauma, rehabilitation, e- and m-health).

For medications already being on the market, for instance, advancements and implementation of pharmacogenomics and pharmaco-metabolomics as standard in healthcare can reduce adverse effects and better estimate the efficacy of a treatment including multi-medication (ToA-12).

In terms of policy and legislation, international alignment is needed, for example with EMA and the FDA, on guidelines on how to treat digital evidence (ToA-30).

Healthcare systems are heterogeneous depending on the (European and continental) region and country but the health needs are comparable, and solutions could be found through transnational collaboration. In the field of PM, this allows and even requires in some cases the development of common strategies, standards, and frameworks. In this way, PM innovation can support both, capacity building of the health workforce, e.g. through virtual learning, and increase service delivery through for example, e-health, telemedicine, point of care diagnostics and self-care medical innovations. International partnerships including the private sector can support the development and use of new technologies for health. Including the need to address cultural and regulatory differences, the importance of building trust, and the potential for increased efficiency and cost-effectiveness through shared resources and expertise.

Considering that PM is a global topic, with excellent experts and initiatives located around the globe, a coordinated approach, e.g. through the EP PerMed, is needed, involving organisations from European countries as well as international organisations, including third countries to the Horizon Europe framework program to:

- Act as transnational communication and cooperation platform (ToA-24) to pool resources and expertise, the opportunity to create and access diverse patient populations and data sets (achieve the critical mass and needed data diversity, ToA-18), and the potential to overcome regulatory and cultural barriers.
- Promote the harmonisation of value, definitions, standardisation of treatment and diagnostic procedures and standards for a global approach, like ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) or, dedicated for PM approaches, EUSTANDS4PM (ToA-43, ToA-36)
- Promote PM-related multidisciplinary research and innovation throughout the entire value chain (ToA-09, ToA-50).
- Promote the translation of PM research results into clinical practice (ToA-09, ToA-52).
- Promote the uptake of PM innovations by the market and ensure patient benefit (ToA-24, ToA-52).

- Create evidence by monitoring of and communicating about successful PM implementation in healthcare systems, e.g. benefit of different size and type of systems to have trials on a small scale or examples of implementation on a large scale. Sharing of knowledge, e.g. promotion of Best Practises examples and Show Cases (ToA-26, ToA-28) as well as boarder visualisation, dissemination and specific transfer of knowledge and new ideas.
- Providing socio-economic evidence that PM has created value for society (ToA-44, ToA-46), considering equity, e.g. equal access to new technologies and innovation.
- Develop and promote cooperation options and models (ToA-24, ToA-51) with the need to address issues of data privacy and security, the potential for conflicts of interest, and the need to establish clear agreements and protocols.
- Reduce, through all the above-mentioned activities, health disparities and improve health outcomes for all citizens worldwide (ToA-42).
- Foster education and training activities for all involved stakeholders at all levels (ToA-10, ToA-49, ToA-47, ToA-52).

The past years demonstrated the willingness and the importance of knowledge exchange in the field of PM between European Member States and international partners, including the wider distribution and knowledge exchange of innovative PM practices. Important steps were taken to identify and connect the European and international PM community. Global collaborations started to foster strategic reflections as well as joint investment in PM R&I through ICPerMed, ERA PerMed, and the thematically focused CSAs of the ICPerMed family connecting Europe with the Latin America and the Caribbean (LAC) region, China, and Africa.

The structure and interlinks are to be strengthened and broadened through joint funding activities, stimulating transnational research and the development of networks, but also common strategic developments. Ultimately, these efforts deployed through specific support activities will foster optimal policy development and appropriate implementation of PM. EP PerMed could be a lever to activate regional, national, and continental communities, to interlink them locally and also transnationally and across continents.

The EP PerMed should seek involvement of all European Members States and regions and international partners, independent of their current status on PM implementation. This is essential in order to coordinate activities and exchanges on a global level. All European and international participating organisations will contribute to the development of the Partnership, and benefit from and leverage its outputs, to achieve the overall impacts (chapter 6).

ToAs focusing specifically on international collaboration are listed below while international collaboration can contribute to the majority of ToAs presented in other chapters, particularly chapter 3 (see references indicated above).

4.3.1. Transnational genomic studies for PM

Genetic variants influence the risk for diseases for an individual or a group of individuals but also the efficacy of a drug or adverse reactions to treatments. The understanding of the human genetic diversity, e.g. revealed through genome-wide association studies (GWAS) and next-generation sequencing, provides both, the baseline to understand the biology of a disease and the response to treatment of the individual or a group of individuals. Research programs, clinical studies and PM approaches that concentrate only on one population of a specific genetic background risk to be

inefficient, incomplete and not broadly applicable, including ethnic groups and citizens with different immigration or migration backgrounds.

ToA-56 Genome-wide association studies within and beyond Europe

ToA-57 More widely implemented, ethical and secure genetic screening programs

5. Alignment with other EU Partnerships and EU initiatives

This SRIA will support the future EP PerMed, which will be one of several European Partnerships in the Cluster Health and there are more to be established in the next years within Horizon Europe. The SRIA will also be a valuable source for these initiatives and others supporting PM and prevention strategies.

Several already running or planned European Partnerships will have a strong connection to PM and the goals of EP PerMed, such as the

- Innovative Health Initiative (IHI a public-private Partnership funding health research and innovation),
- Transforming Health and Care Systems (THCS; Enabling health and care systems transformation through research and innovation),
- ERA for Health (ERA4Health, European Research Areas for Health) or
- the foreseen Partnership on Rare Diseases which will build on the European Joint Programming for rare diseases (EJP RD) initiative.

Furthermore, other European and national consortia or initiatives and institutions are central for the successful development and implementation of PM, such as

- the International Consortium for Personalised Medicine, ICPerMed
- the European Strategy Forum on Research Infrastructures, e.g. ECRIN, EXLIR, EATRIS, BBMRI or EURO-Bioimaging.
- The 1 Million Genomes initiative (1+MG)
- European Institute of Innovation and Technology, EIT Health
- European Medicine Agency, EMA
- European Molecular Biology Laboratory, EMBL
- …

Therefore, numerous representatives or partners of the above-mentioned initiatives were among the almost 70 interview partners, joined the ICPerMed workshop in January 2023 or were taking part in the ongoing discussion and exchange for this SRIA as well as the preparation of the EP PerMed proposal.

After these initial and fruitful steps for the SRIA preparation, also when EP PerMed is established, it will align for example according to the SRIA of the mentioned other European partnerships and communicate and were possible cooperated to optimise the tasks and impact of the EP PerMed activities.

