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How to Integrate Personalized Medicine into Prevention? Recommendations from the Personalized Prevention of Chronic Diseases (PRECeDI) Consortium

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Abstract
Medical practitioners are increasingly adopting a personalized medicine (PM) approach involving individually tailored patient care. The Personalized Prevention of Chronic Diseases (PRECeDI) consortium project, funded within the Marie Skłodowska Curie Action (MSCA) Research and Innovation Staff Exchange (RISE) scheme, had fostered collaboration on PM research and training with special emphasis on the prevention of chronic diseases. From 2014 to 2018, the PRECeDI consortium trained 50 staff members on personalized prevention of chronic diseases through training and research. The acquisition of skills from researchers came from dedicated secondments from academic and nonacademic institutions aimed at training on several research topics related to personalized prevention of cancer and cardiovascular and neurodegenerative diseases. In detail, 5 research domains were addressed: (1) identification and validation of biomarkers for the primary prevention of cardiovascular diseases, secondary prevention of Alzheimer disease, and tertiary pre-

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vention of head and neck cancer; (2) economic evaluation of genomic applications; (3) ethical-legal and policy issues surrounding PM; (4) sociotechnical analysis of the pros and cons of informing healthy individuals on their genome; and (5) identification of organizational models for the provision of predictive genetic testing. Based on the results of the research carried out by the PRECeDI consortium, in November 2018, a set of recommendations for policy makers, scientists, and industry has been issued, with the main goal to foster the integration of PM approaches in the field of chronic disease prevention.

The Promise of Personalized Prevention

Personalization of healthcare is a driver of innovation in research, healthcare systems, and industry. Policy makers, healthcare professionals, citizens, and private companies need proper advice to realize its potential. The Personalized Prevention of Chronic Diseases (PRECeDI) consortium is a Marie Skłodowska Curie Action (MSCA) project funded within the Research and Innovation Staff Exchange (RISE) scheme that aimed at providing high-quality, multidisciplinary knowledge through training and research in personalized medicine (PM), with specific reference to personalized prevention of chronic diseases. PM approaches are already being implemented especially in the fields of disease diagnosis and treatment with the use of biomarkers; however, development and implementation of such approaches for chronic disease prevention needs further investigation and concerted efforts for proper implementation in healthcare systems.

We must be explicit about the new potential benefits that disease prevention can bring in the context of PM. Technological advances, jointly with current demographic trends and the expectations of citizens, have the potential to widen the gap between available resources and the requirements for healthcare. As highlighted by the European Steering Group on Sustainable Healthcare, the implementation of sustainable healthcare requires a shift from treatment of established disease to disease prevention and early diagnosis, and it relies on the need to engage citizens in taking greater responsibility for their health in order to establish a more participatory healthcare model [1]. Despite the tremendous increase in life expectancy in Europe in the last 50 years, the latest Eurostat reports that the average number of years of life lived with some disability in Europe is 19.4 for females and 17.7 for males [2]. Although it is acknowledged that prevention in healthcare can improve the quality of life at a very reasonable price by reducing the years of life spent with disability, only 2.8% of health expenditure is for prevention activities [3]. Personalized prevention approaches bring the promise of being even more effective and cost-effective by using the latest advancements in life sciences and (digital) technologies to stratify healthy individuals based on individual and environmental factors, in order to target precise primary, secondary, and tertiary prevention interventions. Such an approach is supported by a highly cited 2008 editorial in *New England Journal of Medicine*, which reported that "… if preventive care could be provided only to those who are going to get the illness, it would be more cost-effective" [4].

PRECeDI

Laying the Foundation for Making Personalized Prevention a Reality

The PRECeDI consortium consists of 8 beneficiaries and 3 partners, of which 7 are academic institutions and 4 nonacademic, including 2 small and medium-sized enterprises (SMEs), and it received funding from the Horizon 2020 (H2020) European Union's Eight Framework Programme for Research [5–7]. During 4 years (2014–2018), 28 early-stage researchers and 22 experienced researchers were seconded for an average of 3 months from academic to nonacademic institutions and vice versa, for training in research projects related to the personalized prevention of chronic diseases, including cancer, cardiovascular diseases, and Alzheimer disease.

Different projects were carried out, from basic research to economic evaluations, from health service organization issues to physician education, including ethical, social, and policy issues in PM, supported by a team of leading EU scientists. The consortium is embedded in existing cooperative structures, such as ICPerMed [8] and TO-REACH [9], the IMPACT-HTA project funded from the H2020 program [10], and the Joint Action iPAAC funded by the Third EU Health Programme [11].

