



ESF Forward Look

## Personalised Medicine for the European Citizen

Towards more precise medicine for the diagnosis,  
treatment and prevention of disease (iPM)



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We hope that by broadly disseminating this Forward Look to the heads of ESF Member Organisations, the European Commission directorates and the various important stakeholder groups identified in the report, the recommendations will be widely implemented for the future benefit of all European citizens.

**Professor Liselotte Højgaard**  
*EMRC Chair*



# Foreword



Personalised medicine has become increasingly important in the future of healthcare. Promises have been made of dramatic reductions in healthcare expenditure alongside improvements in the efficacy and safety of interventions that will be tailored to the specific needs of each individual. Examples are already available in which detailed information about the biological makeup of an individual has been successfully used to identify the most appropriate treatment. It is argued that, by increasing treatment effectiveness in specific individuals and reducing risk and expenditure associated with treating patients with an inappropriate drug, such approaches herald a new era of cheaper, more effective healthcare. To make the transition from targeted therapies to personalised medicine and ultimately personalised healthcare, however, a much wider vision is required. Personalised medicine has the potential to embrace a truly pro-active, pre-emptive and preventive approach to the health and wellbeing of all citizens. If this potential is to be realised, however, we must gain a clear understanding of what is required to achieve it and begin to lay the foundations now that will allow us to benefit in the future.

In order to define the vision of personalised medicine, the ESF initiated a foresight exercise, or Forward Look: 'Personalised Medicine for the European Citizen – towards more precise medicine for the diagnosis, treatment and prevention of disease'. The aim of this Forward Look was to identify the most pressing issues affecting the development and implementation of personalised medicine and make recommendations on how they could be appropriately addressed. It was recognised from the outset that this approach has implications that extend far beyond the healthcare profession. Any

effort to redefine our approach to healthcare by definition affects society as a whole. However, when the approach also includes considerations such as the collection and large-scale integration of personal data, which may be used to tailor healthcare interventions in personalised medicine, it also presents numerous ethical, legislative and regulatory challenges, not to mention organisational considerations. This Forward Look therefore started from the premise that expert opinion should be sought from the widest possible areas with the full support of all ESF Standing Committees including the Standing Committees for Life, Earth and Environmental Sciences (LESC), Medical Sciences (EMRC), Social Sciences (SCSS), Physical and Engineering Sciences (PESC) and the Humanities (SCH).

The Forward Look was organised around a series of meetings designed to facilitate discussion of core areas among experts in relevant fields. The first workshop, which took place in London in September 2011, explored the place of technology in personalised medicine. Here, the drive provided by technological developments was considered alongside the demand for new technologies and the application of existing ones to predict timelines for the development and implementation of personalised medicine. In the second workshop, held in The Hague in October 2011, the future of personalised medicine was explored from the perspective of different disease areas. Using cancer, rare diseases and cardiovascular disease as examples, a series of considerations were identified that are likely to define the future direction of this new approach to healthcare and influence the likelihood that it can be successfully implemented. All of these considerations were then taken forward into a workshop held in Dubrovnik in February 2012 to discuss the over-

arching issues affecting the future development and implementation of personalised medicine in Europe.

In April 2012, a meeting of key stakeholders in the future of personalised medicine was held in Rome. This meeting brought together representatives from, among others, patient groups, regulators, industry and academia to discuss a series of recommendations arising from the three previous workshops. As a result of these discussions, a circle model was developed in which the core vision of personalised medicine is supported by a series of recommendations in core areas such as data handling, decision-making, translational research and infrastructure. These recommendations focus on creating the necessary conditions for personalised medicine to be established across Europe. They build on existing European strengths, such as biobanks, as essential infrastructures to support a revised classification of disease and provide guidance on the conditions that will be required to ensure maximum benefit in the future. They indicate important areas where advances must be made and highlight the human and physical resources that must be put into place now in order for personalised medicine to become a reality. Finally, in keeping with the vision of keeping individual citizens at the heart of the process, recommendations are made on ensuring the participation of all stakeholders in the development of the approach.

We are grateful to all the experts who have dedicated valuable time to supporting this ESF Forward Look. We believe that the insights and recommendations generated through this process will provide the foundations for the introduction of a new approach to healthcare that could soon benefit all European citizens. Importantly, they provide a basis for Europe to build on its strengths and ensure that investment is not wasted through poor planning. We hope that stakeholders throughout Europe will come together to support this vision and ensure that personalised medicine becomes a viable and sustainable reality.

**Professor Liselotte Højgaard**, *EMRC Chair*

**Professor Milena Žic-Fuchs**, *SCH Chair*

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**Mr Martin Hynes**, *ESF Chief Executive*



# Executive Summary



The way we understand and treat disease is changing rapidly. The list of conditions for which there is no satisfactory treatment is increasing and, even when treatments are available, many patients either do not respond or experience unacceptable side effects. Our increasing capacity to describe a person's biological makeup has led to the realisation that many of these problems are explained by the variability in our individual characteristics. Consequently, it is clear that we must move away from a one-size-fits-all approach and towards healthcare that is tailored to the needs and characteristics of the individual.

Personalised medicine is a new approach to classifying, understanding, treating and preventing disease based on data and information on individual biological and environmental differences. It seeks to integrate data on the entire dynamic biological makeup of each individual as well as the environmental and lifestyle factors that interface with this makeup to generate a complex, individual phenotype. Using this information, models can be generated to identify the most appropriate healthcare choices, from treatment to prevention, in individual citizens. In essence, personalised medicine represents a shift from reactive medicine to proactive, pre-emptive and preventive healthcare.

The ESF Forward Look on 'Personalised Medicine for the European Citizen' brought together experts from a wide range of disciplines to identify core issues affecting the development and implementation of personalised medicine in Europe. In particular, it sought to address the conditions that will be necessary to make personalised medicine a reality and the challenges it will face. The outcome is a comprehensive set of recommendations designed to ensure that the necessary frameworks

are established to support a long-term vision not only of personalised medicine but of truly personalised healthcare.

Personalised medicine can be considered as a data-driven approach. As a critical first step in the development of personalised medicine, traditional disease classifications will need to be reevaluated. Rather than focusing on constellations of symptoms or on a particular organ or system, diagnosis will increasingly focus on integrating information from multiple sources, not only genomics and other 'omics technologies but also environmental and lifestyle data. This new disease taxonomy cannot be established, however, without first collecting and integrating vast amounts of data from as many individuals as possible in representative samples of the European population.

The challenge of data collection for personalised medicine is already beginning to be met by a series of biobanks that have been established throughout Europe. The importance of this work cannot be underestimated, yet it must also be recognised that this is only the beginning. This infrastructure must now be consolidated and expanded into an interoperable European network. To this end, it will be necessary to harmonise protocols for data collection and handling, address cross-border issues associated with data sharing and identify ways not only to integrate the enormous range of relevant biological datasets but also to link them to contextual information on environmental variables, lifestyle, nutrition, etc.

Data relevant to personalised medicine are not only generated in the clinic and the laboratory. Citizens and patients are increasingly taking advantage of social media and new technologies to share information about their own health and lifestyle.

