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Contents

I- Executive summary

ICPerMed (www.icpermed.eu) is a newly established platform of over 30 European and international partners representing ministries, funding agencies and the European Commission (EC). The central aim of ICPerMed is to align and encourage joint efforts in personalised medicine research and implementation. This is the report of the First ICPerMed Workshop entitled „INNOVATIVE CONCEPTS ON DATA GENERATION AND USE FOR PERSONALISED MEDICINE RESEARCH" which took place in Milan from 26th to 27th June 2017.

From the work carried out so far by ICPerMed, (big) data, the potential for using this data and also the challenges in generating reliable datasets have turned out to be some of the key issues in fostering research and implementation in the field of personalised medicine. In line with this, the aim of this first ICPerMed workshop was to identify current knowledge, best practices and new advances in the field of Personalised Medicine (PM) and the use of data in this context.

The workshop facilitated the exchange of experiences and ideas between ICPerMed members and international high-level experts in PM. It was organised around five parallel working panels focusing on five key topics: Prevention in PM; the Reclassification of genetic diseases; the Impact of data analysis in PM research; Successful PM approaches; and New tools in PM.

During the workshop, the panels developed strategic recommendations which will enable ICPerMed to prioritize the next steps regarding the implementation of PM, in line with their own objectives. The translation of new knowledge, new tools and technology into improved patient outcomes will contribute significantly to enhancing healthcare systems. The three main lines of research focus on the improvement of prevention, specific diagnosis (biomarkers) and more effective therapies (e.g. pharmacogenomics).

A set of recommendations was developed, with some conclusions that were common to all panels, indicating the necessity to increase efforts in the following areas:

European infrastructures: In the short and midterm, it will be necessary to involve **more and more European facilities** involved in Personalised Medicine research, for example to expand on and improve Biobanking.

Training: the training of all stakeholders was recommended, including continuous training for clinicians in the use of new technology and big data dissemination.

Shared policies and data protection: The development of **shared policies** for informed consent across Europe is fundamental, as is the development and implementation of new EU legislation on **data protection** to ensure that it supports personalised medicine.

Standardisation and harmonisation: In the long term, the **standardisation and harmonisation** of all steps of data production, from the patient to the final database and its utilisation, has to be achieved.

The outcomes of the First ICPerMed Workshop are published by ICPerMed and will be integraed in future recommendations, guidelines and vision papers.

II- Workshop Introduction

The First ICPerMed Workshop on Personalised Medicine "INNOVATIVE CONCEPTS ON DATA GENERATION AND USE FOR PERSONALISED MEDICINE RESEARCH"; was co-hosted by the General Regional Foundation for Biomedical Research of Lombardy and the Italian Ministry of Health.

The workshop was structured around three sessions: An open plenary session, five parallel Working Panels focused on five key topics (WP 1 on Prevention; WP 2 on the Reclassification of genetic diseases: unresolved limitations and challenges; WP 3 on the Impact of data analysis in PM research; WP 4 on Successful PM approaches and WP5 on New tools - impact and research strategies in PM) and the Final plenary session which included recommendations and experiences from the different panels.

Open Plenary session

Dr. Marina Gerini (Director General of the Regional Foundation for Biomedical Research) and Dr. Gaetano Guglielmi (Head of Office 3, General Directorate for Research and Innovation in Healthcare, Italian Ministry of Health) gave a warm welcome to participants and reaffirmed that the purpose of the workshop was to foster advancements in research on PM as well as its practical application.

The Chair of ICPerMed, Dr.Mairead O'Driscoll (Health Research Board in Ireland) opened the plenary session by illustrating the opportunities offered by PM, followed by a presentation of the ICPerMed Action Plan.

Two keynote presentations ensued. The first, regarding the impact of data on PM research, was made by Professor Jaak Vilo of the Department of Bioinformatics at the University of Tartu in Estonia. The second presentation, concerning data collection and management in PM research, was given by Professor Alfonso Valencia, Director of the Life Sciences Department of the Barcelona Supercomputing Centre and Head of the Spanish Node of ELIXIR.