6. Impact pathway for the SRIA for PM

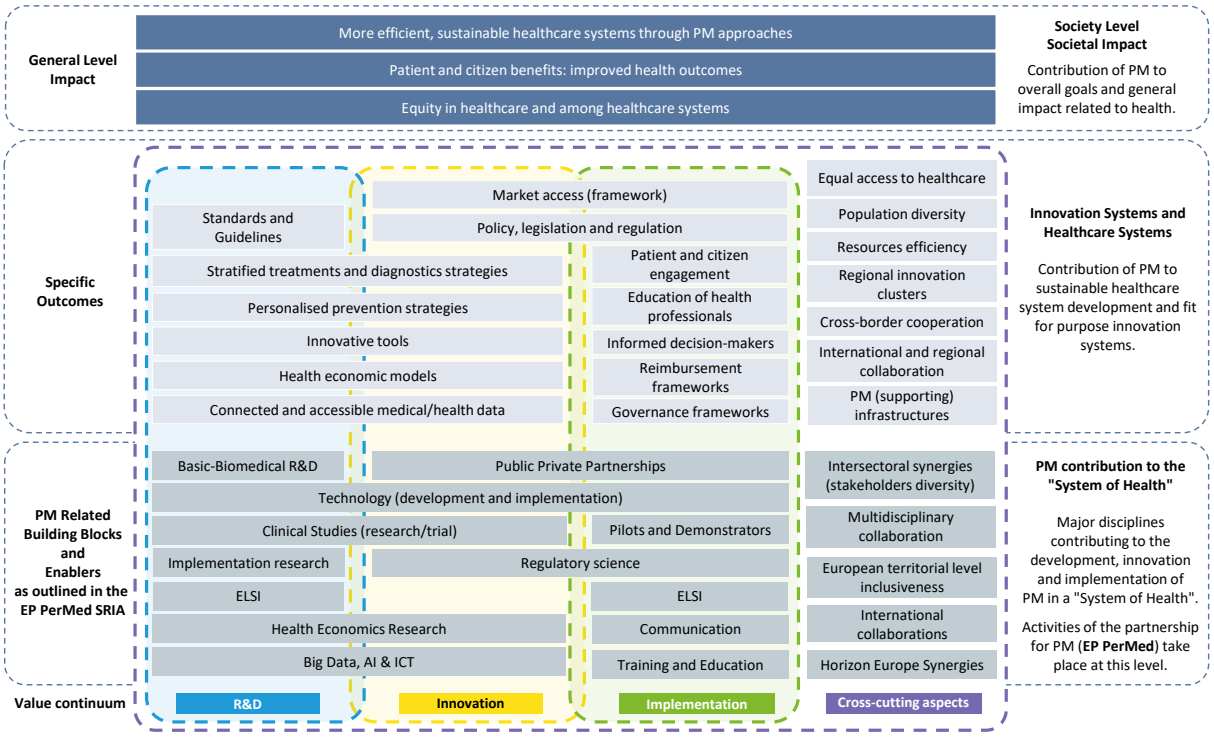

Figure 9: *Overview of the impact pathway of how the Strategic Research and Innovation Agenda, SRIA for PM, will contribute to a System for Health in Europe. The figure includes three different levels (from the bottom to the top): 1) different building blocks that are presented in the SRIA under different headings: R&D, Innovation, Implementation and Cross-cutting aspects, 2) expected outcomes to which the SRIA will contribute, and 3) impact on a more overarching level. Certain topics are for practical reasons positioned under a specific heading but are important for the whole value continuum such as ELSI, regulatory, clinical studies etc.*

The SRIA for PM outlines challenges, objectives, and expected outcomes of actions proposed to overcome the challenges described, and aims thereby to foster PM research, innovative and a better implementation of PM approaches.

This section outlines how the implementation of this SRIA, so PM per se, will contribute to the harmonisation of healthcare and sustainable healthcare system development as well as the innovation systems in health, and hence will contribute to higher impacts on society level (see also fig. 9):

First level: The value continuum and the PM System of Health

The first level is directly related to this SRIA, the different identified PM building blocks and the value continuum. It visualises the need to interconnect the value continuum in a bidirectional manner, supported by overarching activities. Through the translation of the SRIA into concrete activities, the EP PerMed will directly contribute to the PM System of Health and produce results as creation of a PM project portfolio, developed strategic papers, connected stakeholders (events, transfer of knowledge through communication, sharing of Best Practice, education and awareness activities, expert boards), and increased skills (education and training activities).

In detail: the 57 ToAs presented in the SRIA for PM are the core elements of this strategic document. They are presented content-wise in sections that can be seen as PM-related “Building Blocks” or

"Enabling Frameworks". Together, the ToAs and the building blocks/ enabling frameworks are placed in and connected along the main areas crucial for an effective development of PM, also called the value continuum: "interdisciplinary research efforts", "successful innovation" and "implementation of PM approaches into healthcare" as well as "overarching activities". They represent the major disciplines contributing to the PM development, innovation and implementation in healthcare. Although placed in specific chapters, many ToAs are relevant for the entire or more than one element of the PM value continuum. Jointly, they form the PM System of Health and support/allow the PM knowledge gathering that can be directly supported through dedicated activities of a European Partnership for PM, i.e. EP PerMed.

Second level: Innovation Systems and Healthcare Systems

The second level shows the expected outcomes of the first level activities and therewith the contribution of PM to

- sustainable healthcare system development,
- the harmonisation of access to and availability of the most effective healthcare to patients and citizens,
- the innovation systems.

The outcomes are visualised within the context of the given value continuum (research, innovation, implementation or overarching activities) but mainly to outline through which chain element they are the most pushed forward although the respective outcomes are essential for more than one and, in the majority of cases, for the entire System of Health.

The first level building blocks/ enabling frameworks will contribute to reach the second level outcomes. However, they are not the only factors that will influence healthcare and innovation systems. Other factors have also to be considered that are not directly connected to PM. This second level is hence highly influenced by PM developments but not controlled by a Partnership consortium or cannot be tackled directly by a Partnership for PM.

Third level: Higher level impact

The highest indicated impact level shows the contribution of PM to overall goals and the general impact related to health. The long-term aim of PM and a future Partnership is to ensure lasting impact at multiple levels. Developments in PM will contribute to:

- More efficient, sustainable and PM-based healthcare systems;
- Improved health outcomes for patients and citizens;
- Equity in healthcare and among healthcare systems.

Joint actions in the field of PM, e.g. via a Partnership, will stimulate countries to faster embrace the potential offered by PM, which in turn will improve health outcomes within sustainable healthcare systems through research, development, and implementation of PM approaches for the benefit of patients, citizens, and society.

7. Concluding remarks

This SRIA for personalised medicine (PM) presents **57** so called "**Triplets of Action**", short "**ToAs**", along the PM value continuum, including research areas, actions related to innovation and support of PM healthcare implementation. The respective ToAs are complemented by overarching activities vital in supporting PM and the regional as well as international perspective. Some of the identified and described ToAs are not exclusively contributing to the chapters where they are listed, but also to others along the PM value continuum. In this document, the authors compiled, with the essential support of experts and stakeholder, valuable recommendations and conclusions to enable the future development and adaption of PM approaches for the benefit of patients and sustainable healthcare systems.

This effort is a contribution to the continued development of the achievements and efforts made over several areas and sectors over the last decade and beyond. Research and technology efforts and accomplishments, policy and strategic consideration and experience as well as economic reflections, opportunities and challenges and finally healthcare and people's need and abilities will continue to define the next steps for PM development and implementation in Europe and beyond. As in the SRIA of the CSA PerMed (2015) and other related documents, like the ICPerMed "Action Plan" (2017) or similar documents for example of European Partnerships in the Health Cluster, this document should be a source of inspiration, analysis and ideas for all PM related stakeholders and initiatives on European, national and regional but also international level.

The aim of this SRIA is to support the future European Partnership for Personalised Medicine (EP PerMed), which will be established in 2023/24. The Partnership will build on the successes of ERA PerMed, an ERA-Net Cofund, supported by 42 partners from 32 countries and co-funded by the EU. ERA PerMed partners have during the last 5 years funded in total 111 transnational research projects in the field of PM, with an investment of over 130 Mio. €. The EP PerMed will go further by supporting the way of research along the value continuum via the PM-specific innovation system and facilitate equal access and the implementation in health systems. This document gives crucial guidance with distinct chapters and the specific ToAs in each of them (Note: some ToA affect more than one area of the PM "System of Health").

As many authors, institutions, funders and contributors for this SRIA will also be actively involved in the establishment and organisation of EP PerMed, it is ensured that many aspects, opportunities and recommendations described in the document will be taken up and put into action via EP PerMed. Thus, the SRIA will be a crucial input also for the structure and activities within the PM value continuum of the future and it is foreseen to update this document (likely to be planned by and crucial activity of the EP PerMed, once established).

The EP PerMed will consult the SRIA for PM and its ToAs, when building work packages, tasks and activities as well as respective "Key Performance Indicators, KPIs" together with timely conditioned deliverables and milestones. KPIs are critical (key) quantifiable indicators of progress toward the intended result/s and achievements. They will be related to a wide range of PM supporting and fostering measures, like the funding of EU co-funded Joint Transnational Calls (JTCs), tools, events and other activities to provide a focus for strategic and operational improvement, create an analytical basis for decision making and help focus attention on what matters most. Managing with KPIs is the basis for working to improve performance using leading indicators, which are precursors of future success, that will later drive desired impacts indicated with lagging measures.