Data shared by patients have already been used effectively for research purposes and it is apparent that this sort of citizen-led collaboration can serve to accelerate clinical research. If solutions can be found to embrace the potential of such initiatives, it is conceivable that they could be used to generate cost-effectiveness data, monitor long-term outcomes of personalised interventions and contextualise data obtained in the clinic and the laboratory. Furthermore, ensuring that citizens are able to play an active role in their own healthcare and supporting the wellbeing of others in their communities is an important aspect of promoting future participatory healthcare. The challenge will now be to overcome potential ethical and legal hurdles to safeguard privacy and ensure that personal information is not used inappropriately.

Irrespective of the source of the data used to inform and optimise personalised medicine, the data must first be converted into evidence that can inform decision-making processes. The development of increasingly tailored interventions will require new clinical trial designs to take account of the shift in focus from population to individual. Similarly, more robust models are required to identify prevention strategies. Such changes in the approach to obtaining evidence for the efficacy and safety of therapeutic and preventive interventions will inevitably necessitate revised regulatory frameworks. Health technology assessment and reimbursement will also need to adapt to changes in the type of evidence applicable to personalised medicine. In addition, it will need to employ models that address individual benefit in the context of overall cost-effectiveness evaluations and that take account of social and ethical considerations. The frameworks and models that support healthcare will thus need to be reconsidered at all levels as we move towards the introduction of personalised medicine.

As the evidence base is established for personalised medicine and supported by resources such as large reference datasets, the challenge will be to translate that knowledge into tangible health benefits for European citizens on a day-to-day basis. The long-term vision of the approach is to be able to access a comprehensive, contextualised dataset for each citizen and use the information to identify those measures that will best support the health and wellbeing of that person. To achieve this, powerful information and communication technology will be required. For instance, modelling can be used to generate virtual patients, such that each citizen might conceivably have a virtual twin that can be used to model and predict outcomes such as response to therapeutic or preventive interventions.

Healthcare has traditionally been organised around organ- and system-based specialities, which in turn inform the classification of disease. With the development of a new disease taxonomy in personalised medicine, the boundaries between these specialities is likely to blur rapidly. As personalised medicine is introduced, therefore, the structure of the healthcare profession will need to undergo a radical overhaul. The first step in this process must inevitably be interdisciplinary interaction. Expertise will need to be shared between existing medical specialities in order to define future directions and understand how to deal with the insights obtained from a revision of disease classification.

Cross-disciplinary interaction is not only an issue for the healthcare profession. In an increasingly data-driven approach to healthcare, clinicians must work together with bioscientists and technologists to develop the necessary tools for use in personalised medicine. Bioscientists must understand, for instance, what information healthcare professionals need and in what format to help them make appropriate decisions on patient care. Technologists must understand the nature of the interaction between healthcare professionals and patients in order to design appropriate tools and interfaces. Healthcare professionals must also understand the needs of citizens and patients, some of whom will take increasing responsibility for their own healthcare decisions, while others will demand another type of interaction with the healthcare system. To achieve this level of cross-fertilisation, widespread consultation of stakeholders will be required along with infrastructure that facilitates interaction among professionals from different disciplines and specialities.

The infrastructure required for personalised medicine goes further than biobanks and cross-disciplinary working models. Education and training programmes will need to be established at the earliest stages to ensure that appropriately trained professionals are available to support the future development and implementation of personalised medicine. In addition, interdisciplinary career structures will need to be established and their continuity guaranteed if young professionals are to be attracted in sufficient numbers. Education is not only about professionals, however. If European citizens are to take advantage of the opportunities provided by personalised medicine and become active participants in its continued refinement and implementation, health literacy in the wider population must be actively promoted. Access to core technologies must also be guaranteed throughout Europe, firstly to safeguard against inequalities but

also, importantly, to ensure that the data which will continually refine the models applied in personalised medicine can be obtained from the widest possible population sample.

With all these and other considerations in mind, the ESF Forward Look on Personalised Medicine for the European Citizen proposed a series of recommendations under four core headings:

**1. Data handling:**

Comprehensive, accessible and interoperable datasets must be generated to support the development of a new disease taxonomy and allow for its ongoing refinement and application.

**2. Models and decision-making processes:**

Models and decision-making processes must be revised to reflect a focus on the individual citizen at all levels, from assessment of the safety and efficacy of interventions, through health technology assessment and reimbursement, to diagnosis, treatment and prevention.

**3. Interdisciplinarity, participation and translational research:**

Emphasis must be placed on stakeholder participation, interdisciplinary interaction, public-private and pre-competitive partnerships and translational research in order to develop the frameworks that support the vision of personalised medicine and healthcare.

**4. Infrastructure and resources:**

Dedicated funding and governmental support must be provided to ensure the availability of core infrastructure, including access to core technology and frameworks for education and training of professionals and the wider community.

It is hoped that the detailed recommendations in each category will now be taken up by stakeholders throughout Europe to ensure the successful introduction and sustainable implementation of personalised medicine for the benefit of all European citizens.



# 1.

## Introduction



Our approach to healthcare is undergoing a radical shift in emphasis. We are now moving away from the era of blockbuster drugs designed to treat the majority of patients with common conditions towards an approach in which the health of patients can be managed according to their individual characteristics. Factors such as genetic and biological makeup, lifestyle, and environmental exposures are being used to tailor treatment of existing disorders, respond more rapidly to developing diseases, and take preventive measures in those at risk of future disease. This new healthcare model, commonly known as personalised medicine, has the potential to generate a progressive shift from reactive medicine to proactive, pre-emptive, participative and preventive healthcare. Its introduction, however, has wide-ranging implications for all stakeholders, from individual European citizens and society to institutional, regional and European policymakers. To maximise the potential for Europe to benefit from the introduction of personalised medicine and lay the foundations for its implementation, the European Science Foundation (ESF) launched a Forward Look foresight exercise: Personalised Medicine for the European Citizen – towards more precise medicine for the diagnosis, treatment and prevention of disease.

To achieve the vision of personalised medicine, we must recognise the position of individual citizens, and the communities they belong to, at the centre of the healthcare process. The development of tailored treatment and prevention strategies will depend upon our ability to first interpret the significance of biological variation within the context of environmental variables across large sections of the population. Thus, without the participation of citizens who are willing to share data and information, the scientific and technological foundations

for personalised medicine cannot be built. The innovative use of technology and on-going learning also has the potential to foster citizen-led healthcare and greater personal ‘health agency’ across the life course. Patients will no longer be mere recipients of information provided by the medical profession but increasingly active contributors to the generation and interpretation of their own data. Citizen-level participation in healthcare, however, will be enhanced by the active participation of other stakeholders. Health professionals, for instance, will need to play an active role in the development of technologies such as decision-support systems and diagnostic algorithms to facilitate a new approach to healthcare. The challenge now is therefore to ensure that all stakeholders, including citizens, health professionals, industry, regulators, healthcare providers and funding bodies, participate in defining the future of personalised medicine.

The aim of the ESF Forward Look on ‘Personalised Medicine for the European Citizen’ was to identify the needs of all stakeholders in terms of research programmes, infrastructures, policy and education. Key issues to be addressed included the justification for investment in personalised medicine, the implications of its introduction for different groups within a multidisciplinary and multicultural space and the strategy required to ensure effective implementation and integration of new approaches. To this end, the ESF brought together groups of experts from a wide range of fields to discuss topics within three broad domains: the role of technology in personalised medicine, the challenges and opportunities for specific disease areas and the overarching themes that will influence the future of personalised medicine. Based on the discussions that arose during these meetings and a series of



interviews with opinion leaders, recommendations were discussed at a meeting of stakeholders in Rome in April 2012.