Professor Vilo illustrated that IT can further enable PM when it is integrated into a single infrastructure. He explained how the Estonian IT architecture includes population, health and vehicle data as well as databases for document management, banking and telecommunications. He explained how a well-integrated variety of clinical data can enhance PM and emphasised the importance of high-quality electronic health data analyses and good genetic databases.

Professor Alfonso Valencia described the various strategies in Data collection and Management in PM Research and introduced **ELIXIR Europe**. ELIXIR brings together leading life science organizations in managing and safeguarding the massive amounts of data being generated in publicly funded research. The impact of the infrastructure services delivered within the five technical Platforms established within ELIXIR will be informed by four examples (or 'Use Cases'): marine metagenomics, crop and forest plants, rare disease and sensitive human data.

III- Summary of the working panel results

Five parallel working panels (WP) were convened and asked to respond to a series of questions that had been given by ICPerMed in advance. The outcomes are summarized below.

III A. Specific Working Panel Reflections:

WP 1: Innovative Concepts for Data Generation and Data Use in Personalised Preventive Medicine.

The Session began with a keynote presentation "Predictive, Preventive and Personalised Medicine: Innovative European Concepts and Effective Implementation" by Prof. Dr. Olga Golubnistchaja (EPMA, University Hospital Bonn, Germany).The expert panel, with Dr. Vincenzo Costigliola (EPMA, EMA, Belgium) as rapporteur, discussed the main issues and challenges of Personalised Preventive Medicine: Innovative concepts of prevention using data obtained from new methods and establishing research data targeted on the prevention of frequent pathologies.

Panel answers to the lead questions posed by ICPerMed:

- *Do successful personalised preventive strategies already exist?*

Successful strategies were identified by the panel and include: vaccination against infectious diseases, maternity training for the prevention of perinatal asphyxia, improvement of modifiable risk factors for non-communicable diseases, such as healthy life-style in (pre) diabetes, personalised treatment of suboptimal health conditions according to the patient phenotype (individualised patient profile).

- *Which data sets are needed/most promising for the development of personalised prevention strategies?*

Individualised patient profiling is needed to predict pathology development and progression before the clinical manifestation of illness or disease.

- *Which levels of personalised prevention are most promising (primary, secondary or tertiary)?*

Primary prevention aims to prevent disease or injury before its onset. Secondary prevention aims to reduce the impact of a disease or injury that has already occurred. Tertiary prevention aims to soften the impact of an ongoing illness or injury that has lasting effects. All prevention levels should be taken into consideration. However, the most promising and cost-effective approaches are at the primary level. A recommendation could be to start with the creation of individualised patient profiling, including health and environmental data, to predict pathology development and progression before the clinical manifestation of ill health or disease.

- *Who would benefit from such strategies and who should/could pay for them?*

If the younger populations could benefit, it would result in a reduction of costs and a better quality of life for the elderly of the future.

Any form of public-private partnership is advisable with a primary investment by the State and additional budgets coming from insurance companies and direct payers.

- *How can new technologies be utilized in prevention?*

It is important to make technologies attractive to companies with potential to develop new products in the specialised area of "diagnostics and monitoring for prevention" (financial motivation). To make the most of such opportunities, corresponding regulations should be established by policy-makers to create a market and motivate the end-users (medical units and specialised centres, stratified patient groups).

- *Can the harmonization of data and making data accessible to policy makers help prevention?*

Harmonization and accessibility of data is an essential step in the overall process, as is the integration of all data sets, creating a link between health and non-health data, maintaining adequate control and constant evaluation and analysis of the resulting big data.

Further remarks, in addition to those recommendations common to other panels:

There is a need to increase investment in prevention in order to enhance access to preventive medicine with the objective of improving the health and well-being of an ever-increasing number of people.

New instruments and more personalised programmes need to be developed for effective prevention. ICT technologies, such as smart phones and wearable devices, are key elements for data collection as is tele-medicine.

Interaction between risk factors such as genetic, environmental and demographic ones should be analysed. The importance of systems biology on prevention needs to be considered.

Research on healthcare services is needed to implement effective prevention so as to reach as many individual subpopulations as possible.