8. Annex

8.1. Tables

Table 1: *Technology Readiness Levels (TRLs) and the value chain*

TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Basic principles observed. Focus on new discoveries.	Applied research. Technology concept formulated.	Experimental proof of concept.	Technology validated in the laboratory.	Technology validated in relevant environment.	Technology demonstrated in relevant environment.	System prototype demonstration in operational environment.	System complete and qualified.	Actual system proven in operational environment.
Basic research		Pre-clinical research		Late pre-clinical research	Phase 1 Trial	Phase 2 Trial	Phase 3 Trial	Phase 4 Trial
Research			Translation and Technology Development				Commercialisation	

Table 2: *Technology readiness levels (TRL), general explanation and example for medical devices.*

TRL 1	TRL 2	TRL 3	TRL 4	TRL 5	TRL 6	TRL 7	TRL 8	TRL 9
Basic principles observed. Focus on new discoveries.	Applied research. Technology concept formulated.	Experimental proof of concept.	Technology validated in the laboratory.	Technology validated in relevant environment.	Technology demonstrated in relevant environment.	System prototype demonstration in operational environment.	System complete and qualified.	Actual system proven in operational environment.
Generation of fundamental scientific knowledge. Focus on new discoveries, e.g. biomarker discovery, understanding of disease mechanisms.	Concrete research idea and hypothesis is formulated.	Experimental /initial proof of concept demonstrated with a limited number of *in vitro* & *in vivo* trials including the expected device characteristic.	Proof of concept and safety of the device is demonstrated *in vitro*, *ex vivo* or *in vivo* conditions (non-GMP, Good Manufacturing Practice). System components integrated and tested regarding preliminary efficiency and reliability.	Pre-clinical studies including good laboratory practice (GLP) animal safety & toxicity. GMP manufacturing process and quality controls identified. Classification of the device by appropriated regulatory body established. Accreditation when appropriate initiated	Medical device prototype demonstrated in operational environment. Clinical testing and safety demonstrated. Required accreditation in progress.	Medical device final product design is validated. Final prototypes intended for commercialization use produced and tested. When applicable, accreditation complete.	Manufacturing process validated. Pre-market application submitted and approved for medical device. Device demonstrated in real life conditions, support structure in place for technical problems.	Medical device ready to be acquired by the clients and end user.

8.2. List of Triplet of Action, ToAs

SRIA ToA No.	Title
1	New targets for personalised therapies making use of an improved understanding of disease mechanism
2	Metabolic profiling
3	Clinically relevant experimental models
4	Robust and reproducible preclinical studies
5	Single-cell technologies in combination with AI and ML for PM
6	Early considerations of security, efficacy, and evidence for advanced therapies (ATMPs)
7	New treatment modalities for PM
8	Medical devices and in-vitro diagnostics to support PM innovations
9	A collaborative approach between pre-clinical and clinical research
10	Active involvement of patients in PM research
11	More biomarker evidence for PM
12	Combination Treatments
13	Broader biomarker approaches to enable more informed health decisions
14	Validity and Prognostic Value of a Polygenic Risk Scores
15	Medical cohorts for collecting high-quality health and molecular data
16	Standardisation framework for data integration and data-driven in silico models for PM
17	PM clinical research in a wide variety of disease indications
18	Inclusive clinical PM research that avoids bias
19	Online recruitment strategies to support PM clinical research
20	Proof of concept for personalised prevention strategies
21	Development of personalised preventive medicine strategies and therapies
22	Implementation Research in PM
23	Health and patient-centred outcomes research in PM
24	Early cooperation between public research and the private sector
25	Improved Intellectual Property (IP) regulations for PM-based approaches
26	Expanded knowledge on value for PM
27	Adapted payment models for PM
28	Value based reimbursement models for PM
29	Incentives for enterprises supporting research and development
30	Early consideration of regulatory frameworks and authorities
31	Keep the regulatory framework up to date with innovation
32	Clinical trial design adapted to smaller patient groups
33	Improved market access for companion diagnostics
34	Test Beds in hospitals
35	Accessibility and knowledge of genomic tools for healthcare professionals
36	Use of pharmacogenomics and pharmaco-metabolomics in standard healthcare
37	Establishment of chronic disease management along with PM
38	Develop and implement NGS testing
39	Efficiency and value of PM approaches consider the full healthcare chain
40	Establishment of Learning Healthcare Systems (LHS)
41	Establishment of decision support systems facilitating PM
42	Patient-centred care pathways

43	Data collection by healthcare professionals for PM
44	Availability and accessibility of real-world data and real-world evidence
45	Feedback loops from clinical application and patients experiences to R&I
46	Create evidence and communicate PM success stories
47	Improved awareness for patients and citizens for PM
48	Training and Education of people and patients
49	Training and Education of healthcare professionals
50	Interdisciplinary PM research projects co-developed with experts in social sciences
51	PM innovations in a regional environment
52	Network of regional innovation hubs
53	Aligning regional funds for PM
54	Connected large-scale health databases
55	PM adapted and focused biobanks and real-world data registries
56	Genome-wide association studies within and beyond Europe
57	More widely implemented, ethical and secure genetic screening programmes

8.3. Full-text of “Triplets of Action, ToAs”

Chapter 3.1 Research

01 - New targets for personalised therapies making use of an improved understanding of disease mechanism	
Challenge	Personalised treatments are not yet widely available across disease areas due to lack of understanding of disease pathologies, lack of knowledge of treatment targets, and lack of effective treatments/drugs.
Objective	Pre-clinical research efforts to understand the relevant disease pathologies and identify the most promising treatment targets and accompanying biomarkers are needed. In a second step, for each potential target a verification is needed that the target is indeed detectable or druggable.
Outcome	More targets for the development of targeted treatment/drugs are available.

02 - Metabolic profiling	
Challenge	Extending the analyses of the individual metabolic profile by NGS (next generation sequencing) to (healthy) citizens, mainly focusing on mitochondrial and germline mutations on metabolic pathways has a high and as yet unrealised potential for supporting PM approaches.
Objective	Whole genome or whole exons analysis could be extended to genes related to metabolism performed for each citizen/patient. Thus, an individual map of metabolic vulnerability could be created. Integration of the data with lifestyle, type of alimentation, smoke and alcohol abuse, etc. might enable to addressing personalised diets and suggestions of lifestyle for the prevention of cardiac, metabolic diseases and cancer. The tools for this kind of analysis and interpretation of genomic data need to be established.
Outcome	Metabolic vulnerability can be predicted and allows recommendations for personalised diets and lifestyle that are beneficial for the individual in preventing disease, especially in the field of non-communicable diseases.

03 - Clinically relevant experimental models	
Challenge	Due to the complexity of personalised diseases states preclinical model development is still challenging. There is still a lack of robust preclinical models that can sufficiently and reliably replicate patient stratification. Further scientific and technological advances are needed.
Objective	Research is done to develop new or to improve preclinical models that finally proof clinical relevance. Validation of the models is conducted in different labs to demonstrate the robustness of the models and thereby show reproducibility of research outcomes. Detailed technical reports how to set up and use the models are generated within cardiac, metabolic diseases and cancer. The tools for this kind of analysis and interpretation of genomic data need to be established.
Outcome	New and advanced preclinical models for PM approaches for various disease areas are in place and are further disseminated among the relevant research communities.

04 - Robust and reproducible preclinical studies	
Challenge	Due to the complexity of PM, to date, preclinical models do not accurately reflect patient heterogeneity in a single model. Deep molecular phenotyping to uncover the heterogeneity of diseases, as well as the variability in response and tolerability of treatments, is crucial for model improvement. A more realistic strategy, which would reinforce the pathophysiological understanding of PM, would be the combination of different animal models that together represent patient variation.
Objective	The use of several models when modelling complex disease, in order to represent different features of the disease would be appropriated. It requires preclinical experimentally tractable models recapitulating as much of the human pathophysiology, representing an unevaluable opportunity to identify preclinical stages of diseases, to build diagnostic and prognostic practices, make adequate differential diagnoses and design advanced therapies.
Outcome	Predictive validity, the ultimate goal of preclinical work, may be further enhanced by testing therapies in diverse genetic backgrounds as different animal models that more closely reflect the outbred human population and, therefore, may better capture the breadth of pathophysiology seen in patients.