This report presents the main themes and issues identified during the ESF Forward Look. It considers the issues affecting the future of personalised medicine from a number of different perspectives. Firstly, it seeks to understand the role of technology in terms of the demands from medicine, the drive for change created by technological innovation and the challenge of data integration. It then explores some of the key considerations for different disease areas as we move towards personalised medicine. Finally, it highlights some of the overarching issues affecting the future of personalised medicine across disease areas and disciplines. These insights are then used as a basis for recommendations and proposed timelines to support the establishment and future sustainability of personalised medicine for the European citizen.

## 2. How do we define personalised medicine?



The terms we use to define our goals play a crucial role in determining how different stakeholders engage with the process, and indeed the strategy we develop to ensure that the goals are achieved. Perhaps as important as the terms we choose, however, is an awareness of how they are understood by others. Personalised medicine can be broadly described as a customisation of healthcare that accommodates individual differences as far as possible at all stages in the process, from prevention, through diagnosis and treatment, to post-treatment follow-up. In practice, however, what people understand the term to mean varies widely and no single definition has been agreed upon. Many other terms, such as *genomic medicine*, *stratified medicine* and *precision medicine* are frequently used synonymously with *personalised medicine*. Whether or not consensus is achieved on terminology, an awareness of how the different terms are understood will help us to avoid miscommunication due to assumption of shared understanding.

Much of the impetus for the discussion of personalised medicine has come from the explosion of data arising from genome sequencing. For many, the promise of personalised medicine lies in the prediction of disease risk, treatment response and safety profile based on genomic sequence data. Thus, many consider personalised medicine to be synonymous with genomic medicine<sup>1</sup>. Unfortunately, this view creates a number of problems. Firstly, it is far too narrow in its vision. The range of information that can conceivably be used to customise healthcare is far greater than genome sequence data

1. Simmons LA, Dinan MA, Robinson TJ, Snyderman R. Personalized medicine is more than genomic medicine: confusion over terminology impedes progress towards personalized healthcare. *Person Med* 2012; 9(1):85-91.

alone. Consequently, a long-term vision of a true systems-based approach to healthcare would be hindered by the perception that personalised medicine is merely about prediction based on individual genome sequencing. In addition, the receptiveness of stakeholders to the development and implementation of personalised medicine could be influenced by the growing perception that genomics has not lived up to expectations and has not yet delivered on the promise that it would explain susceptibility to a whole host of diseases. We must therefore be in a position to respond to criticisms of personalised medicine based upon the misconception that it refers to genomic prediction alone.

Another commonly used term is *stratified medicine*<sup>2</sup>. This refers to the identification of subgroups of patients with a particular disease who respond to a particular drug or, alternatively, are at risk of side effects in response to a certain treatment. Indeed stratified medicine is already being used in the clinic. Drugs such as gefitinib and erlotinib, for instance, are being used to treat patients with non-small-cell lung cancer who have mutations in the epidermal growth factor receptor (EGFR)<sup>3,4</sup>, and vemurafenib is being used for the treatment of metastatic melanoma in patients with BRAF V600 mutations (see Box 1)<sup>5</sup>. By identifying those

2. Trusheim MR, Berndt ER, Douglas FL. Stratified medicine: strategic and economic implications of combining drugs and clinical biomarkers. *Nat Rev Drug Discov* 2007; 6(4):287-93.

3. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isoe H, *et al*. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010; 362(25):2380-8.

4. Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, *et al*. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011; 12(8):735-42.

5. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P,

patients who have a specific molecular subtype of the disease, it is possible to provide more effective, targeted treatment. Almost certainly, stratification is an important step towards personalised medicine. Indeed it is a core element in any effort to customise healthcare based on individual differences. At present, the term is largely applied to the use of treatments with companion, disease pathway-specific diagnostics in order to determine whether a patient is likely to respond to a given therapy. Nevertheless, the concept need not be restricted to such approaches and can equally be applied to risk stratification for prevention. For instance, tools such as the Framingham risk score for coronary heart disease has long been used to stratify patients according to their likelihood of suffering a coronary event and to take preventive measures accordingly. An important consideration for the introduction of personalised medicine, therefore, may be to raise awareness of those examples in which stratified approaches have already begun to be used effectively in the clinic. Nevertheless, stratified medicine may only be one element of personalisation and does not communicate the broader vision for the potential of this approach<sup>6</sup>. Furthermore, some stakeholders see stratified medicine as serving the purpose of group classification according to relevant criteria rather than working towards the individualisation of treatment. *Precision medicine* is an alternative term that reflects the targeting of the specific elements responsible for pathology in a given individual at a particular point in time<sup>7,8</sup>. In other words, it is about providing the right medicine to the right patient at the right time. The term encompasses the use of tools for stratification and takes into account the myriad factors that can influence the development of disease in a given individual, including not only genomic and biological factors but also environmental and lifestyle influences<sup>7,9</sup>. Precision medicine therefore seeks to move away from symptom-based taxonomies towards the molecular characterisation of individuals in a multi-layered system that serves the needs of clinic and research.

Larkin J, *et al.* Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011; 364(26):2507-16.

6. Brand A. Public Health Genomics and Personalized Healthcare: a pipeline from cell to society. *Drug Metab Drug Interact* 2012; 27(3): 121-123

7. Mirnezami R, Nicholson J, Darzi A. Preparing for precision medicine. *N Engl J Med* 2012; 366(6):489-91.

8. National Research Council Committee on a Framework for Developing a New Taxonomy of Disease. *Toward Precision Medicine: Building a Knowledge Network for Biomedical Research and a New Taxonomy of Disease*, 2012.

9. Cesuroglu T, van Ommen B, Malats N, Sudbrak R, Lehrach H, Brand A. Public health perspective: from personalized medicine to personal health. *Pers Med* 2012; 9(2): 115-119).

It can be argued that a core goal of personalisation is to acknowledge the position of patients and citizens at the centre of the endeavour, not merely as receivers of care but as active contributors of data and as participants in the process of decision-making. Thus, the future of medicine might best be considered as predictive, preventive, personalised and participatory, a view now known as proactive P4 medicine<sup>10,11</sup>.

The concept of P4 medicine highlights the future potential of personalised approaches to healthcare. By virtue of its predictive, preventive and participatory elements, P4 medicine goes beyond targeted therapy and instead embraces the concept of individual and collective wellbeing. The principles of stratification are as applicable to prevention as they are to drug treatment. Likewise, precision is an element of risk assessment and on-going management, and not just targeted of therapy. Participatory medicine highlights the role of citizens in maintaining their own health and wellbeing, as well as providing the data that will help to support the wellbeing of others through increased understanding of individual variation, population needs and response to therapeutic and preventive measures. Nevertheless, the future of personalised healthcare need not imply complete transfer of responsibility from the healthcare profession to the individual as a default mechanism. For some individuals, such as the elderly, disabled or very young, responsibility for personalised healthcare could be partially or entirely delegated back to the healthcare system either by choice or inability to manage the necessary information or actions.

In summary, personalised medicine can be variously understood as genomic, stratified and precise and as encompassing the principles of proactive P4 medicine. All of these different elements will need to be taken into consideration when planning the future of the approach – embracing the potential of genomics but not restricting analyses to one limited information source, for instance, or using stratified medicine as a starting point but laying the foundations for a wider view of personalisation. Likewise, we must be aware of the meanings people associate with the terminology used and, most importantly, their reactions to it. Interestingly, both *personalised* and *medicine* can be problematic – the former because many, particularly within the medi-

10. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat Rev Clin Oncol* 2011; 8(3):184-7.

