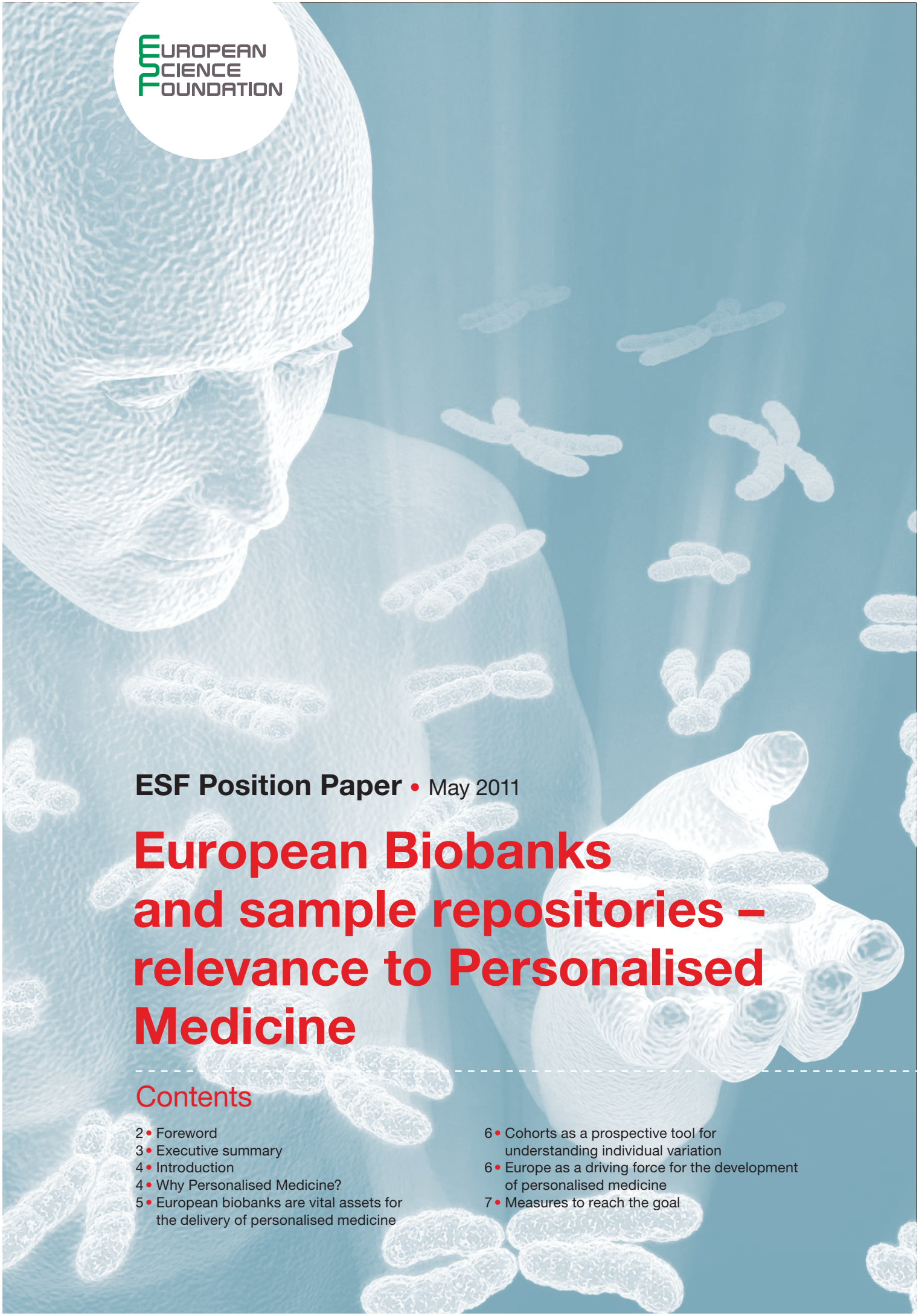

EUROPEAN SCIENCE FOUNDATION

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European Biobanks and sample repositories – relevance to Personalised Medicine