05 - Single-cell technologies in combination with Artificial Intelligence (AI) and Machine Learning (ML) for PM	
Challenge	An earlier and more accurate disease diagnosis, personalised therapy selection and population health monitoring is needed to reach the full potential of PM, for example based on early cellular pathological changes.
Objective	Single-cell technologies could support the development of new diagnostics by applying single-cell spatial approaches to longitudinally acquired patient samples and/or patient-derived disease models obtained from well-defined cohorts, covering health, early stages of disease, disease progression and response to therapy. New AI-driven analytics are essential for the analysis of such large datasets. The predictive computational models may lead to the identification of new, more informative, molecular, and cellular biomarkers that are directly linked to the mechanisms that drive disease onset and progression. This approach may also identify new drug targets for disease modifying therapies.
Outcome	The increased knowledge of the early molecular and cellular changes that drive the onset of diseases will lead to improved disease screening and detection, precise and personalised interventions and earlier detection of therapy resistance and relapse in patients – and even prevention. The identified new drug targets enable the healthcare industry to develop disease-modifying therapies, incl. cellular and RNA-based therapies, to intercept disease.

06 - Early considerations of security, efficacy, and evidence for advanced therapies (ATMPs)	
Challenge	There are several new methods and technologies for advanced therapies in the pipeline with potential for PM approaches, but they are too premature to be translated into clinical practice. These advanced therapies or ATMP (advanced therapy medicinal products) include gene

	therapy, somatic cell therapy and tissue-engineered medicines. They may contain one or more medical devices as an integral part of the medicine (combined ATMP).
Objective	New advanced therapy approaches for PM need to be enabled to show proof of safety, efficacy, and functional evidence to allow the fast development into clinical practice. These new approaches are mostly applications of stem cell therapies.
Outcome	Several new advanced therapy approaches are accelerated in direction of clinical studies.

07 - New treatment modalities for PM	
Challenge	New technologies and a more detailed understanding of disease mechanisms do not always lead to improved PM treatment options yet. New modalities of treatment could help overcome this gap between knowledge and clinical applicability.
Objective	Development of new treatment modalities building on an understanding of the biological mechanisms is needed. To be able to personalise treatment based on multi-dimensional diagnostics we need to develop a range of treatment options such as Advanced Therapy Medicinal Products and technologies including cell and gene therapies, and oligonucleotide-based drugs. The development of a therapeutic “tool-box” will be supported. Furthermore, the development of the targeted delivery of these new modalities needs to be addressed.
Outcome	A new, broader range of treatment options/modalities allows more individuals to get the right treatment reaching the right target based on a precise diagnosis.

08 - Medical devices and in-vitro diagnostics to support PM innovations	
Challenge	The potential of medical devices and in vitro diagnostics to support PM approaches are not yet fully utilised.
Objective	Research into the development of medical devices and in vitro diagnostics that address medical and market needs should be supported. In vitro diagnostics using for example micro-samples of blood or other fluids for a faster and more affordable use. Pre-clinical or clinical researchers should be encouraged to cooperate with medical device experts for setting up pre-clinical studies and identifying or establishing suitable patient cohorts. This could be done by partnering with suitable medical organisations Guidelines could be developed for medical devices and in vitro diagnostics to reach the market. This may include preclinical testing. The development of implantable biosensors and smart wearable biosensors for continuous patient monitoring, specifically on chronic diseases.
Outcome	Assure safety, security, and feasibility and accelerate the time-to-market of medical devices in order to utilise their potential to contribute to PM approaches.

09 - A collaborative approach between pre-clinical and clinical research	
Challenge	Integration of pre-clinical research with clinical research and public health is complex and often difficult when lacking a collaborative approach. Researchers and clinicians have diverse ways of thinking and decision making. Only a limited number of clinicians participate in research, which

	is a bottleneck for developing and implementing PM approaches. In consequence, the translation of research (from bench to bedside) is not yet optimal, as too few promising results from fundamental research reach the clinical research stage
Objective	A two-way interaction is required from fundamental to clinical research and vice versa. Dedicated exchange formats and networks within institutions or regions could be established. Clinician scientist programmes that already exist in some countries and regions could be a taken up more widely. Dedicated research funding programmes could be set up that require collaboration between the preclinical and clinical field.
Outcome	An interdisciplinary collaborative ecosystem between fundamental and clinical researchers is in place. This will lead to both more comprehensive and faster uptake of PM approaches from pre-clinical to clinical research and implementation – with the ultimate aim that "Today's research is tomorrow's healthcare".

10 - Active involvement of patients in PM research	
Challenge	The active involvement of patients or patient representative in research projects is increasing, but there is still room for improvement. So far, not enough sustainable resources and tools for educating and training citizens, patients and patient advocates are in place, hindering their active participation across the entire research and development lifecycle of PM. An active participation of patient representatives can increase the relevance and applicability of research results.
Objective	Foster involvement of patients and citizen representatives in PM developments from the early stages of research, e.g., through mandatory involvement of these stakeholders in research and development projects. Train patient representatives so that they can contribute to research projects at all stages, e.g., by co-designing research activities or information campaigns about research outcomes. Support investigators who commit to focus their research endeavours on patient-oriented research. A mentored patient-oriented research career development award on the European level might be established.
Outcome	PM research is accompanied adequately by citizen and patient representatives. The involvement of patients in PM research result in PM approaches that better follow the patients' needs, have a higher potential to be accepted by the end users and will be more easily applicable in healthcare.

11 - More biomarker evidence for PM	
Challenge	Not enough suitable biomarkers are available to guide treatments, clinical studies, and disease progression or remission. More in-depth knowledge and experience in interpreting biomarker data is needed.
Objective	Further development of biomarker discovery and analytical methods should be supported. This should be done as public-private activities with involvement of end users. The framework for running clinical validation studies of biomarkers and diagnostics should be improved.

	Specifically, it is needed the research for new software that allows the bioinformatic interpretation of complex set of analytical data used for biomarkers validation and diagnostics. Quality control and cross-validation studies for the different methodologic and analysis techniques and the validation of the bioinformatics interpretation of the data would be as well required.
Outcome	Biomarkers and diagnostics are available to diagnose and follow disease progression and treatment outcomes in a real-world clinical setting. Biomarkers are available to identify the right patient cohort for the right treatment and for the right clinical study.

12 - Combination Treatments	
Challenge	When developing treatment biomarkers, the focus is on detecting the effect of one drug. The reality is that in principle almost always treatments are combined. There is not enough knowledge yet about the effects of such combinations, so that patients often do not receive the most effective combination of treatments.
Objective	Tools and biomarkers need to be developed to enable a systematic multimodal diagnostic and a system level understanding of PM treatments, considering multi-medication and comorbidities. Methodologies for a follow-up of each patient in a real-world context should be developed, and the data generated should be used for further improving the system level diagnostics and treatments.
Outcome	Precision health is implemented, and individual treatments are much more effective, also in cases of combination treatments and multimorbidity.

13 - Broader biomarker approaches to enable more informed health decisions	
Challenge	There is still a high risk for biases in and accuracy of AI approaches, including the understanding and consideration of complex biological processes. Currently, mainly single-biomarker approaches are promoted by industry for their interventions. There is a need to develop inclusive models of 'signatures or marker profiles, considering several relevant pathways, thus going beyond single markers.
Objective	Identify methods to seek unbiased inference and inclusion of multilevel data by fostering the collaboration between data sciences and pre-clinical/clinical disciplines. Validation of epigenetics biomarkers useful as an early detection tool for certain diseases (e.g., oncology). Identification and validation of expression biomarkers (epigenomics and transcriptomics) in buccal swabs and/or blood, as well as liquid biopsy analysis (especially using extracellular vesicles samples) that could determine early detection of certain diseases and improve the efficacy and affordability of the disease screening.
Outcome	Shift from a single-biomarker approach to multiple tests and comprehensive characterisation to inform several choices and options that health professions and patients can consider. This will lead to improvement in robustness and interpretation of personalised diagnosis outcomes.