11. Weston AD, Hood L. Systems biology, proteomics, and the future of health care: toward predictive, preventative, and personalized medicine. *J Proteome Res* 2004; 3(2):179-96.

cal profession, argue that medicine has always been personalised, and the latter because it is inherently focused on the clinic rather than the wider implications of healthcare. Although the widespread use of the term *personalised medicine* is unlikely to disappear, great care will be needed to avoid misunderstanding among the different stakeholders who will shape its future.

## 2.1 Recommendations

### All stakeholders in personalised medicine must:

1. Pay attention to the effects of language and terminology used in relation to personalised medicine.
2. Take every opportunity to correct the misconception that personalised medicine refers to genomic prediction alone.

### Healthcare professionals must:

1. Raise awareness of examples in which stratified approaches have already begun to be used effectively in the clinic as precursors of a wider vision of personalised medicine.

### Box 1: From genomic to personalised medicine – multiple genomes, multiple cell types

Genomic medicine has commonly been perceived in terms of its potential to provide information on a given individual's risk of developing a disease<sup>12</sup>. According to this logic, once an individual's genome sequence has been obtained, it should be possible to use this information to predict disease risk, particularly when assessed in the context of other data obtained through 'omics technology, environmental sampling, lifestyle information, etc. In practice, however, this will only be part of the story in personalised medicine. The human genome does not remain stable over an individual's lifetime and somatic mutations in different cell types can play an important role in many diseases, particularly cancer<sup>13</sup>. A genome sequence obtained from peripheral blood cells, for instance, could suggest that an individual is not at risk, whereas a sequence obtained from another cell type in the same individual could reveal incipient disease. In personalised medicine, therefore, analysis of the genome is unlikely to be restricted to a single sequencing procedure in a given individual but rather will occur at multiple timepoints and using single-cell sequencing<sup>14</sup>. Indeed, a possible scenario is the collection of a reference germline genomic sequence for each individual against which other sequencing data can be compared over the lifespan<sup>15</sup>.

Of course, it is not only an individual's genome sequence that is subject to change. Epigenetic changes, for instance, can occur at different points in an individual's lifespan and in a manner specific to a given cell type<sup>16</sup>. Consequently, it is unwise to restrict analyses either to a single genomic sequence or to a single cell type. Peripheral blood is a common focus for analyses due to its accessibility. However, much important information may be missed if we restrict analysis to this particular cell type. Nevertheless, access to tissues is likely to be a major hurdle for personalised medicine, since invasive techniques to harvest tissue samples from different organs are unlikely to be acceptable in most situations. In order to maximise the opportunities to obtain relevant data in a given individual, it is likely that advances will need to be made in areas such as single-cell analysis and minimally invasive tissue sampling.

12. Hall WD, Morley KI, Lucke JC. The Prediction of Disease Risk in Genomic Medicine. *EMBO Reports* 2004; 5: S22–S26.

13. McDermott U, Downing JR, Stratton MR. Genomics and the Continuum of Cancer Care. *N Engl J Med* 2011; 364 (4): 340–350.

14. Tian Q, Price ND, Hood L. Systems Cancer Medicine: Towards Realization of Predictive, Preventive, Personalized and Participatory (P4) Medicine. *J Intern Med* 2012; (2): 111–121.

15. <http://www.itfom.eu/>

16. Relton CL, Smith GD. Epigenetic Epidemiology of Common Complex Disease: Prospects for Prediction, Prevention, and Treatment. *PLoS Med* 2010; 10: e1000356.

**Box 2: Stratified medicine – laying the foundations for future personalisation**

One of the foundations of personalised medicine is the ability to subdivide groups of patients with a particular disease into those whose condition will respond to a given treatment and those who will not. This approach is already proving to be highly effective, with drugs now available that target, among others, diseases such as metastatic melanoma and cystic fibrosis in patients carrying specific mutations. Through the use of companion diagnostic tests and targeted therapy, the foundations are thus being laid for the future of personalised medicine.

**Vemurafenib for the treatment of metastatic melanoma**

Metastatic melanoma has a very poor prognosis, with a life expectancy of only a few months in affected patients<sup>17</sup>. Furthermore, there is a low response rate and only limited improvements in survival with many approved chemotherapeutic drugs. Around half of all melanomas, however, carry mutations in the *BRAF* gene, and 90% of those cases involve an activating mutation known as BRAF V600E<sup>18</sup>. Evidence is now available to show that an inhibitor of the mutated BRAF protein, vemurafenib, leads to a significant improvement in overall and progression-free survival in patients with metastatic melanoma and the BRAF V600E mutation<sup>19</sup>. On the basis of these findings, vemurafenib has been approved for the treatment of metastatic melanoma with the BRAF V600E mutation as detected by an approved companion diagnostic test<sup>20</sup>. This is just one example of a drug that can be used effectively in a subset of patients with a specific biological profile but that would not be appropriate for all patients with the disease.

**Ivacaftor for the treatment of cystic fibrosis**

Cystic fibrosis, the most common inherited disorder affecting white patients, is caused by mutations in an epithelial ion channel known as the cystic fibrosis transmembrane conductance regulator (CFTR)<sup>21</sup>. Until recently, no treatments were available that targeted the underlying cause of the disease. A drug has now been developed, however, that potentiates the function of the CFTR channel in a subgroup of patients carrying a specific mutation. Ivacaftor enhances the activity of CFTR channels containing the missense *G551D* mutation, which is present in 4% to 5% of patients with cystic fibrosis. A recent study showed that, compared with placebo, ivacaftor treatment led to sustained improvements in lung function and other symptoms in patients with at least one *G551D-CFTR* mutation<sup>10</sup>. The drug was approved by the US Food and Drug Administration (FDA) in early 2012 for use in patients over 6 years of age who have a *G551D* mutation in the *CFTR* gene<sup>22</sup>. Importantly, however, the labelling indicates that, if the patient's genotype is unknown, an FDA-approved companion diagnostic test should be used to assess the presence of the mutation. In addition to being a milestone in the treatment of cystic fibrosis, this is another clear example of the potential of personalised medicine, since the drug is effective in a specific group of patients who can be identified on the basis of the mutations responsible for their disease. Interestingly, marketing authorisation for ivacaftor was provided in just three months, one of the shortest FDA approval processes on record.

17. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, *et al.* Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; 27(36):6199-206.

18. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, *et al.* Distinct sets of genetic alterations in melanoma. *N Engl J Med* 2005; 353(20):2135-47.

19. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. *N Engl J Med* 2005; 352(19):1992-2001.

20. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002409/human\\_med\\_001544.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002409/human_med_001544.jsp&mid=WC0b01ac058001d124)

[http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/202429s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202429s000lbl.pdf)

21. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, *et al.* A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. *N Engl J Med* 2011; 365(18):1663-72.

22. [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/203188lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/203188lbl.pdf)



## 3.

# What can personalised medicine offer?



For personalised medicine to be effectively introduced across Europe, stakeholders must first be clear about the benefits it can offer. At the same time, we need to be realistic about the potential of the approach and avoid inflated claims that could reduce confidence in the likelihood that it will deliver on promises.