How PRECeDI Contributes to the Integration of PM in the Prevention of Chronic Diseases

Based on the results of the research carried out by the PRECeDI consortium, a set of recommendations for policy makers, scientists, and industry has been drawn up, with the main goal to foster the integration of PM approaches in the field of chronic disease prevention. As a reflection of the work carried out during the project,

most of the recommendations fall in the "translational phase of research in genomics," as defined by Khoury et al. [12], in "T1 (seeks to move a basic genome-based discovery into a candidate health application)" and "T3 (attempts to move evidence-based guidelines into health practice, through delivery, dissemination, and diffusion research)."

In particular, these recommendations fall within the 5 research domains of PRECeDI [5]: "Identification of biomarkers for the prevention of chronic diseases; economic evaluation of predictive genomic applications; ethico-legal and policy issues surrounding personalized medicine; sociotechnical analysis of the pros and cons of informing healthy individuals on their genome; identification of organizational models for the provision of predictive genetic testing."

In addition, when formulating the recommendations, the PRECeDI consortium considered 2 main additional documents: the Strategic Research and Innovation Agenda (SRIA) published in 2016 by the PerMed consortium [13] and the report published in 2017 from the PHG Foundation (Hall and Luheshi [14]; Ricciardi and Boccia [15]). PerMed SRIA reported 5 challenges for the further implementation of PM in Europe, namely: "Developing Awareness and Empowerment; Integrating Big Data and ICT Solutions; Translating Basic to Clinical Research and Beyond; Bringing Innovation to the Market; Shaping Sustainable Healthcare" [13]. The 2017 PHG Foundation Report, as recalled by Ricciardi and Boccia [15], incorporated a public health perspective and reported 6 prerequisites to implement the future of personalized healthcare: "Achieving better genetic literacy for professionals and for the public; engaging citizens in the discourse; improved governance, consent and trust in healthcare; feeding and harnessing the data – knowledge cycle for better health; adopting and adapting the Health Technology Assessment framework for the evaluation of the new technologies; and retaining humanity and community in health and care."

Taking into account that personalized prevention can only be successfully implemented when handled as a truly cross-sectoral topic, our recommendations integrate the perspective of experts across the entire healthcare value chain that are represented in the PRECeDI consortium.

As a matter of fact, the recommendations are also the result of the discussions of the one-day PRECeDI workshop "Policy Development in Personalized Medicine" held in Amsterdam on March 15th, 2018 [16], that convened experts and representatives of relevant stakeholders in the field of PM. The experts participating fully endorsed the document.

These recommendations are formulated as a direct output of the research results and the scientific publications produced by the PRECeDI consortium. The implementation of the recommendations will benefit citizens, patients, healthcare professionals, healthcare authorities, and industry and ultimately seek to contribute to better health for Europe's citizens.

In order to be fully shared and endorsed by relevant authorities and decision makers, this document has been published and open to a public consultation via the PRECeDI website [6].

Below, we report the recommendations that are based on the results of the projects carried out within the 5 research domains of PRECeDI that integrate the 2 sets of aforementioned recommendations (PerMed consortium [13]; Ricciardi and Boccia [15]) (Table 1).

Recommendation 1

Recommendation 1 is based on the "identification of biomarkers for the prevention of chronic diseases" research domain.

Biomarkers have the potential to stratify populations because they can help to indicate an individual's risk or resistance to disease as well as the potential response the individual may have to different treatments. There is also an expectation that this may lead to better targeting of preventive interventions by defining the disease and targeting the treatment based on a person's molecular pathology.

R1. Personalized interventions for the prevention of chronic diseases require robust evidence of efficacy and/or effectiveness of the new technology when implemented in healthcare.

In particular, large trials evaluating the efficacy of disease risk communication based on broad-range newly discovered biomarkers (vs. risk communication based on the solely traditional risk factors) on behavioral change among healthy subjects at increased risk are required for targeted evidence-based primary preventive interventions. For biomarkers that allow discriminating high-risk subjects, large trials evaluating the efficacy of medical interventions are required among such high-risk subjects for targeted evidence-based primary and secondary preventive interventions.