WP 2: Reclassification of Genetic Diseases: Unresolved Limitations and Challenges

Prof. Dr. Tonon (San Raffaele Scientific Institute, Italy) started with an introductory talk on the impact of next generation sequencing approaches to disease classification. The Working Panel then followed on, with Prof. Dr. Nataša Debeljak (University of Ljubljana, Slovenia) as rapporteur, and focused on the key issues arising from the continuous evolution of genetic information e.g. suitable integrative methods for disease subtyping and biomarker discovery, as well as the tools that are available in the various medical specialities.

The panel decided to adopt a more comprehensive definition of genetic disease and predisposition, not focusing only on Mendelian, monogenic diseases, but extending the recommendations also to multifactorial conditions.

Panel answers to the lead questions posed by ICPerMed:

- *What lessons have been learned in research regarding disease reclassification?*

A new taxonomy of disease based on molecular data is emerging and needs to be harmonized with established clinical classifications, not only at national/regional level, but also at European level. Genetic and pharmacogenomics data, combined with phenotypic and multi-level pathological information, should be generated to move towards this new taxonomy. It needs to be characterized and validated in independent populations in order to be approved by the regulatory agencies, with the practical implementation of these approaches in all EU countries.

Patient stratification is too fragmented, leading to interventional and classification models that are not useful in practice. Benchmarks should be established, based on genomic and phenotypic information that will enhance prevention and provide diagnostics and treatments for the general population.

- *What are the key research issues regarding disease reclassification and its implementation into healthcare systems?*

There is a pressing need to standardize terminology, reporting methods and patient registries.

A uniform format needs to be adopted to collect genomic and clinical data and the personnel responsible should be trained in this regard. The standardization of available laboratory methods with regular updates is also important. In addition to this clinical terminology across countries needs to be harmonized and integrated with other initiatives in Europe, such as the European Reference Networks (ERN). The whole chain has to be economically sustainable.

The development of new tools for big data processing is required, especially for general practitioners, in order to for them to be able to implement and transfer genetic information to the patients or the general population.

Common implementation of shared policies in relation to informed consent should be encouraged across Europe. There is a strong need for education and dissemination.

In line with ongoing initiatives (e.g. BBMRI), biobanking efforts at the European level should be fostered, building upon rigorous protocols, and should be shared across countries.

In line with ongoing initiatives in systems medicine, integration tools for multimodal analysis need to be developed, integrating various datasets as well as behavioural and phenotypic information from animal models and the general population.

- *Who should/could be the responsible driver and key player for such a process?*

Key players are experts in each field, consensus panels, European clinical societies, European reference networks (ERN), research institutes, universities, health care providers, regulatory agencies, patient societies, bio-ethicists.

- *How should/could biomedical and ICT experts, as well as companies, be integrated?*

This is a daunting effort. Certainly, the basic training of all key players in computational medicine and the biomedical community is advisable in order to bridge the gap between these two worlds. Also, ad-hoc scientific meetings involving experts from these two backgrounds would be helpful.

WP 3: Impact of Data on Personalised Medicine Research

Prof. Dr. Valérie Barbié (Swiss Institute of Bioinformatics, Switzerland) and Virginie Hivert (EURORDIS, France), as rapporteur, discussed the existing challenges and innovative ideas concerning PM. This included the generation of cost-effective high-throughput data; data storage and processing; data integration and interpretation, as well as its individual and

global economic relevance; with an update of important developments in the analysis of big data and forward strategies to accelerate the global transition to PM.

The discussion started off with the concept "from bed to bench and back to bed" and with the need for an economically sustainable whole value chain. In particular, they stressed that the success of research in the field of PM will heavily rely on our capacity to generate, collect, share and analyse high-throughput data.

Panel answers to the lead questions posed by ICPerMed:

- *Are there already examples of best practices or lessons learned regarding data analysis in personalised medicine?*

High-throughput technologies have grown in the past 10 years. Citizens today have great expectations that Personalized Health will very soon improve their quality of life and the quality of medical care. Indeed, it is expected that access to huge volumes of previously unexploited data will allow researchers to better understand rare or complex pathogenic mechanisms, discover new drug targets or re-position existing drugs, with the potential to transform health management. But the journey from raw data generation to life-transforming discoveries is complex and heterogeneous and many elements can hinder success on the way. It is therefore the responsibility of the scientific community to identify potential hurdles and maximize the chances of success at each step of the research process.