### 3.1 The European citizen

Personalised medicine is commonly described as a shift away from a one-size-fits-all approach towards one in which healthcare is based on the individual biological makeup of each citizen within a specific sociocultural and environmental context. For those who become ill, what this means in practice is the promise of safer, more effective treatments, and indeed, this promise is already being delivered in the form of stratified medicines to treat specific tumour subtypes in particular<sup>23</sup>. However, the longer-term promise is of increased potential for prevention of disease based not only upon genetic prediction but also upon monitoring of physiological status over the life course. Patients who are willing to participate fully can hope to receive not only tailored treatment once diseases have developed, therefore, but also tailored prevention strategies based on a continuously updated biological profile<sup>24</sup>.

23. Schilsky RL. Personalized medicine in oncology: the future is now. *Nat Rev Drug Discov* 2010; 9(5):363-6

24. Brand A, Lal JA on behalf of the Public Health Genomics European Network (PHGEN II). European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies: the 2012 Declaration of Rome. *Drug Metab Drug Interact* 2012; 27(3): 177-182

Despite the assertion that medicine has always been personalised, it is clear that in many areas citizens have not felt that they are fully in control of the decisions made about their wellbeing. Personalised medicine could provide the means for citizens to exert more control over their health without having to rely directly on professional healthcare. For instance, the use of biofeedback systems to monitor even simple variables such as blood pressure, cholesterol and glucose could allow adequately informed citizens to take corrective measures directly without having to go to their physician. This is a potentially empowering step for European citizens. The promise of empowerment, however, raises issues of health literacy, responsibility and access<sup>25</sup>. Variable engagement is likely to be a given, particularly among certain groups and many issues will need to be addressed to ensure that inequalities are not unwittingly introduced.

### 3.2 The healthcare profession

Just as patients can hope to receive safer, more effective drugs according to their individual characteristics, healthcare professionals will benefit from increased confidence in the therapeutic decisions they are required to make. Greater certainty of the appropriateness of a treatment will be provided by a combination of increased availability of diagnostic information and improved decision-support systems provided by advances in information and communication technology (ICT). The outcome of

25. Sørensen K, Brand H. Health literacy: the essential catalyst for the responsible and effective translation of genome-based information for the benefit of population health. *Public Health Genomics* 2011; 14(4-5): 195-200

increased confidence in therapeutic decisions might reasonably be expected to have a positive impact on the physician–patient relationship. However, the complexity of the data that support the decision may place different demands on the physician to communicate therapeutic rationale to the patient. Healthcare professionals might therefore expect, and indeed demand, additional technological support and education to facilitate that process.

Personalised medicine will inevitably go hand in hand with a reclassification of diseases<sup>26</sup>. Currently, most diseases are diagnosed based on constellations of symptoms, usually centred on a particular organ or system. With the increasing availability of biological data, it is becoming possible to classify pathology according to the molecular pathways and physiological changes involved. Such a change in disease taxonomy could be particularly important in chronic diseases such as inflammatory disorders, many of which may share common aetiologies despite displaying different phenotypes in different individuals<sup>27</sup>. Reclassifying disease phenotypes in this way will lead to greater insight into complex diseases and allow treatment of patients with conditions that currently prove to be intractable. Importantly, the subclassification of existing diseases that is likely to be the precursor of a wider reclassification of disease phenotypes should create opportunities for existing drugs to be used more effectively, and even for drugs that have proven not to be effective in large, unstratified groups of patients with an existing disease classification to prove their efficacy in patients with a particular subtype of disease.

Another key feature of personalised medicine is the potential for a life-course approach to healthcare in which data are collected and integrated into an individual health readout throughout a person's lifetime<sup>28,29</sup>. Such an approach offers greater opportunity for prevention by assessing individual risk of developing specific diseases. It also provides greater opportunity for early intervention following the identification of pathological changes. Furthermore, it means that individual citizens could begin to generate their own baseline physiological

data. This could result in improved recognition of relevant pathological changes without having to assess health based on population values.

### 3.3 Reimbursement bodies and other stakeholders

A common promise is that personalised medicine will reduce healthcare expenditure. For some, it might even be considered a benchmark for the overall success of the approach. Evidence is available to support this view based on analyses of stratified approaches to cancer therapy. For instance, by spending €1.7 million on EGFR mutation testing in the French health system, €69 million has been saved on the cost of gefitinib therapy in patients with non-small-cell lung cancer who would not benefit from receiving the drug<sup>30</sup>. Similar observations have been made in colon cancer, where patients carrying mutations in *KRAS* do not respond to EGFR antagonists, resulting in a saving of €30,000 on treatment if patients are first screened for EGFR status. Nevertheless, those responsible for reimbursement are understandably sceptical of claims that the introduction of new technologies or treatments will lead to overall cost savings. Indeed, it can be argued that personalised medicine has the potential to increase healthcare expenditure if not managed effectively.

In personalised medicine, an increased emphasis on diagnostics and pre-emptive testing will come at a cost. Aside from the direct cost of investment in diagnostics technology, false-positive diagnosis in even a relatively small proportion of patients might be expected to increase expenditure due to the costs of unnecessary treatment. The hope is that such costs will be offset by long-term reductions in expenditure through effective prevention or early intervention, particularly in chronic diseases. Similarly, the cost of investing in new technology and infrastructure is hoped to offer more cost-effective healthcare for future generations. Furthermore, it should not be forgotten that drugs considered unsuitable for large, unstratified groups could be highly appropriate for the defined subgroups predicted to become the focus of personalised medicine. Thus, expenditure could be predicted to increase as a result. The important question for reimbursement agencies is whether short-term expenditure will offer tangible short-term benefits, irrespective of longer-term outcomes. A realistic expectation could thus be

26. Brand A. Public health genomics – public health goes personalized? *Eur J Public Health* 2011; 21(1): 2–3

27. Renz H, Autenrieth IB, Brandtzæg P, Cookson WO, Holgate S, von Mutius E, *et al.* Gene-Environment Interaction in Chronic Disease: a European Science Foundation Forward Look. *Allergy Clin Immunol.* 2011 Dec; 128(6 Suppl):S27–49.

28. Cesuroglu T, van Ommen B, Malats N., Sudbrak R, Lehrach H, Brand A. Public health perspective: from personalized medicine to personal health. *Personalized Medicine* 2012; 9(2): 115–119

29. Cesuroglu T, van Ommen B, Malats N, Sudbrak R, Lehrach H, Brand A. Public health perspective: from personalised medicine to personal health. *Personalized Medicine* 2012; 9(2):115–19.

30. [http://ec.europa.eu/research/health/pdf/personalised-medicine-conference-report\\_en.pdf](http://ec.europa.eu/research/health/pdf/personalised-medicine-conference-report_en.pdf)

cost containment rather than reduction, along with improved public health and quality of life. In other words, personalised medicine might reasonably be expected to generate a more efficient, rational use of resources. A more realistic promise is thus an improved return on investment.

For industry, the future may be difficult to predict and dependent upon decisions taken by other stakeholders. In principle, personalised medicine could provide an opportunity for more streamlined introduction of medicines to the market and also restored opportunities to market drugs that are effective in specific populations but currently restricted in the larger population of patients due to lack of efficacy overall or safety issues in certain groups. The opportunity to reintroduce so-called fallen angels could benefit both industry and the community as a whole. Clinical trials could become more streamlined by selecting more appropriate patient samples. However, it is also likely that new testing models will need to be developed. *In silico* testing could also be an important advance in helping to streamline clinical development. Aside from these potential benefits, substantial new opportunities can be expected in the diagnostics and medical devices fields, as can obvious openings for the ICT industry<sup>31</sup>.