Where intervention studies cannot be performed, however, the use of large datasets, Big Data from collaborative research projects, should be considered for the evidence of effectiveness. In order to ensure timely results

Table 1. The PRECeDI Recommendations

PRECeDI Domains	PRECeDI Recommendations
Domain 1: Identification of biomarkers for the prevention of chronic disease	*R1.* Personalized interventions for the prevention of chronic diseases require robust evidence of efficacy and/or effectiveness of the new technology when implemented in healthcare.
Domain 2: Economic evaluation of predictive genomic applications	*R2.* In addition to what is reported in R1, a comprehensive evaluation of the value (outcomes/cost) of the new technology should also include evidence on the social aspects and context-related dimensions to better support the clinical decision-making process. Genetic or genomic applications with evidence of efficacy, effectiveness, and cost-effectiveness should be implemented in clinical and public health practice.
Domain 3: Ethico-legal and policy issues surrounding personalized medicine	*R3.* The era of genomics requires that we clarify and validate the obligations and responsibilities of the research community, research participants, and the general public including patients through collaboration and dissemination of high-quality ethical, policy, and legal analysis.
Domain 4: Sociotechnical analysis of the pros and cons of informing healthy individuals on their genome	*R4.* A dedicated effort is necessary to stimulate further implementation of evidence-based interventions in healthcare, such as testing of family members in cases of hereditary cancers or cardiovascular diseases.
Domain 5: Identification of organizational models for the provision of predictive genomic applications	*R5.* The integration of genomic sciences in other medical specialties should be promoted through new delivery models involving different healthcare professionals and new professional roles, in order to guarantee the use and sustainability of existing and new genomic applications in practice.

for the use of such predictive biomarkers, the collection of such evidence by action research should be foreseen in the course of implementation and accompanied by collection of genetic data to allow for state-of-the Mendelian Randomization studies to mimic conventional trials.

In these situations, a clear commitment to hypothesis to be tested in advance is needed as is the case with (the registration of) classical trials.

For tertiary prevention, the adoption of accurate biomarkers for precise monitoring and early prediction of disease progression should be encouraged.

This recommendation is based on the results of the biomarkers identified (and validated) for the prevention of diabetes [17, 18], Alzheimer disease [19], and head and neck cancer [20–22].

Recommendation 2

Recommendation 2 is based on the "economic evaluation of predictive genomic applications" research domain.

The growing availability of genomic technologies is contributing to the shift of the medical approach towards PM, where medical decisions are based on an individual's characteristics, including the genomic profile. This has made the assessment of the performance of genomic tests crucial for clinical and public health practice. In fact, in order to maximize population health benefits, it is essential to distinguish genomic tests with proven efficacy and/or effectiveness and cost-effectiveness and support their implementation.

R2. A comprehensive evaluation of the value (outcomes/cost) of genetic and genomic applications should include evidence on the efficacy and/or effectiveness of the new technology (i.e., analytic validity, clinical validity, clinical utility), social aspects (ethical, legal, and social implications, and personal utility), and context-related dimensions (e.g., economic evaluation, delivery models, organizational aspects, and consumer viewpoint) to better support the decision-making process.

Genetic or genomic applications with evidence of efficacy, effectiveness, and cost-effectiveness should be implemented in clinical and public health practice (i.e., programs that include tools for identifying affected women at higher risk for inherited breast and ovarian cancers or familial history-based screening for BRCA1/2; universal or <70 years of age-targeted colorectal cancer-based Lynch syndrome screening; cascade screening of familial hypercholesterolemia). The genomic or genetic testing programs and their implementation should be developed and pursued based on the characteristics of target popula-

tions and healthcare systems to ensure an appropriate translation of evidence into the "real world."

The implementation of a genetic or genomic application should be continuously assessed, measuring the population health impact and relative value of new technologies.

Adherence to the programs should be monitored, and the education and training of clinical and public health professionals should be promoted with the aim of reducing inappropriate use in healthcare.

This recommendation is based on the results of a systematic review for the identification of the domains for an appropriate evaluation of genetic/genomic technologies [23, 24]; systematic reviews on the cost-effectiveness of genomic applications [25–27]; a perspective on the main characteristics to consider for an appropriate implementation [28, 29]; 2 surveys on (1) patient experience throughout the delivery pathways and (2) knowledge and attitudes of European public health professionals on the delivery of genetic services and a systematic review on patient management [30–32].

Recommendation 3

Recommendation 3 is based on the "ethico-legal and policy issues surrounding personalized medicine" research domain.