An interesting example is the Swiss Personalized Health Network, where all the key stakeholders are involved in the governance: Government – Health – Research – Patients.

- *Which data sets are needed and which existing or upcoming developments are crucial?*

In terms of the "quality of pre-analytical phases", the recommendation was to capture experimental processes, ensure best documentation and develop a clear data management plan. Other needs are guidelines (writing or dissemination of existing ones); showcasing the return on investment of putting data together for the various stakeholders; and appropriate information and training. Mapping and perspective should be provided by ICPerMed, along with an engagement plan, and the opportunity of bringing people together to write guidelines.

- *Which approaches to utilise existing data sets are already known and which should be developed?*

The quality of data should be ensured according to the objectives to be achieved, in line with the FAIR principles (Findable, Accessible, Interoperability, and Reusable). National implementation of the General Data Protection Regulation (GDPR) should be harmonized, as should the mapping of a legal framework, best practices in the various countries, and data sharing initiatives and results. EU-wide informed consent would simplify data sharing and use. Default consent („tick to refuse consent" instead of „tick to consent") and dynamic consent could be considered.

There was also a call for funding case studies showing the value generated by PM, and for work on the workflow of PM to identify the meaning/impact of data at every step along the value chain.

- *How can we achieve comparable and aligned data sets in Europe in the near future?*

One suggestion was to create a feedback loop on decision outcomes and implement a medical treatment feedback process. Other ideas included incentives/governance/support for data collection, and the sharing and re-use of the data. It is important to identify stakeholder practices, give priority to projects that contain medical records-based and patient-relevant outcomes and investigate how better to interact with the IT industry in Europe.

WP 4: Successful PM Approaches in Oncology and Rare Diseases

The session was opened by Prof. Dr. Janna Saarela, from the Helsinki University of Technology in Finland, together with Prof. Dr. Capobianco (CCS. University of Miami, USA/CNR) as rapporteur. The focus was on successful strategic activities to assist patients and citizens that have achieved a better knowledge of the factors that may influence the personalised approach to prevention, diagnosis and treatment of cancer and rare diseases. Dr Saarela went on to illustrate two highly collaborative personalised medicine programs. The first program, Finnish Genomes Empowering Personalized and Predictive Health, utilizes the new sequencing technologies to improve diagnostics of rare diseases and makes use of the genome and health big data of the population cohorts to translate the genetic discoveries into health care and prevention. The second program, Individualized Systems Medicine in Cancer, utilizes genome and molecular profiling as well as in vitro drug sensitivity testing to impact the treatment of AML in real time.

The panel decided to use well-characterised examples (case studies) as the basis for their discussions. From each of these examples, some relevant conclusions were derived together with challenges for the future (specifically indicated in almost all cases).

Panel answers to the lead questions posed by ICPerMed:

- *Why is it worth focusing on rare diseases?*

A lot has been learned at molecular level: genomics has indeed been revolutionary. However, treatments that reflect genomics-driven discoveries are available only to a limited extent. Genomics potential is far from being fully exploited.

- *What are the major lessons learned so far from the existing practical examples for personalised diagnosis and treatment?*

Among the lessons learned is that the integration of molecular phenotyping and/or omics profiling with clinical data is going to redefine aetiology and/or pathophysiology of oncogenesis and cancer in particular and diseases in general, and tailor both diagnosis and treatment.

PM not only provides the framework for researchers as they explore how genomics interact with diseases in order to foster drug R&D, but is also drastically transforming the way therapies are being developed. The targeted therapeutic methodology has a widespread impact on genomics, medical devices and drug development and is also going to radically change health systems.

- *How important are biomarkers for personalised medicine?*

PM depends strongly on biomarkers in order to better categorize disease, prognosis and response to target treatment. Special emphasis has been given to making meaningful clinical use of biomarkers, with a need for rapid and economical evaluation.

Impacts from next generation biomarkers are also expected for clinical trials, due especially to re-phenotyping induced by NGS-driven molecular profiling, to be combined with clinical profiles.