### 3.4 Recommendations

**All stakeholders in personalised medicine must:**

1. Avoid inflated claims about the potential of personalised medicine during early stages of planning and implementation.

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31. Brand A, Holgate ST, Kristiansen LV, Lehrach H, Palotie A, Prainsack B. The future of technologies for personalised medicine. *New Biotechnol* 2012; 29(6): 625-633

## 4.

# What are the technological considerations for personalised medicine?



A defining feature of personalised medicine will be its capacity to integrate complex information from multiple data sources and to generate a usable output to support the health of individual citizens. Given the requirement for data handling on a massive scale that this implies, we can say with confidence that personalised medicine as it is currently envisaged will not exist without advanced technologies, particularly in relation to data generation and handling. Genomics, epigenomics, proteomics, metabolomics, lipidomics and other 'omics technologies, such as analysis of the microbiome, will be required alongside imaging and physiological monitoring to generate biological data. All of this information, along with additional data on environmental exposures and lifestyle, for instance, will need to be stored and, most importantly, integrated, analysed and interpreted. Furthermore, existing technologies may be exploited more effectively when fully integrated with upcoming technologies. This will require ICT solutions that can handle comprehensive biological datasets and convert them into a meaningful output that will inform individual healthcare decisions.

## 4.1 Beyond data collection

Data collection is unlikely to be a rate-limiting step for personalised medicine. In the last 20 years, our capacity to collect detailed biological information has advanced at an enormous rate. Next-generation sequencing technology, for instance, now makes it possible to obtain entire genome sequences in a single day<sup>32</sup>. Similar advances are being made in other 'omics technologies, making it possible now to characterise individual metabolic profiles, protein expression and localisation, mRNA expression and even epigenomic signatures in specific cell types. However, for this information to be useful in order to predict individual risk, disease course, treatment response and the likelihood of adverse events, we must be able to integrate and interpret different datasets and link the findings to specific outcomes in individual citizens.

Data collection is only useful if we can ensure that the collected data are of a sufficient quality. In order to integrate information from multiple sources, we must ensure that it is well characterised and compatible. Even when comparing data obtained in different laboratories using the same 'omics technologies, issues arise over the way samples have been handled, analyses carried out, and results annotated. If the goal is to integrate information, not only across multiple 'omics platforms but also with other technologies such as imaging to achieve reliable spatial and temporal resolution, the issue of compatibility is magnified greatly. The technology required to support personalised medicine thus faces a massive data-handling challenge.

32. Scudellari M. The 24-Hour, \$1,000 Genome. *Canc Discov* 2012 (2): 6.



Furthermore, the technological challenges of data handling will be complicated by the need to respond to ethical, legal and governance issues that come with responsible linkage, integration and management of personal data.

Until recently, developments in ICT were driven mainly by ‘big’ physics and the entertainment industry. In the genomic era, however, bioinformatics has begun to place greater demand upon ICT infrastructure and the movement towards personalised medicine is likely to become a key driving force for ICT development. For instance, whereas processing power has continued to obey Moore’s law, doubling every two years, the last five years have seen sequencing power increase by factors of 10. Thus, our data-generation potential, particularly through ‘omics technology, far outstrips our resources for their analysis. The demands placed on ICT by personalised medicine are not limited to processing power, however. Storage of the vast amounts of data that are being generated may itself become a limiting factor and great care will be required when considering solutions such as data compression, since these can have a profound effect on the subsequent usefulness of the information. Similarly, without careful planning of how stored data is annotated, organised and shared, it may be impossible to achieve the necessary integration.

To understand the technological challenges for the future of personalised medicine, it is important to focus on three key areas. Firstly, what are the demands from medicine and healthcare? These will determine whether technology can meet the expectations of a core group involved in the implementation of personalised approaches. Secondly, what does technology have to offer personalised medicine? This represents the technological push towards progress in the field and can be expected to drive many of the developments that occur. Thirdly, how can information be effectively integrated to provide a complete systems-based readout of the health status of an individual in a given environment? This will prove to be a benchmark for the success of personalised approaches to medicine and healthcare. In each of these areas, the needs of the individuals whose health will be served by personalised medicine will be paramount. Without taking citizens into consideration, no such developments can achieve their potential.

## 4.2 Medicine

The demands that will drive technological development in personalised medicine currently come mainly from the medical profession. Whatever the

potential offered by technological advances, if they are not seen as beneficial to the day-to-day work of clinicians, they are unlikely to be taken up.

The demand from the medical profession will continue to be first and foremost for technology that effectively supports decision-making and facilitates delivery of healthcare. Clinicians will expect information to be provided quickly and in a format that indicates a clear course of action. For technology to be useful to healthcare professionals, it must also help them to provide straightforward responses to the concerns of patients about future illness, treatment options and opportunities for prevention.

In order to support the clinical decision-making process, complex data will need to be presented in an easily interpretable form. The demand from the medical profession, therefore, will be for uncomplicated technological interfaces that are fully integrated into their normal working lives. This does not equate with a reductionist approach, however. Healthcare professionals will increasingly expect information to be integrated from multiple sources, including ‘omics approaches and imaging, and fed into continually refined algorithms to support their choice of an appropriate course of action for each patient or individual.

### 4.2.1 The next 5 years – providing proof of principle

In order to accept the introduction of technology to support personalised medicine, the medical profession will initially expect to see proof of principle. At this early stage in the introduction of personalised medicine, there is a risk of reducing confidence among healthcare professionals and service users by making unsubstantiated grandiose claims. Clinicians will therefore need to know that the technology can offer tangible benefits. Thus, the first step will be to demonstrate the clinical utility, validity and relevance of all new technologies.

On-going analysis of health status across the life course of an individual will require the identification of stable biomarkers. Furthermore, their purpose and applications will need to be clearly defined in each case. Although all biomarkers can be defined as indicators of a biological state, their uses vary from diagnosis and monitoring of treatment response through to assessment of disease prognosis and prediction of treatment response. In each case, their clinical or research utility will need to be clearly defined. A key step will be to validate existing biomarkers and confirm their utility for risk stratification and prediction of outcomes. Similarly, the diagnostic tests that will be required for pre-selective screening will need to show a reliability



of close to 100%. If the viability of these elements can be demonstrated individually, it is likely that healthcare professionals will be convinced of their potential to be integrated into more complex models. Furthermore, it will be critically important to assess the true clinical benefit of ongoing monitoring of biomarkers, particularly in asymptomatic, apparently healthy individuals (see Box 3). Of particular concern is the risk of overdiagnosis and false-positive results<sup>33</sup>.

Early efforts to provide a proof of principle might benefit from focusing on a single complex disease area. In addition to demonstrating benefits in terms of a clear healthcare need, this would also allow researchers to identify gaps and begin to define targets for future development. Possible options include diseases such as diabetes, rheumatoid arthritis, asthma or cardiometabolic disease. It would also be valuable, however, to explore the approach in a more tractable and tightly defined condition such as subtypes of non-small-cell lung cancer or breast cancer, where tangible benefits might be demonstrated in a shorter period of time.