14 - Validity and Prognostic Value of a Polygenic Risk Scores	
Challenge	Complex multifactorial disorders may be caused by the interplay of genetic and non-genetic risk factors. Polygenic risk scores (PRSs) are one way to aggregate the effects of many genetic variants and estimate the risk for a certain disease in a single quantity. However, reassessment of the performance of a given PRS in independent data sets is a precondition for establishing the PRS as a valid tool to this end.
Objective	Test the validity and prognostic value of a Polygenic Risk Scores
Outcome	Generalised options for using PRS, better prediction and health outcomes

15 - Medical cohorts for collecting high-quality health and molecular data	
Challenge	Access to high-quality health and molecular data is still limited. The aim that health data should be accessible, interoperable, and re-usable is not yet reached. In addition, the necessary algorithms and machine learning tools are not yet in place.
Objective	Medical cohorts are a valid tool for structuring and annotating health and molecular data. Additional systems and tools should be created for improving the accessibility of health data under the given regulatory framework. New significant algorithms and machine learning tools for PM approaches should be developed for the analysis of the data in various disease areas. Specific software and specialised clinicians for the interpretation of genomic and other types of data are needed to be able to integrate the software in the clinical decision support systems. Pilot projects or point of care calls could improve and showcase data utilisation and outcomes. Electronic health record with complete recorded profile of each person from their birth, including a broad type of data (genomic, proteomic, metabolomic, etc.) for improving early disease diagnostics.
Outcome	More well-structured medical cohorts are established and provide qualitative data for research and care. A couple of well characterised and validated algorithms and machine learning tools are ready to be implemented into healthcare. Data generated within healthcare is utilised to a larger extend for generating valuable information on health outcomes, for improving healthcare and for a realistic cost estimation.

16 - Standardisation framework for data integration and data-driven in silico models for personalised medicine	
Challenge	There is a lack of a standardisation framework for health data collection, analysis, and interpretation. The need for reproducible capturing sample and data processing, lack of data standards and common terminologies and data protection and privacy issues.
Objective	Foster the development of a standardisation framework for data integration and data-driven in silico models for PM, standards for use-cases supporting and data reuse. The standardisation of disease codes would enable interoperability. FAIR principles and the use of metadata shall be

	fostered in PM research, in order to assure the findability, accessibility, interoperability and reusability of the health research data.
Outcome	A federated data model with well annotated and large multi-national data sets and well-connected repositories within the healthcare system would facilitate a broader health data access and reuse and the acceleration of PM research.

17 - PM clinical research in a wide variety of disease indications	
Challenge	Clinical trials for PM approaches are costly and complex to be set up. In addition, it is difficult to identify the right patient cohorts, mainly due to the small size of these cohorts and due to the lack of precise diagnostic data. Some disease areas, e.g., cancer, are already quite advanced in this field. Others lack behind, even though there are very promising approaches for PM applications.
Objective	Funding of clinical research, if possible, including early clinical trials, in PM covering a wide variety of diseases, in particular the large field of noncommunicable diseases.
Outcome	Results and reports of PM clinical studies for different disease areas are available for further implementation into healthcare.

18 - Inclusive clinical PM research that avoids bias	
Challenge	Due to uncomplete datasets, PM approaches are not broadly applicable and lack to target the right interventions, i.e., underrepresentation of certain groups of patients or populations. The critical mass and necessary baseline of information is not yet available.
Objective	Boost the participation/representation of different groups in clinical research and clinical trials in multiple dimensions (age, gender, socio-economic status, races, etc.); more diverse, equitable and inclusive biomedical research that could truly guide and support PM.
Outcome	PM applications are broadly (internationally) applicable and in different settings (age, gender, socio-economic status, genetic backgrounds, etc.).

19 - Online recruitment strategies to support PM clinical research	
Challenge	Current data protection regulations prevent easy access to patients, which makes setting up clinical trials and recruiting patients difficult. Stratification amplifies this as it leads to a development of “rare diseases” with only few patients per stratification group.
Objective	Online recruitment strategies (e.g., patient registries) should be set up, sharing patient cohorts, and adhering to data protection regulations. Support to improve infrastructure/network for patient recruitment across Europe and globally.

Outcome	Easier and faster, but still ethical access to patients for clinical trials.

20 - Proof of concept for personalised prevention strategies	
Challenge	To get a full picture of the potential of and evidence for personal prevention that replace "one-size-fits-all" approaches. Preventive interventions require well-defined risk classification so that personalised preventive strategies and specific treatments could be applied to cohorts with a documented increased risk to develop a disease, instead to the general population as a whole.
Objective	Establishment of pilot research projects for personal prevention to discover and validate surrogate cancer biomarkers with both prognostic and predictive value to detect and monitor the efficacy of interventions in clinical trials and beyond. New personalised approaches are developed and tested that exploit the growing knowledge of molecular and biological disease mechanisms. Large scale studies to gather evidence of the personal, health economic and societal benefits of preventive measures (primary, secondary and tertiary).
Outcome	Proof of concept for several personal prevention approaches allowing to understand the basis of risk and identify individuals or groups that will optimally benefit the most from interventions. New approaches that exploit the growing knowledge of molecular and biological cancer mechanisms should be developed and implemented.

21 - Development of personalised preventive medicine strategies and therapies	
Challenge	There is a constant increase of burden for healthcare systems for all, high and low-income, countries for communicable and non-communicable diseases resulting in high demands for healthcare providers due to increasing patient numbers and high treatment costs. For the development of personalised preventive medicine strategies and therapies, there is a need to identify and validate markers that indicate the risk to develop a disease before its manifestation (primary prevention) or for early disease detection (secondary prevention).
Objective	Identification and combination of various factors (individual, genetic, multi-omics and environmental) to determine individual's risk. An integrative approach combining all these risk factors together will provide a more comprehensive and accurate assessment of risk for each individual. Identification of polygenic risk scores for stratified disease risk prevention, considering all factors in the disease progress (e.g., host factors in infectious diseases). Promotion of personalised prevention strategies and therapies, such as early detection of multiple diseases, personalised vaccines, and immunotherapy. Development and validation of epigenetics biomarkers that could be used for detecting predisposition or higher risk for certain diseases at population level (e.g., in oncology). Personalised prevention through faster and affordable blood analyses of biomarkers and predictive diagnosis (e.g., new-born screening, hereditary disease etc.), as well as non-invasive tests through biomarkers analysis e.g. in blood and buccal swabs. Liquid biopsy analyses e.g., also in extracellular vesicles to increase the sensitivity of the sample to allow early detection of diseases. Introduction of implantable technologies and wearable biosensors for monitoring patients fostering telemedicine. Utilisation of microcapsules and other nanomedicine technologies for disease diagnostic within the human

	body. Development of clinical trials for these advanced medical devices and nanotechnologies to allow a faster market access.
Outcome	The burden of diseases can be lowered through a preventive approach, with early detection of diseases and preventive therapies, such as vaccines. Chronic patients can be better monitored through the utilisation of e.g., wearable biosensors or mHealth monitoring apps, improving their quality of life. The development of faster and affordable biomarkers and detection new techniques for early detection and predictive diagnosis can spread the disease screening in the whole population for a more equity and efficacy preventive strategy.

22 - Implementation Research in PM	
Challenge	Due to the complexity of PM approaches, that usually require the combination of various diagnostic tools, technologies, therapeutic or preventive interventions, and due to the complex contextual factors of the healthcare settings implementation of PM approaches are difficult. Quite often PM approaches work in small-scale pilots at a specific place where they have been developed but fail to be scaled-up on national level or to be transferred to other countries.
Objective	Implementation research in a multidisciplinary setting engaging a wide range of stakeholders will be conducted to analyse the complex implementation challenges of specific PM approaches and to reveal the factors essential to be addressed in order to make the implementation of these approaches successful. PM implementation research will analyse information in real time, will assess the performance and will develop guidelines for scaling-up, for refinements, adaptations as well as for transfers to other locations.
Outcome	Increased knowledge, number of articles and tools on PM implementation research will be available that will support decision makers and healthcare providers in their capacity to learn from real world settings and to implement and to up-scale PM interventions.

23 - Health and patient-centred outcomes research in PM	
Challenge	Although the vision of patient-centred care is well promoted in health policy there is still a lack of evidence on patients' satisfaction and quality of life with PM approaches, since PM is a new model in healthcare. Unlike clinical trials that consider very specific measurable data a broader view on clinical outcomes and health impact is required in healthcare on the long run.
Objective	Health and patient-centred outcomes research will be conducted to analyse a broad range of measures in context with specific PM approaches including patients' reported quality of life and satisfaction.
Outcome	New knowledge, evidence-based findings, and evaluation studies on health outcomes of PM approaches will be available and will support health systems in the implementation of high value care.