Contents

Foreword

New and emerging technologies based on improved molecular profiling and a better understanding of factors that lead to or protect individuals from illness are currently challenging the existing structures for healthcare delivery. The transition from the long-established "*one-size-fits-all*" approach to a new healthcare strategy based on individual genomic, proteomic and metabolomic profiles likely will provide an opportunity and a framework in which our current healthcare structure may be transformed. The impact of these developments will likely reshape the way pharmaceutical industry develops and targets new drugs, profoundly affect the available tools for healthcare professionals, and enable individualised prediction, prevention and treatment of illness. This emerging medical field and its underlying technologies have been integrated under the term "Personalised Medicine".

In recognising the importance of Personalised Medicine, including in a broader sense how this may impact not only the existing systems for healthcare delivery but also in a global sense influence how society deals with health and disease, the European Medical Research Councils (EMRC), in collaboration with ESF standing committees for Life, Earth and Environmental Sciences (LESC), Physical and Engineering Sciences (PESC), Social Sciences (SCSS) and the Humanities (SCH), have recently launched a Forward Look, a foresight exercise on Personalised Medicine (www.esf.org/iPM). The overall aim of this ESF Forward Look is to analyse in a systematic way the complex and constantly moving field of personalised medicine to provide policy advice that will help prepare Europe for these changes.

The present ESF Position Paper, which is authored by the scientific chairs for the ESF Forward Look on Personalised Medicine and supported by four ESF standing committees, is endorsed by 13 distinguished and leading scientific experts. Rather than introducing the area of Personalised Medicine, the Position Paper focuses on the importance of tissue sample collections and European cohorts as essential elements of particular European strength that may ensure a continued leading role for Europe in the area of Personalised Medicine.

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Cover
Human Chromosomes (Computer artwork)
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Executive summary

Europe is a leading player in the establishment of a radical reinterpretation of our approach to healthcare known as personalised medicine. As a result of previous European investment in research infrastructure, many of the most valuable tools employed to lay the foundations for this approach are located within Europe. Continued investment will nevertheless be required to fully exploit this key European competitive advantage. In this position paper, the chairs of the scientific committee responsible for the recently established ESF Forward Look *Personalised Medicine for the European Citizen* (iPM) highlight those areas in which the new EU strategic Framework Programme (FP8) can play a key role in supporting these developments.

The stratified approach to healthcare that underpins personalised medicine is dependent upon obtaining a detailed description of individual biological variation in connection with environmental, societal, and lifestyle factors that influence the development of disease. In order to achieve this, an enormous range of biological samples and patient-relevant data must be collected, catalogued, and stored in biobanks. Large numbers of individuals – sometimes up to hundreds of thousands – with shared characteristics (known as cohorts) must be regularly monitored. This approach allows current healthcare concerns to be addressed while simultaneously pursuing future goals to manage and prevent disease. Consequently, personalised medicine facilitates a more appropriate response to the changing healthcare needs of an aging, demographically fluid European population and ensures maximum flexibility in the implementation of cost-control measures.

Europe currently boasts some of the most valuable population and patient cohorts, as well as some of the most extensive biobanks that are available worldwide. The value of these tools, however, is rapidly lost if they are not adequately maintained. The methods used to collect data change over time, and new questions arise that require analysis of different patient or demographic groups. If the maintenance and updating of study cohorts and biobanks is made a priority for future research spending at both European and national levels, Europe will maintain and strengthen its current advantage. Furthermore, such investment is predicted to yield benefits beyond healthcare, including insights into policy-resistant problems such as the co-occurrence of obesity and poverty.