Proof of principle will also require demonstration that the infrastructure and resources can be developed to support future integrated approaches. As a matter of urgency, steps should therefore be taken to fully exploit biobanks and clinical sampling programmes and to ensure Europe-wide access to the technological support and logistic infrastructure that will drive the future development of integrated models, including the establishment of core reference datasets<sup>34</sup>.

### Box 3: Personal omics profiling – proof of principle for personalised medicine?

A recent high-profile publication reported the results of a study designed to provide a proof of principle for personalised medicine<sup>35</sup>. The article describes how genomic, transcriptomic, proteomic, metabolomic and autoantibody profiles were collected at multiple time points in a single individual to generate a dynamic integrative personal omics profile (iPOP). Unlike in most previously reported studies, the subject was an apparently healthy individual (the corresponding author of the article) and the collection of an enormous volume of data over a 14-month period allowed information to be obtained on the individual's dynamic iPOP during periods of health and disease.

As a proof of principle for personalised medicine, the study by Chen *et al.*<sup>36</sup> includes a number of interesting aspects. Firstly, whole-genome sequencing revealed evidence of increased risk for diseases including type-2 diabetes, thus supporting the use of genomic profiles for assessment of disease risk. The use of iPOP, however, goes far beyond genomic risk assessment. On-going monitoring revealed the onset of type-2 diabetes with a sharp increase in blood glucose and elevated HbA1c. This occurred immediately after respiratory syncytial virus infection, which was paralleled by complex changes in other 'omics profiles. Similarly, dynamic changes in the iPOP were observed earlier in the study period following human rhinovirus infection, possibly reflecting immune responses. Although many of the changes observed in the iPOP during the development of diabetes and during infection could be recognised through transcript profiling, others only became apparent through proteomics or analysis of combined data sets.

A defining feature of personalised medicine is its emphasis on individual data rather than merely on averaged population data. This approach allows data pertaining to a specific individual to serve as a baseline for identifying pathological changes, and indeed for monitoring health. In the study by Chen *et al.*, the authors point out that the detailed responses observed in a single patient might have been masked in a large study group as a result of interindividual variation. This does not mean that populations cannot be considered, however, but rather than they are not the starting point. As the authors of the study point out, comparison of longitudinal iPOP data from large groups of individuals could itself help to elucidate the various mechanisms underlying a complex disease such as type-2 diabetes. Indeed, such analyses could provide a basis for meaningful subclassification of diseases and redefinition of diagnoses according to phenotype and underlying mechanism.

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33. Moynihan R, Doust J, Henry D. Preventing Overdiagnosis: How to Stop Harming the Healthy. *British Medical Journal*; 2012; 344: e3502.

34. European Science Foundation, "European Biobanks and Sample Repositories – Relevance to Personalised Medicine," ESF Position Paper (May 20, 2011), <http://www.esf.org/publications/science-position-papers.html>.

35. Chen R, Mias GI, Li-Pook-Than J, Jiang L, Lam HY, Chen R, *et al.* Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes. *Cell* 2012; 148(6): 1293–1307.

36. C Dennis, *The Rise of the "Narciss-Omel"* (*Nature*, 2012).

Interestingly, in response to the identification of developing type-2 diabetes, the author implemented dietary measures to control his glucose levels. It can be argued that using iPOP to guide lifestyle changes that control or prevent disease itself provides a proof of principle for personalised healthcare, not only prescription of personalised medicines. We might question, of course, how representative such a response would be of the behaviour of citizens from different cultural and social groups. The ability to respond to an identified or predicted health issue is likely to depend upon health literacy and other factors. Thus, the success of personalised healthcare will depend upon its adaptability to the needs of different individuals, not all of whom will be in a position to engage proactively with their own health and wellbeing.

A less satisfying outcome of this work for the corresponding author was an increase in his insurance premiums to prohibitive levels based on his having type-2 diabetes. Yet, the opportunity to make lifestyle and dietary changes to maintain his own health reportedly led him to conclude that this was an acceptable trade-off<sup>37</sup>. Furthermore, he notes that he has benefited from medical advice offered by colleagues when he has presented the data at scientific conferences. Perhaps this observation also hints at an early proof of principle for crowd-sourced health advice within personalised medicine?

Finally, the authors suggest that combining large dynamic datasets such as the one presented in their article could serve as an important resource for personalised medicine. This highlights an important question for the future of personalised medicine, that is, will information gained from individual monitoring and treatment automatically be available for research purposes? What seems clear is that the ongoing development and optimisation of healthcare would benefit greatly from such an approach. However, its implementation may not be straightforward and it is clear that issues relating to interoperability, patient choice, privacy and ethical use of personal information will first need to be addressed.

#### 4.2.2 The next 10 years – introduction

Once clinical utility has been demonstrated for core technologies, health professionals will be more likely to support the introduction of a personalised approach to medicine and healthcare. During this next phase of development, the demand is expected to be for increasingly integrated information that goes beyond individual ‘omics approaches while continuing to support rapid clinical decision-making. Algorithms will need to be based on the interaction between different ‘omics and environmental (including lifestyle-related) data and, increasingly, to be integrated with imaging technology<sup>37</sup>.

37. Brand A. Public health genomics – public health goes personalized? *Eur J Public Health* 2011; 21(1): 2–3

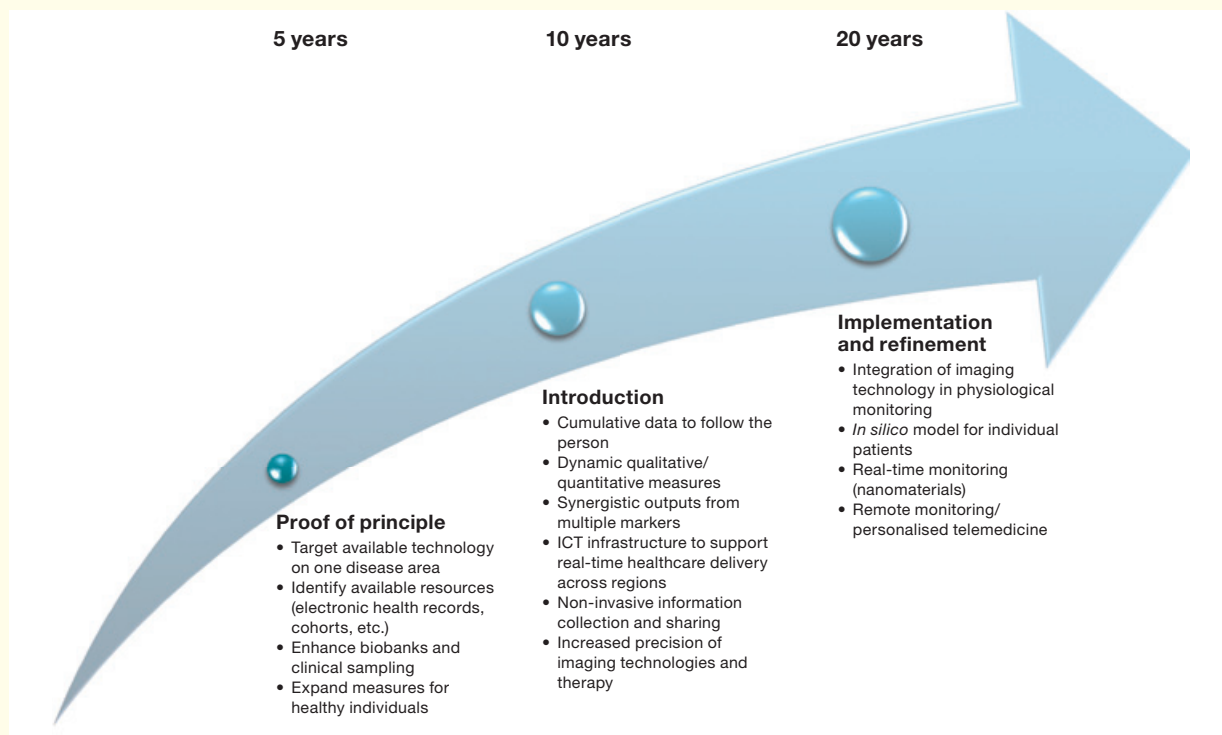
As personalised medicine is introduced, emphasis is predicted to shift away from patients (i.e. those with clinical symptoms) and towards healthy citizens, with increasing emphasis also being placed on prevention. Technology will be required to support lifelong monitoring of individual health. One way in which this could occur is through the use of electronic health records. However, many hurdles will need to be overcome if this approach is to achieve its full potential<sup>38,39</sup>. A long-term vision could include the creation of personal medical records that would follow each individual from birth (or even prenatal life) and across geographical space. However, this would present not only technological challenges but also legal and ethical hurdles relating to the handling of data defined as ‘sensitive’ or ‘personal’ within the European space. In particular, solutions will need to be found to the cross-border issues presented by an increasingly mobile European population.