Chapter 3.2: The Innovation System

24 - Early cooperation between public research and the private sector	
Challenge	An early cooperation with the public and private sector is needed to get PM into the market / health systems.
Objective	Facilitate the communication of successful PM research projects between public institutions and industry and SMEs. This could be achieved by establishing an appropriate communication platform. This approach could be supported or even developed by existing platforms, e.g., EIT Health. The platform should also provide a forum to understand user needs, with users, HC professionals, patients, citizens. Innovations that serve no users will not be successful even when brought to the market.
Outcome	PM research achievements are communicated public and private sector in a timely manner; public-private partnerships are formed which will increase the chances to get PM innovations into the market and accessible to the patients and citizens. User needs are adequately considered when developing innovations.

25 – Improved Intellectual Property (IP) regulations for PM-based approaches	
Challenge	The development of PM approaches and products poses significant challenges in the field of Intellectual Property (IP) strategy/agreement. In many technologies underpinning PM, IP protection is limited and complex in use (e.g., in the case of algorithms and artificial intelligence or databases) thus failing to convey proper protection where needed. In some parts, this uncertainty derives from too vague definitions and a lack of international consistency. Thus, IP rights for PM products may differ significantly in important markets.
Objective	A clear IP protection is fundamental to channel R&D investments and support entrepreneurship. Establish a clear IP regulation that consider both the public and private partners. Support ad-hoc training programmes, especially in relation to data and data processing systems.
Outcome	More safety for industries who invest in PM, especially in Small and Medium Enterprises (SMEs) and start-ups, while still allowing for public-private partnerships

26 – Expanded knowledge on value for PM	
Challenge	We need to expand our knowledge on value beyond the clinical and health economic domains. Reimbursement strategies (diagnostics and therapeutics) are needed which have a value perspective and not an exclusive cost one (value over time and not the costs of the diagnosis and therapy itself). So far, we have a good understanding regarding HTA value, on the health economy side. But there are other repertoires of value, e.g., how does a treatment affect a person's social functioning, or their capabilities. Currently there is no systemic way to address this.

Objective	The matrix of value needs to be broadened, beyond the clinical and health economic value. Evidence development studies should be performed, considering clinical and economic data of PM approach benefits and challenges that might occur in different healthcare systems. In addition, Interdisciplinary research projects are needed that address societal issues and develop methods for ethically dealing with personal data. Further research is needed to broaden the matrix of value systemically. The value question goes beyond ethics; it is relevant for regulation as well.
Outcome	Health economic evaluation and assessment of PM will be more "personalised", considering ethical and regulatory aspects. This would result in fairer and broader health economic evaluation and implementation approach. Reimbursement regulations are in place when PM diagnostic tools or therapies are ready for clinical practice.

27 – Adapted payment models for PM	
Challenge	Existing payment models cannot capture dependency of diagnostic and treatment nor the data acquisition.
Objective	Adapted payment models for PM must be developed by the responsible stakeholders. For example, the Drug Rediscovery Protocol (DRUP)-like trials with pragmatic risk sharing models are a promising first step for that.
Outcome	Adequate payment models exist, leading to faster and easier implementation of PM approaches into healthcare systems

28 – Value based reimbursement models for PM	
Challenge	Often new treatments approaches are available, but they are not implemented. Sometimes this is due to arguments that evidence of cost-benefit is lacking. There is a need for a new paradigm on how to collect data for pricing. Convincing and PM adapted cost-benefit analysis are missing. Reimbursement strategies (diagnostics and therapeutics) are needed which have a value perspective and not an exclusive cost one (value over time and not only the costs of the diagnosis and therapy itself).
Objective	Research in novel health economics models that could demonstrate value to payers is needed. These should be better suited to PM approaches/treatments. Also, access to real-world evidence (RWE) is crucial, that allows the follow up of clinical effects in combination with testing and development of new models for health economic assessment
Outcome	Payers embrace both the concept and the value proposition and adapt accordingly. That could increase the "pull" mechanisms for PM innovation to be implemented in health systems. Effective and sustainable treatments are available for more patients and strategies for reimbursement are in place.

29 – Incentives for enterprises supporting research and development	
Challenge	Enterprises do not have the proper incentives in place to allow PM developments, including incentives tackling the costs (e.g., for treating a disease intervention compared to long-life treatment drugs).
Objective	Adapt policies to encourage innovation. Develop risk and cost sharing models that allow enterprises to make the paradigm shift from treating symptoms to curing a disease. Add an open dialogue with the pharma industry/MedTech about the challenges with pricing and reimbursement models building on sharing risks. Support to pilot and demonstration projects.
Outcome	Incentivised environment for industry (pharmaceutical and diagnostics) which allows to focus on PM-based approaches and at the same time ensures long-term sustainability for industry. The resulting lower risk for commercial research and development accelerates innovation.

30 – Early consideration of regulatory frameworks and authorities	
Challenge	Pre-clinical research in PM is not always well-informed about the requirements of the regulatory framework needed for later translation and implementation. This can slow down or even prevent the implementation of PM approaches into commercial products and clinical practice.
Objective	More networking and early guidance about the requirements of the regulatory framework (e.g., IVDR, MDR) should be offered already in pre-clinical research. On a similar line, an early dialogue with EMA (European Medicine Agency) /NCAs (National Competent Authorities) should be supported where relevant.
Outcome	A research community that is informed about the regulatory framework, follows measures for a smooth innovation and implementation process of PM and considers all methodological standards.

31 – Keep the regulatory framework up to date with innovation	
Challenge	Research and innovation within PM are developing very rapidly and if the regulatory framework is not kept up to date accordingly, the new and improved treatments will not reach the patients. For example, traditional regulatory and HTA strategies cannot be supported by the much smaller patient groups in PM-based clinical trials.
Objective	Analyses, evaluation, and development of existing regulatory frameworks. Identify and implement new models for regulatory/HTA strategies
Outcome	A regulatory framework that enables PM approaches and supports equity across and within societies and which makes implementation of PM-based treatments in healthcare practically possible.

32 – Clinical trial design adapted to smaller patient groups	
Challenge	There is a lack of evidence from small patient groups to allow the approval and decide on reimbursement levels.
Objective	Where large double-blind studies cannot be performed and efficacy is lacking, develop tools that include real world data to build evidence. Support continued evidence generation post introduction of new treatments/therapies.
Outcome	Clinical trial design available that is adapted to smaller patient groups, allowing studies that build evidence on outcome measures and thereby feed into reimbursements models fit for purpose.

33 – Improved market access for companion diagnostics	
Challenge	The development and full-value chain integration of comprehensive innovative diagnostics is an essential prerequisite to achieve personalisation of therapeutic interventions. PM can only realise its potential if companion diagnostics (CDx) are not only developed, but also marketed and applied in clinical routine. Currently, lots of therapeutic potential is lost due to insufficient use of existing testing options. Regulatory fragmentation poses an important bottleneck in this context.
Objective	Market access regulation as well as reimbursement policies should set incentives to support the approval and application of companion diagnostics, allowing faster market approval and uptake. Risk sharing strategies between industry and healthcare payers & providers will enable a more rapid access to companion diagnostics for patients.
Outcome	A regulatory framework that enables PM approaches and supports equity across and within societies and which makes implementation of PM-based treatments in healthcare practically possible.

Chapter 3.3: Implementation

34 – Test Beds in hospitals	
Challenge	Successful PM approaches are not implemented into the health system/s and the healthcare setting
Objective	Install 'Test beds', e.g., in (university) hospitals, that create the environment for conducting rigorous, transparent and replicable testing of PM approaches, computational tools and new technologies. Funding of 'Test beds' could be supported through demonstration pilot funding. They can also serve as knowledge and dissemination hubs for other clinics around Europe to visit and exchange knowledge
Outcome	PM approaches are tested under a suitable, real-life setting. This will speed up validation and implementation of these approaches. In replicating hospital conditions, 'Test beds' serve both, companies, and healthcare professionals, to test the suitability of their innovative healthcare ideas or devices. The time for product development is shorter and access to wider markets is accelerated.