To capitalise upon prior investment and harness the potential of existing European strengths in the field of personalised medicine, we recommend that FP8 include special calls to address the maintenance, sustainability and further development of European cohorts and biobanks. Key areas for investment include the following:

- Inclusion of data on biomarkers, imaging studies, and other variables in existing cohorts
- Harmonisation of data collection protocols
- Long-term follow-up to take into account the delayed effect of environmental factors
- Targeted funding to address gaps in existing cohorts that cannot be filled retrospectively, including the identification of new migrant populations
- Research into societal, regulatory, and ethical dimensions to ensure maximum societal gain from personalised medicine
- Establishment of relevant facilities for biostatistics and bioinformatics

Introduction

Recent advances in biomedical research have generated an unprecedented opportunity to understand the factors underlying the development of disease in individual patients. Identifying those elements that predict the individual response to treatment and predispose a person to disease when exposed to the right combination of environmental triggers holds the key to a radical change in our approach to medicine through the stratification of treatment and prevention. This is the basis of *personalised medicine*. The importance of this shift from a global to an individualised approach to healthcare has been clearly recognised by European and global stakeholders and will receive significant attention in discussions leading to the definition of a new strategic EU Framework Programme.

The chairs of the scientific committee responsible for the recently established ESF Forward Look *Personalised Medicine for the European Citizen* fully support this development. The aim of the present ESF position paper is therefore to highlight those areas of the developing field of personalised medicine in which Europe can capitalise on existing strengths over the coming years given appropriately focused investment.

Why Personalised Medicine?

Delivery of healthcare in Europe is faced with the challenge of controlling ever-growing costs while satisfying an increased demand for quality. In addition, the burden of disease is continually evolving. The factors responsible for this development include demographic changes brought about by an ageing population and the effects of migration, changes in environmental factors, including social and lifestyle factors, and also pathogen evolution. Biomedical research must therefore succeed not only in identifying solutions to these problems but also in ensuring that they are rapidly implemented in the most appropriate contexts.

Evidence-based medicine, which lies at the heart of current western approaches to healthcare, relies mainly on the statistical interpretation of data from large clinical trials. Although this is a well-tested strategy that will continue to inform medical practice, it is limited by a general failure to take into account more than a few personalised indicators such as weight and age. Therapeutic decisions are currently based on average values from large studies, irrespective of a patient's individual characteristics, and treatment strategies are therefore not always effectively targeted. While these problems could in principle be addressed by analysing specific sub-groups of patients with shared characteristics after completion of a clinical trial, this type of analysis is generally discouraged because it can produce misleading (false positive) results. In addition, it necessitates the use of follow-up studies of already time-consuming and costly clinical trials, thereby slowing the translation of research findings into clinical practice.

Recent years have seen the emergence of technology that allows individual patient features to be described in detail. Harnessing the power of these approaches thus provides an opportunity to move beyond an emphasis on the *average* patient and towards individualised assessment of treatment strategies. Incorporating such information into clinical practice is the basis of personalised medicine.

So-called *high-throughput* technology in biomedical research has made it possible to describe in more detail the specific biological makeup of large numbers of individuals. The ability to sequence a person's entire genome paved the way for large-scale *genomics* studies, and since then a host of *–omics* approaches have begun to describe other elements such as the partly heritable characteristics that are not encoded in a person's DNA (epigenomics), the expression patterns of their genes (transcriptomics), the range of proteins in their cells (proteomics), their metabolic profile (metabolomics), and the composition of their bacterial flora (metagenomics). Understanding the variation in these aspects of an individual's biological makeup through the use of advanced bioinformatics tools is the key feature of this new personalised strategy to understanding and treating disease.

Unlike the approach used in clinical trials, the studies required for the development of personalised medicine typically involve analysis of data from large population-based cohorts (groups of individuals with shared characteristics, such as gender, age, the environments they grew up in, etc.), clinical history and biological sample collections. Combinations of these data and materials are often referred to as biobanks. The combination of carefully characterised biological samples and detailed clinically relevant information provided by biobanks makes them a valuable additional component of a research infrastructure that facilitates a more detailed classification of disease subtypes and acts as a driving force for the development of personalised medicine in the 21st century. Hence, current goals may be addressed alongside ongoing efforts to manage and prevent disease in the future. As a result of the significant efforts of the

European Commission to support ongoing initiatives such as the European Research Infrastructure Consortium (ERIC) and the European Strategy Forum on Research Infrastructures (ESFRI), Europe now leads the way in establishing the foundations of research into personalised medicine.