- *What are the differences in personalised diagnosis and treatment between cancer and other diseases?*

Despite scientific advances in genetics, researchers have identified only a small fraction of the genetic component of most diseases. Genetic tests for many diseases (including cancer) are needed to develop scientific information for prevention, early diagnosis, therapy and new treatment R&D. Explanation of the genetic basis of rare diseases or cancer may identify novel targets which can lead to

the development of successful drugs or/and the re-use of existing ones. Identification of the somatic mutations responsible for causing cancer may lead to identification of new drugs that target the mutated protein. Transcriptomic technologies like liquid biopsy, in order to assess gene expression profiles prior/during and after therapy can help in predicting disease course and better usage of drugs.

The targeted next generation sequencing (NGS) assay enables simultaneous detection of thousands of genetic variants across the major driver genes relevant to solid tumours. Comprehensive analysis of major cancer driver genes in one single workflow dramatically reduces the cost of molecular profiling and accelerates reporting times. Similar efforts should be made for chronic diseases. Predictive models are on the one hand human-mediated measures, prone to various biases, and on the other hand include inherent systemic stochastic uncertainties.

Clinical outcomes often involve a modelling step, and so comparisons between approaches and integration among omics become critical aspects to aid clinical decision making. When multi-omics experiments are not pursued, cross-validation of heterogeneous data from multiple patient cohorts becomes a necessity, likewise the interoperability of the associated clinical and laboratory data becomes a condition of success. PM is shifting this paradigm, as further benefit is sought from other data types, such as genomics, imaging and electronic medical records.

Two other emerging issues are pharmacogenomics to tailor treatment, and regulatory frameworks to provide new personalised research strategies and scientific advice.

- *How can we learn from successful approaches for other disease and vice versa? Transfer of achievements made so far?*

Successful/unsuccessful approaches may be regarded as models for conducting top-down or bottom-up strategies in other conditions. In particular, three points appear central in the light of shared experiences:

- Common perception of complementarity, but space for transferring knowledge between them;
- Common diseases or side effects becoming - once deconvoluted - similar to rare diseases as we learn more from molecular aetiology;
- Rare diseases expected to be subject to re-assessment in light of big data.
- It will be crucial to organize joint efforts across the national health systems of several countries, to enable increased knowledge on genomic profile in cancer and in genetic disease and to obtain data on drugs efficacy and toxicities (Real-world evidence, RWE & Health Economics and Outcomes Research, HEOR). Aligning payers, clinicians and industry to fund innovations through the better use of medicines and patient outcomes is also important. Creating a strong organization for high quality and harmonized data centralization will be mandatory to advance the clinical interpretation of genomic data for both rare diseases and cancer. Urgent consideration is required to solve actual barriers and to avoid a situation where by patient level data remain in local laboratories.

Further remarks:

In short, the challenges are:

1. Clinical intervention level: in relatively fast time by enabling effective translational research
2. Big data relevance: both social and economic value
3. Better use of evidence-based data to foster the utility of Clinical Decision Support Systems

Also, bottlenecks toward PM are present, such as:

1. Generation of cost-effective high-throughput data
2. Different regulatory framework for oncology drug development versus rare diseases
3. Lack of EU harmonization with regard to reimbursement criteria
4. Hybrid education and multidisciplinary teams
5. Safe and sustained data storage, integration, processing and interpretation
6. Respect of privacy and rights of the individuals
7. Making meaningful clinical use of biomarkers (ex liquid biopsy could add significant value due to rapid and economical evaluation)
8. Individual and global economic relevance
9. Pharma industry to support research involving genetics

Special recommendations were made regarding the **Economic value of personalised medicine**:

- Need to define/redefine a business model to guide investments and policy decisions
- Need to have a robust system, and harmonization at many levels (e.g. reimbursement system is key, but fragmented)
- Expand the networks and integrate public, private sectors, HTA, regulators
- Specialized subjects might need more data/evidence exchange
- Relevance of validating in pan cancers
- Catalogues of success stories and databases

WP 5: Impact of New Tools and Research Strategies on PM

The session began with a presentation entitled "New Tools for Personalized Medicine" by Prof. Dr. Christoph Bock (CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences & Medical University of Vienna). Professor Bock introduced key areas of technological progress and highlighted the power of modularity, a concept that has been a major driver of progress in the IT field. A creative combination of existing and new tools is indeed emerging as a major driver of progress in PM.