35 – Accessibility and knowledge of genomic tools for healthcare professionals	
Challenge	Lack of knowledge and of accessibility for healthcare professionals to use genomic tools for their daily work with the patient, not only for the diagnostic and treatment but also for prevention.
Objective	Activities and tools are needed to support all healthcare workers and healthcare providers in their daily routine to consider and interpret genomic information.
Outcome	Increased knowledge, abilities and mindset of all healthcare workers and providers towards genomic tools in PM approaches, which will support the implementation and gain of PM in the healthcare systems.

36 – Use of pharmacogenomics and pharmaco-metabolomics in standard healthcare	
Challenge	Pharmacogenomics and -metabolomics as well as more basic electronic medication plans are currently not yet standard across Europe although their efficacy was already demonstrated
Objective	Make pharmacogenomics and -pharmaco-omics as well as comprehensive electronic medication and treatment plans standard of care across Europe.
Outcome	Reduction in medication induced adverse-effects, better treatment outcomes due to optimised dosing and prevent wrong or not necessary medication and treatment and reduced interaction during multi-morbidities and related multi-medication.

37 – Establishment of chronic disease management along with PM	
Challenge	Chronic disease management has greatly improved in the past, but disease management programmes currently still mostly do not operate along PM concepts and approaches.
Objective	Use PM approaches, e.g., by including multidata consideration, to better understand each patient's situation and personalise the chronic disease management for the benefit of the patient in a structured and standardised approach.
Outcome	Better and more efficient treatment, less adverse effects and most likely reduced costs by PM optimised models, especially in light of frequently occurring multi-morbidity.

38 – Develop and implement NGS testing	
Challenge	Accelerate the approaches to Next Generation Sequencing-based (NGS-based) genetic testing for PM in most of the citizens disrupting economic and social barriers to an individualized genetic test.
Objective	To favour the extended and diffuse use of genomic analysis for citizens, either with active disease/cancer or in health for cure and prevention
Outcome	A genomic "passport" or "avatar", with a whole genome or whole exons analysis performed for each citizen/patient, to address personalised approaches of prevention of diseases and particularly cancers, and favouring lifestyles and individual disease monitoring or surveillance

39 – Efficiency and value of PM approaches consider the full healthcare chain	
Challenge	To develop individualised care programmes and visualise the effects of PM approaches, we need to understand the complete care consumption incl. home care and the individual's own experience in terms of Patient Reported Outcome Measures (PROM) and Patient Reported Experience Measures (PREM). Healthcare needs to be coordinated around the individual instead of around the care centres. Today, healthcare is focusing mainly on productivity instead of efficiency.
Objective	Establish activities that strengthen the possibilities of evaluating complete care chains over time. Support the knowledge exchange and collaboration between clinics and regions across Europe, e.g., to use information driven decision making not only on an individual level but also on a system level. Develop patient centric value-based reimbursement models that incentivise integrated care measuring how well the patient is feeling, reported by the patient, using a method that moves from "What's the matter with you" to "What matters to you". Support the development of AI models that predicts a primary care clinic result from the population mix in the area. To reach a focus on efficiency, healthcare needs to be data driven.
Outcome	The effects of PM can be adapted on the individual patients need, monitored and evaluated using value-based reimbursement models.

40 – Establishment of Learning Healthcare Systems (LHS)	
Challenge	A true Learning Healthcare System (LHS) is not yet implemented. The idea of an LHS describes a health system in which science, informatics, incentives, and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process, [with] patients and families as active participants in all elements, and new knowledge captured as an integral by-product of the delivery experience.
Objective	Clinical data needs to be collected to generate knowledge and to apply it to improving practice. For example, from the Electronic Health Records, clinical registries or other routinely collected sources. Establish an LHS where clinical data (including genomic data) can be accessible for research and AI applications to produce innovation that can subsequently inform clinical care.
Outcome	Research would be informed on real world health issues and could more directly impact clinical care

41 – Establishment of decision support systems facilitating PM	
Challenge	There is still a lack of appropriate decision support systems (e.g., diagnosis, treatment choice, follow-up decisions and prevention) (infrastructure) that are suitable for the implementation into practice.
Objective	It is crucial to developed and integrate decision support systems, which are easy to understand and simple to use, e.g., to help the healthcare practitioners to consider and analyse multiple and diverse data sets.
Outcome	Successful integration and acceptance of PM related decision support systems in clinical practice in hospital and ambulant setting. Allow healthcare professionals to consider multiple data sets without the need to be specialist in all disciplines (epidemiology, modelling, image analysis, biomarker analysis, etc.). This will lead to improved care and treatment outcomes, decreasing adverse effects and time to correct diagnosis or adapt the treatment.

42 – Patient-centred care pathways	
Challenge	The individual's specific health needs and desired health outcomes are currently not or only to small extend considered in healthcare decisions and quality measurements. This hampers the acceptance of PM approaches and interventions.
Objective	Shift the focus from considering solely basic and clinical sciences to also include health systems sciences, including patient-centred care. Adapt national/regional curriculum frameworks for healthcare professionals to enhance communication skills with patients and citizens. Support curricula reforms for healthcare providers to create a new model for care together with patients and citizens. As a basis and in parallel: support train-the trainers' programs on national and European level.

Outcome	Patient-centred care has positive impact on patient satisfaction, treatment adherence and self-engagement. Outcomes and quality of life will be improved, and care disparity and care costs reduced. PM approaches and developed intervention will support patient-centred care and increase both quality of care and patient outcomes.

43 – Data collection by healthcare professionals for PM	
Challenge	High quality data collection from healthcare professionals required for advancing drug development and standard of care on top of patient's care is not realistic in the present healthcare setup.
Objective	Working with patients' groups and healthcare professionals, establish networks of data collection centres of excellence at regional/national level with key hospitals to provide best practices for primary and secondary use of health in a coordinated manner. Ensure data access and install coordinated data collection and data management technical and IT support, e.g. by working with Innovation hubs.
Outcome	Accelerate or revise Drug Development and Standard of care by having access to high quality data in a timely manner. Provide best practices approaches in line with of using the EHDS – European Health Data Space, that give a proof of concept of FAIR data, while protection the patients and ensure high quality data with minimum standardisation of data collection, storage, and use

44 – Availability and accessibility of real-world data and real-world evidence	
Challenge	Optimisation of and innovation in PM is highly dependent on the availability of and access to high-quality real-world data (RWD) and real-world evidence (RWE). This in turn requires the availability and accessibility of high-quality interoperable data regarding patient characteristics, therapeutic interventions and integrated (both clinical and patient reported) outcomes data. Both availability and access are currently not optimal and represent a bottleneck in PM research.
Objective	Frameworks, tools, and incentives should be developed, that support the healthcare systems in producing and using integrated data sets. These should be made available for secondary data use according to FAIR (findability, accessibility, interoperability, and reusability) principles.
Outcome	Improved treatment outcomes and sustainability of healthcare systems through better and faster development and monitoring of PM approaches.

45 – Feedback loops from clinical application and patients experiences to R&I	
Challenge	Feedback loops from the patients and healthcare system back to the research community and the innovation system/players are not yet in place. "Information silos" need to be opened out and should be avoided. The tools and knowledge generated are not synchronised with the needs of healthcare and patients.

Objective	Develop and establish tools/platforms to allow feedback loops from the patient/healthcare system providers and payers back to the research community.
Outcome	Better and faster refinement of already implemented, secure and tailored PM approaches in diagnosis and treatment.

46 – Create evidence and communicate PM success stories	
Challenge	Many new methods and treatments never reach the patient. The very same time, healthcare needs to be adapted in order to be ready to uptake new developments.
Objective	Create a collaborative-partnership environment so that the healthcare system better utilises new or refined tools and knowledge developed. Showcase the good examples. Fund efforts to connect researchers/clinicians across Europe and globally for knowledge and exchanges of personnel.
Outcome	More new treatments and knowledge is integrated into clinical practise and reach patients.