Building on Existing Strengths

Europe's privileged position in establishing the foundations for personalised medicine is dependent upon the quality of the population-based cohorts and clinical sample collections it has developed. Effective utilisation of these unique resources will make it possible to monitor trends in population health and assess the impact of healthcare policy. In addition, they will act as an ongoing discovery platform that can be continually adapted to the changing healthcare environment.

Research funders in other regions, such as the US, have recognised the importance of cohorts for disease research and diagnostics. If European medical research is to capitalise on its current leading position in personalised medicine, it is vital that existing cohorts in Europe receive adequate resources to be maintained at the highest level and expanded where necessary.

Key areas for investment:

- Inclusion of data on biomarkers, imaging studies, etc. in existing cohorts
- Harmonisation of data collection protocols
- Long-term follow-up to take into account the delayed effect of environmental factors
- Targeted funding to address gaps in existing cohorts that cannot be filled retrospectively, including the identification of new immigrant populations
- Support for relevant facilities for biostatistics and bioinformatics
- Integrate research on societal and ethical perspectives

European biobanks are vital assets for the delivery of personalised medicine

In order to understand the factors underlying individual variability in biological makeup in the context of social and lifestyle (environmental) differences, data need to be analysed from as many as hundreds of thousands of study participants. While costly, the collection and maintenance of samples and data from study cohorts is therefore crucially important to the success of research into personalised medicine. A key return on such investment, however, is the capacity to make continued use of existing resources and streamline the translation of research findings into clinical practice.

The value of a population or patient cohort decreases rapidly if the collection is not maintained and updated or if follow-up of study participants is not organised. The relevance and sustainability of a cohort for use in clinical research is defined by the type and quality of its biological samples, the amount of patient-relevant information it contains and the ability to cross-reference that information. The methods used to record phenotypes, diagnostic criteria, and environmental features change over time, however. Furthermore, as knowledge advances, new questions arise that require analysis of different groups of patients or demographic populations, some of which may not be covered by existing cohorts. Ongoing efforts to update and improve phenotypic and environmental datasets are therefore essential in order to facilitate the cutting edge research that will drive personalised medicine.

As a result of previous European research investment and the particular organisation of healthcare within Europe, many of the world's most valuable patient and population cohorts are located in European countries. This places Europe in a unique forefront position, with a particular responsibility to make use of these opportunities and lead the way in developing the clinical research that will serve as the foundation for a revolution in personalised medicine. If the maintenance and expansion of these cohorts is made a priority for future research spending at both European and national levels, Europe will maintain and strengthen its current advantage and capitalise on previous investments. In turn, this will improve healthcare globally.

Cohorts as a prospective tool for understanding individual variation

The use of cohorts allows ongoing analysis of the development of disease according to combinations of intrinsic and environmental factors. Most importantly, cohorts allow a prospective approach to be taken in which the development of disease (and its corollary, protection against that same disease) can be analysed over time in well-characterised populations. This sort of in-depth analysis of individual biological makeup in the context of environmental (including lifestyle and other social) factors is central to achieving a clearer understanding of why some people develop a particular disease or fail to respond to a given treatment.

Genetics is understood to be a key factor determining individual variation in susceptibility to disease. Recent years have seen a surge in genome sequencing, including the 1000 genomes project (www.1000genomes.org), and genome-wide association studies (GWAS), the latter of which have led to the identification of robust associations for 1888 single nucleotide polymorphisms in 210 different diseases and other heritable traits (www.genome.gov/gwastudies). Although these associations explain only a fraction of the genetic contribution of common diseases, they have already yielded a large number of targets for use in functional studies. Importantly, the vast majority of these findings have involved the use of European study samples. In fact, large European sample collections probably account for the largest proportion of ongoing and planned cohort-based studies worldwide.