The discussion, with Prof. Dr. Pietro Liò (University of Cambridge, UK) as rapporteur, focused on the impact of new tools in PM (tools were defined in a broad sense, including assays, devices and software) and highlighted the need for research and technology development along these lines in order to advance PM.

First, the group assembled a list of key tools and technologies relevant to PM and estimated the timeframe and geographic scope on which each of them should be researched and implemented.

Panel answers to the lead questions posed by ICPerMed:

- *Are there already examples of best practice for new tools in personalised medicine?*

Some of the examples identified were in Rare diseases (IRDiRC, European Reference Networks), cancer (TCGA, ICGC -> impact of data sharing; MAPPs: http://efpiamapps.eu/), genomic medicine (Genomics England), hepatitis C in Spain (40k patients in 2 years, mandatory genotyping, driven by patient pressure), INCa breast cancer screening (France).

Antimicrobial resistance is an important field of application for various tools developed to advance PM; this includes next generation sequencing, personal microbiome,

metagenomics, and metabolome profiling, machine learning, international data exchange and economic modelling.

- *What are the major lessons learned so far?*

Implementing a PM approach is usually complex (in part due to complexities of the healthcare system). Political commitment is a major success factor. There is a need to integrate diverse stakeholders and a need for standardization of clinical protocols. Rapid development of tools requires fast and flexible regulatory policy. It is important to use new tools in better/smarter ways for clinical impact. Diagnosis does not always mean therapy. Bioinformatics has become the single biggest bottleneck.

- *Which could be the best approaches to support health providers and the health system with new tools?*

Some examples are: access to epidemiological databases; monitoring tools for healthcare quality, and disparities (e.g. implemented in the form of Health Data Cooperatives); facilitating pilot studies for PM; and systematic incorporation of representative patient feedback (e.g. Responsible Research & Innovation tools, consensus conference, citizen forum, etc.).

- *What are the crucial inputs through medical informatics and ICT so far and for the future?*

Medical informatics, bioinformatics, and ICT provide the enabler and "glue" between data production, data analysis, and medical decisions; ICT needs to be better integrated into European Reference Networks. Other important inputs are basic science and technology development in bioinformatics, medical informatics, ICT, genomics, molecular biology, phenotyping and lifestyle profiling.

- *How could research benefit from such tools?*

Some benefits include discovery of new biology; reality check for biological understanding; new technologies; new challenges for research and development; and large-scale databases available for re-analysis and hypothesis generation/testing, resource for massive-scale data mining.

Further remarks:

Based on this list of emerging tools and technologies, the most relevant topics for progress in PM were identified and explored in more detail.

Biomarker-driven medicine. Molecular biomarkers stratify patients into disease subtypes and facilitate personalised therapy. Important research priorities include:(i) moving beyond single-gene biomarkers and embracing multi-omics tools; (ii) funding more and smarter replication studies; (iii) better connecting technology development, data analytics, and clinical validation; (iv) making biomarker research future-proof by assembling re-usable sample collections; (v) improving practical and regulatory workflows for the development and approval of biomarker-therapy combinations.

Genomics data interpretation. Next generation sequencing is a key enabler of PM. To maximize its impact, several directions should be pursued with high priority: (i) build the infrastructure and political commitment to maintain robust genetic diagnostics in the public domain, thus avoiding privatisation and monopolisation of human genome information; (ii) standardize phenotype information across borders and language barriers using ontologies; (iii) emphasize data sharing in line with recommendations of the Global Alliance for Genomics and Health; (iv) invest into high-throughput tools for connecting genotype to cellular phenotype and biological functions.

Artificial intelligence, machine learning and simulation. Computational methods are transforming medicine by integrating massive datasets into biomedical research and clinical practice. Research along these lines should

focus on: (i) collecting and aggregating massive datasets in ways that make them widely accessible to computational analysis; (ii) organizing large-scale initiatives for continuous benchmarking of computational methods; (iii) fostering the "reproducible research" paradigm including open source and open data; (iv) developing methods for multi-scale modelling (molecule/cell/organ/patient); (v) emphasizing training, education and sustainable career models to overcome the bioinformatics bottleneck.