47 – Improved awareness for patients and citizens for PM	
Challenge	There is currently a lack of awareness of patients and citizens for PM and its concept and abilities. The general population needs to be informed about PM approaches, including diagnostic, therapeutic and prevention strategies.
Objective	Increase the PM knowledge of patients and citizens. Work with key patients' organisations and non-governmental organisations (NGO), representing different populations (gender, age, ethnic, etc.). Develop web-based tools to support the knowledge and awareness for PM approaches as well as a platform for the public exchange about PM in general and innovative approaches in specific.
Outcome	The impact of "Internet Fake Information" is significantly reduced. A "pull" effect for PM approaches in diagnosis, treatment and prevention by patients and citizens is created, and the request of the population to access existing and develop new PM approaches is increased. Perception and ethical challenges linked to PM are overcome and therewith acceptance is increased. The impact of PM is accelerated, leading to better standards of care.

48 – Training and Education of people and patients	
Challenge	To get PM approaches successfully into the health systems and to the patients, the benefit and value of PM need to be communicated appropriately to the public.

Objective	The active participation of people and patients in research and the implementation of PM from the early stages would inform patients and thereby foster the uptake of PM approaches into the health systems.
Outcome	PM research is accompanied adequately by people and patients thus the development is of more value and the patients are aware of them, which fosters the knowledge and support a fair access for people and patients.

49 – Training and Education of healthcare professionals	
Challenge	Medical communities, at the start of their career and constantly during their professional practise, need to be trained in PM approaches.
Objective	Establish healthcare professionals (HCP) PM buy-in by integrating PM as part of their curriculum and continuous training of HCP during their professional career.
Outcome	The right competencies and knowledge are available to implement PM approaches for improved health and care.

50 – Interdisciplinary PM research projects co-developed with experts in social sciences	
Challenge	The societal impacts that arise with PM research and implementation are not yet fully understood.
Objective	Interdisciplinary and co-developed research projects should be established, e.g., with experts in social sciences. They should address societal and ethical issues of PM and develop methods for ethically dealing with personal data. A possible output could be publications, recommendations and policy briefs.
Outcome	Implementation research is part of scientific projects from the very beginning, fostering the implementation of PM in society. An ethical regulatory framework that supports equity in access to PM across and within societies is in place.

Chapter 4: Overarching activities

51 – PM innovations in a regional environment	
Challenge	Development of medical products (incl. in vitro diagnostics) and therapeutics that address medical and market needs.
Objective	Making use of local innovation systems to ensure early contact for possible cooperation with enterprises and suitable handover points for R&D processes; involvement of clinical/medical experts; establish and maintain forum of experts from technology research and engineering, industrial development, and medical practice.
Outcome	Facilitate the comparison of parallel structures in order to detect and avoid it faulty developments from proof of concept to market-ready products

52 – Network of regional innovation hubs	
Challenge	Regional innovation hubs represent regional actors that may further innovations and drive PM. The potential of the regional innovation hubs is not sufficiently exploited or visible in most of the EU partnerships. The regional innovation hubs integrate multidisciplinary and intersectoral expertise which is required to translate research findings and accelerate the absorption of PM-based approaches.
Objective	The Vanguard Initiative represents a connected network of regional innovation hubs, fostering activities to support innovation and absorption of innovation. The VI Pilot Smart health focusses on PM, but also some of the other pilots contribute to the development of PM. Connecting to the VI brings the actors together that will accelerate access to PM in all EU regions. The connection to national centres and actors will further support innovation in the field to translate novel research results, insights, and solutions into clinical practice, upscale to market access and accelerate the uptake into healthcare systems. The network could share resources, gather the critical mass for global competitiveness and be open for collaboration across the entire value chain.
Outcome	Creating a network supporting innovation in Europe will provide broad access to and uptake of new technologies. Innovative PM approaches for diagnosis, treatment and prevention will be developed faster, and their uptake in regional/national healthcare policies will be improved.

53 – Aligning regional funds for PM	
Challenge	Most regions address health innovation and development towards personalised and preventive medicine in their RIS3 strategies. The RIS3 strategies are the basis for the ESI Funds to be spend. The regionals funds are the largest supporting programme in the EU, but difficult to access and to align with national or other European funding. Under the Vanguard Initiative new funding mechanisms are being developed to overcome some of the funding barriers of the ESI Funds. Alignment mechanisms with other funding sources may alleviate the fragmentation of funding

	mechanisms and hence when applicated in the context of EP PerMed, prove an important asset for innovation and absorption of PM.
Objective	Aligning regional funds with other funding sources to alleviate the fragmentation of funding to accelerate innovation and absorption of PM in EU. This will also support interregional collaboration and stimulate inclusiveness and access to PM-based innovation for all.
Outcome	Reduce the fragmentation of funding for innovation. Improve interregional collaboration and integration in the field of PM. Ensure inclusiveness and access to PM-based approaches for all.

54 – Connected large-scale health databases	
Challenge	Access to large-scale health databases is still limited. So is the number of these databases, as well as the amount, interoperability, and quality of health data available. Multidimensional, time-series data for people of diverse ethnicities will be required to avoid bias – and so will powerful computing infrastructure to analyse these data.
Objective	Support is needed for linking large-scale health databases containing high-quality, multidimensional, time-series data for people of diverse ethnicities including powerful computing infrastructure to analyse these data.
Outcome	Large-scale health databases are accessible, connected and utilised with an adequate balance between privacy and public benefit. They are a valuable resource of high-quality health data for research and healthcare and contribute to speeding up the development and implementation of PM approaches.

55 – PM adapted and focused biobanks and real-world data registries	
Challenge	Biobanks and Real-world data (RWD) registries are powerful data generation tools which employ highly trained staff, standardised and quality-controlled procedures, an elaborate data management system and an adequate infrastructure. Despite the benefits, investment in these infrastructures are still lagging behind. In addition, missing access policy for researchers and innovators makes the valuable source of information greatly unexploited.
Objective	Invest in regional and interregional centralised, connected and interoperable biobanks and health data repositories. Establish access policy for research and innovators which meet ethical and security standards. The legal framework needs to be adapted to allow for sample collection and data collection for a broader systemic analysis. Today, it requires, on the research side a broad ethical approval and informed consent. Need for optimised protocols for biological sample collection to allow systemic multimodal diagnostic approaches not only for one single purpose.
Outcome	Well curated, easily accessible, high quality data infrastructures and biobanks are generated for example as basis for application of Artificial Intelligence (AI) or Machine Learning (ML) methodologies.

56 – Genome-wide association studies within and beyond Europe	
Challenge	PM approaches are often developed with a restricted dataset (for that the right to use the data was permitted) and are therefore often not applicable globally and in different genetic settings. It is still challenging to share genome data cross borders and globally for one common goal.
Objective	Attaining a critical and more diverse mass of data by collaborating with researchers from non-EU countries to develop and train algorithms and models utilised in PM approaches. Identify and link with relevant international PM communities and develop a global PM agenda, integrating and promoting common standards. Ensure that developed approaches are applicable as broadly as possible and not limited to a specific European context and support EU foreign policy contributing to UN development goals. International knowledge exchange programmes where clinicians meet and exchange experiences.
Outcome	Very large and diverse genome-wide association studies uncover many novel genetic factors associated with important diseases. Trans EU coordination efforts improves the international standing of EP PerMed members and partners and implementation of PM at an international level.

57 – More widely implemented, ethical and secure genetic screening programmes	
Challenge	Both patients and society could benefit from comprehensive knowledge of each individual's genetic information. This could even be implemented as a genetic screen for new-borns. However, today access to genomic profiling varies greatly across (EU) citizens, mainly because of economic and social barriers. In addition, ethical and security issues are still a challenge for implementing large-scale screening programmes.
Objective	Demonstrate the benefits of such programs by establishing and supporting pilots to analyse and screen the genetic information on a regional or national level where possible. Learn from countries which have this already in place. Ethical and security aspects have to be considered before such an activity is launched. Establishing a genomic "passport" or "avatar" containing a whole genome or whole exons analysis for each citizen/patient could be considered.
Outcome	Genetic screening programmes and the respective date are available to be utilised when needed to inform and accelerate prevention, diagnostic and treatment, e.g., as actionable genomic variants for specific diseases.

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