Ethical, Legal and Social Issues (ELSI)

ELSI research is a core element of ensuring that the benefits of large-scale biomedical research will reach patients in a socially and ethically robust manner. The sooner such issues are addressed, the greater the societal gain. For instance, although some of the most significant scientific insights in personalised medicine may be achieved through the use of lifelong cohorts starting at birth, important questions still need to be addressed on issues such as the collection and storage of genetic information from children. While taking into account the objective of cost containment in a new framework programme, substantial provision must be made for ELSI research in personalised medicine.

Genetics, including pharmacogenetic/genomic approaches, is only one way of understanding individual variation in disease, however. Priority areas for research into personalised medicine include the analysis of data on life events and environmental factors in relation to, among others, epigenomic, transcriptomic, proteomic, metabolomic and metagenomic characteristics. In order to ensure that the results of these studies have the greatest impact and clinical relevance, the data must be well characterised and continually updated to account for changes in demographics and advances in knowledge. For instance, Europe's population is ageing and at the same time undergoing additional demographic change due to migration. At the same time, epigenetic and environmental influences on disease susceptibility are only just beginning to be understood and the factors that must be assessed in cohort studies are changing rapidly. By ensuring adequate support for the maintenance, updating and harmonisation of methods between the powerful cohorts that have been developed as a result of previous European research investment, we can ensure that Europe continues to play a leading global role in the establishment of personalised medicine. Adequate investment in European cohorts is not only a prerequisite for making personalised medicine a reality, however. By fostering a deeper understanding of the complex interactions between social, environmental, and (epi)genetic factors and health and socio-economic outcomes, benefits would be obtained beyond healthcare, extending to policy-resistant problems such as the co-occurrence of obesity and poverty.

Europe as a driving force for the development of personalised medicine

Europe has a number of crucial advantages in developing and implementing personalised medicine. First, access to healthcare is not dependent on private insurance, which means that the translation of new scientific discoveries into clinical applications in Europe regularly faces fewer practical obstacles than in other parts of the world. This provides opportunities for new drugs and treatments benefiting patients faster. Secondly, the European Union provides an ideal framework for harmonisation that facilitates implementation of general best practices based on shared European values. Thirdly, several EU member states have already begun to implement electronic health records (EHRs), an area that has also been identified and prioritised

within the EU. EHRs greatly facilitate the maintenance and updating of data on large population cohorts, including from clinical trials, and substantially reduce the associated operating costs. In addition, EHRs provide an opportunity to introduce additional (including retrospective) data that has been collected for other purposes. Information on regional differences in other factors could thus facilitate the identification of the environmental determinants of human variation that may have relevance to health and disease. By fully utilising these unique strengths, the greatest benefits can be gained from the establishment of personalised medicine in Europe.

Specifically, we propose the following measures to reach this goal

In the interest of maintaining clear European advantages in personalised medicine, we recommend that the new framework programme (FP8) include special calls addressing the maintenance, sustainability, and further development (including information-technology solutions and quality control) of European population-based and clinical sample collections.

Priority Areas for Personalised Medicine Within Europe

Resources for existing European cohorts

- Expansion and follow-up of existing data sets
- Augmentation of data on the biological characteristics of the general population and of specific groups
- Addition of multidisciplinary in phenotyping (imaging, biomarkers, etc.)
- Harmonisation of data collection and data storage between cohorts

Establishment of new cohorts

- Address gaps in existing cohorts that would be impossible to fill retrospectively
- Establish cohorts for emerging disease areas
- Initiate cohorts that reflect migrant contributions to the European disease pattern

Resources for future studies

- Research on challenges posed by ageing populations and changing healthcare
- Research on societal, regulatory, and ethical dimensions of large-scale databases and cohorts

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