Citizen science, biobanks and health data cooperatives: Patient involvement is essential for the success of PM, not only as sample donors and clinical trial participants, but also as partners and stakeholders. Research along these lines should emphasize: (i) pilot projects that seek to combine aspects of biobanking, citizen science, epidemiology and health data cooperatives; (ii) new ways of obtaining and updating consent (e-consent, mobile devices, dynamic consent, etc.); (iii) monitoring the incentive structures of citizens and other stakeholders.

European infrastructures for PM. To increase the role and impact of European infrastructures for PM, initiatives should focus on the following directions: (i) validated pipelines for data processing in the clinic; (ii) easily accessible, connected databases with suitable governance models; (iii) easy-to-use visualisation, exploration, and analysis tools for non-bioinformaticians; (iv) European supercomputing infrastructures used for PM research.

In addition to these five main points, two additional, cross-cutting topics were identified:

Economic modelling & cost-effectiveness research. To evaluate the societal impact of PM, new tailored methods for economic modelling and cost-effectiveness research need to be developed.

Education and communication for healthcare workers and citizens/patients.

To facilitate broad implementation of PM, all healthcare workers will need some training in IT (computer literacy) and data science. Moreover, patients should be educated to build some level of 'genetic literacy' in order to understand the interplay of genes, environment and lifestyle in the context of health and disease.

In conclusion, new tools are critically important for PM, and research on tool development, benchmarking, and initial applications will advance PM research and implementation.

III B. Common Working Panel Reflections:

A number of key research areas for PM were highlighted in several panels, including prediction, prevention, and treatment. Substantial progress has already been made in establishing a shared cross-disciplinarily language connecting the many fields that contribute to PM – including basic and clinical research, outcomes research, tool development and market-oriented innovation.

The responsible drivers and key players for PM should be a spectrum of players linking two main groups of actors: health professionals and citizens; all the experts in each field (Prediction - Prevention – Treatment – Cure); Consensus Panels, European Clinical Societies, European Reference Networks (ERN), Research Institutes and Universities, Health Care Providers, Regulatory Agencies, Patient Societies and Bio-ethicists.

The following areas were identified by several panels as areas that should be pursued with the highest priority in order to advance the progress of PM:

1. It is essential to examine and involve **Euro-**

pean infrastructures for PM. A more concrete task is to increase collaboration within the local research community with European supercomputing infrastructures and initiatives at the service of life sciences research (and clinical applications) **BBMRI-ERIC** (consent and phenotypic annotation), **ELIXIR**, **EATRIS**, **ECRIN Health-RI (NL)**; with Interdisciplinary Scientific Committees such as **IRDiRC** (The International Rare Diseases Research Consortium), with regulatory agencies such as **EMA**/**FDA** and infrastructure projects. An example isRD-Connect which is a unique global infrastructure project that links up databases, registries, biobanks and clinical bioinformatics tools used in rare disease research into a central resource for researchers worldwide. A special emphasis should be placed on generating biobanking efforts; in this regard BBMRI is working on coordination at European level.

2. **Standardisation and harmonisation of data in all steps**: Genomics, phenotypes data; data from within and outside the healthcare system; Data storage, integration, processing and clinical interpretation. In the short term, the first step is **Interoperability**, the extent to which systems and devices can exchange and interpret shared data.
3. **Common patient and relative informed consent and data protection**. Data protection laws need to focus on facilitating PM development of shared policies for informed consent across Europe. New EU legislation on data protection should be designed to support the implementation of PM.
4. **Education of Health Care professionals and patients**: Education tailored to individual subpopulations in the context of preventive and PM could motivate people at risk, to work on modifiable risk factors. As part of this strategy, stakeholders must emphasize the correct use and dissemination of this data and the need for continuous training in the use of new technologies by clinicians. Personalised medicine must enhance the relationship and collaboration between researchers, doctors and patients, leading to the active participation of all parties involved.
5. **Integration of new technologies and new development**: all working panels indicated the fundamental role for PM of research on **Biomarkers** (accuracy, precision and speed of diagnosis; prediction of clinical outcome; risk stratification; therapeutic decision-making; prediction of efficacy, safety and/or side effects of medications). **Information and communication technologies**, such as smart phones and wearable devices are central for data collection, as is telemedicine.
6. **Translating knowledge into medical applications** requires the application of new tools and technologies that contribute to improving the healthcare system.

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