There is an increasing need for a coordinated effort to foster the development and further harmonization of dedicated policies to integrate genomics policies into existing health systems in a responsible manner. Introducing a common ethically and legally validated policy framework could represent one of the drivers needed to manage a future with increasingly personalized healthcare and a shift in the use of genomic approaches from disease treatment to prevention.

R3. The era of genomics requires that we clarify and validate the obligations and responsibilities of the research community, research participants, and the general public. This can be achieved through collaboration and dissemination of high-quality ethical, policy, and legal analysis. Legal interoperability is necessary to ensure complementarity of goals between researchers in different jurisdictions.

In order to be at the forefront of the currently shifting research landscape, we need to draw on multiple levels of expertise (e.g., law, ethics, medicine, bioinformatics, IT) in an array of multidisciplinary, jurisdictional, and institutional settings.

Finally, a metric assessing the impact of policy development or lack thereof is a fundamental tool to fine-tune guidance to multiple stakeholders.

This recommendation is based on the results of a survey performed among the Europeans Chief Medical Officers on the genomics policies in healthcare [33].

Recommendation 4

Recommendation 4 is based on the "sociotechnical analysis of the pros and cons of informing healthy individuals on their genome" research domain.

Genetic testing of family members of patients affected with hereditary cancers or cardiovascular diseases allows for personalized prevention and it is paramount to find and inform these family members in a timely manner. Several countries are building cascade screening programs and they are discussing how family members can be traced and informed in an ethically responsible and efficient manner. In conditions where genetic testing offers a substantial and quantifiable risk estimate and prevention is available, preventive services should be prioritized. More government involvement is needed as a formally organized screening program could standardize support and information and lead to more equitable healthcare.

R4. A dedicated effort is necessary to stimulate further ethically responsible implementation of evidence-based interventions in healthcare, such as testing of family members in cases of hereditary cancers or cardiovascular diseases. Where guidelines for such genetic testing exist, collaboration between genetic and nongenetic healthcare professionals needs to be facilitated to improve implementation, education opportunities must be provided, and roles and responsibilities towards informing family members must be reconsidered so we can achieve a truly multidisciplinary approach that can realize the potential of PM.

This recommendation is based on the results of a sociotechnical analysis for familial hypercholesterolemia [34].

Recommendation 5

Recommendation 5 is based on the "identification of organizational models for the provision of predictive genetic testing" research domain.

The identification and evaluation of existing genetic service delivery models are important steps towards the enhancement and standardization of genetic service provision. Integration of genetics in all medical specialties, collaboration among different healthcare professionals, and redistribution of professional roles are fundamental elements for the organization of these models. Furthermore, their implementation must hinge on professional

education, adequate funding, and public awareness in the field of genomic medicine.

R5. The integration of genetics in other medical specialties should be promoted through new delivery models involving different healthcare professionals (medical specialists, nurses, technicians, etc.) and new professional roles (i.e., genetic counsellors, genetic associates, genetic nurses), in order to guarantee the use and sustainability of existing and new genomic applications in practice.

Roles and responsibilities (e.g., risk assessment, genetic counseling, genetic testing) should be redistributed among different health professionals to enhance work performance and the standard of care.

It is advisable to define the appropriate model for genetic service provision in a specific setting according to the type of healthcare system and the genetic test provided.

Professional education/training in genomics medicine, laboratory quality standards, and public awareness are essential factors for the successful implementation of genomic applications in practice.

This recommendation is based on the results of a systematic review focusing on existing genetic service delivery models [35, 36]; a perspective on the main characteristics to consider for an appropriate implementation [28, 37, 38]; and 3 surveys on (1) patient experience throughout the delivery pathways, (2) genetic services' delivery models in European countries, and (3) knowledge and attitudes of European public health professionals on the delivery of genetic services [31, 39].

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Statement of Ethics

The ethical approval was not required, as not applicable to our research. According to the study design, no medical treatments nor procedures involving humans nor animals were performed.

Disclosure Statement

The authors have no conflict of interest to declare.

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Author Contributions

S.B. conceived and coordinated the study. R.P. managed the project. S.B., R.P., C.V.D., R.A., and P.B. were involved in Research Domain (RD) 1. P.V., C.D., and A.R. were involved in RD2 and RD5. S.B., W.R., R.P., F.B., M.H.Z., and M.L. were involved in RD3. M.C. and C.V.E. were involved in RD4. M.G., A.J., J.R., and J.M.S. were involved in R5. All authors discussed, drafted, and critically reviewed the manuscript and approved the final version.

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