While citizens are predicted to become the managers of their own data, healthcare professionals will increasingly require dynamic qualitative measures based on quantitative data inputs. This is understood to present an engineering challenge, as it will require the development of appropriate sensors to generate and store real-time information about individual health status. Furthermore, in order to ensure citizen autonomy, ICT interfaces will need to incorporate options for citizens to make informed choices about monitoring and sharing of different types of data.

Integration of multiple data inputs will include not only different technologies such as genomics and metabolomics but also information on multiple markers. If implemented effectively, the usefulness of synergistic outputs can be expected to expand rapidly, on the basis that the value of the information is not simply additive. To support real-time healthcare delivery, however, these demands from medicine will need to be supported by an adequate ICT infrastructure and reference datasets. In addition, the clinical infrastructure must ensure that resources such as imaging are available over a wide geographic range. This will not only support access to healthcare but also ensure that information is obtained from the widest possible population set. Information obtained in medical settings is also likely to overlap with data collected for non-medical purposes. Such an expansion of resources can feed into the integrated models used to continually improve personalised medicine. A key issue to address if this vision is

38. Mirnezami R, Nicholson J, and Darzi A. Preparing for Precision Medicine. *N Engl J Med* 2012; 366 (6): 489–491.

39. Jensen P, Jensen L, and Brunak S. Mining Electronic Health Records: Towards Better Research Applications and Clinical Care. *Nature Rev Gen* 2012; 13 (6): 395–405



**Figure 1.** Projections for medicine

to be achieved, however, is the crossover between research and clinical applications. A critical assumption is that data employed for diagnostic purposes and monitoring should be automatically available for research intended to optimise personalised medicine. However, the implications of this vision will need to be dealt with if it is to become a reality.

**4.2.3 The next 20 years – implementation and refinement**

As the introduction of personalised medicine proceeds in the clinic, the technological demand will be for increased precision and reduced response time. One area in which this is likely to be most apparent is in imaging technologies. Currently, the lag time for diagnostic imaging is mainly determined by data processing and interpretation. In order to achieve the seamless integration of imaging technology into real-time monitoring of health status and treatment efficacy, however, this processing time will need to be reduced without loss of precision. Advances in this area will be crucial to the implementation of fully integrated approaches in the clinic.

Once it has been shown that physiologically meaningful, integrated information can be obtained, medicine can be expected to demand real-time monitoring and continual refinement of the *in silico* models used to inform clinical decision making (e.g. IBM’s Watson<sup>40</sup>). This is likely

to require the development of nano devices and remote-sensing technology, as well as an ICT infrastructure that allows the information obtained to continually update individual models and feed back into the reference models that inform the approach.

**4.2.4 Projections for medicine** (Figure 1)

**4.3 Technology (analysis and information technology)**

Technology is both a driving force for the development of personalised medicine and a response to the needs of health professionals, patients and citizens. Its role might be conceptualised as supporting efforts to increase the healthy lifespan (not simply the lifespan) of all individuals. To achieve this, it must effectively deliver meaningful information on risk prediction, molecular and physiological phenotyping, treatment outcomes and monitoring in a form that supports clinical decision-making. In addition, it must support continued improvement of existing models, not only based on analytical data but also on the experience of end users, including both healthcare professionals and citizens.

**4.3.1 The next 5 years – linear technologies**

Current technologies, principally ‘omics approaches, provide linear information in which individual differences feed forward into binary decision-making.

40. <http://www-03.ibm.com/innovation/us/watson/>



Although the future goal may be to integrate multiple types of information into a single output, demonstration of the utility of individual technologies will be essential to their uptake in clinical settings. It is therefore crucial that we identify which technologies can realistically be moved into the clinic over the next 10 years and communicate with healthcare professionals to prepare the ground for this transition.

To meet the medical demand for proof of principle, substantial efforts will be required to validate existing approaches, including clear evidence of reproducibility. Harmonisation of protocols will be an important consideration if this goal is to be achieved. For instance, the methods used to align and annotate genomic sequences can vary from one laboratory to another. The variation that these procedural differences can introduce into the data obtained, however, can be considerably greater than the individual sequence variation under investigation. Without effective harmonisation of protocols between laboratories, then, it will be impossible to obtain the reproducible data required to build informative models.

Harmonisation applies not only to technological procedures and sample collection but also to data handling. Reproducibility of results will need to be demonstrated in large samples, initially through analysis of established cohorts, and this will require increased availability of linear 'omics technologies. Any future efforts to generate standard algorithms on which to base clinical decision-making will depend on the successful development of this infrastructure and, in particular, the harmonisation of protocols. Without ensuring consistency across laboratories, data processing centres and even large healthcare regions, it will be impossible to compare findings or guarantee the reliability of predictions, diagnosis and choice of treatment or prevention strategies. Quality assurance protocols will thus need to be established at all levels. Furthermore, efforts will be needed to harmonise approaches to data handling for clinical and research purposes, as the distinction between the two domains becomes less clear in personalised medicine.

Harmonisation of procedures forms the basis for reliable data collection from large samples. To obtain maximum benefit, it must be underpinned by the necessary legal and ethical frameworks to support the sharing of data. The technological challenge for data sharing, however, is also one of storage and transfer<sup>41</sup>. At present, our ability to generate bio-

logical data exceeds our capacity to process and store it. Solutions such as data compression carry an enormous risk of losing valuable information and any such measures will require careful standardisation of protocols to ensure comparability of data inputs. An alternative solution could be the use of *in silico* models in which only variable data are used to populate a base model, thereby reducing the volume of invariant data that requires storage. Even under these conditions, however, other limitations such as bandwidth may impact on the data transfer required to populate the models and build complex interaction networks.

#### Box 4: Building frameworks for linear data collection

In the Netherlands, a public-private partnership has been established to facilitate the uptake of linear technologies in the clinic through national harmonisation of sequencing strategies and platforms, data analysis and interpretation, diagnostic decision-making and ethical and legal frameworks. The Centre for Genome Diagnostics (CGD)<sup>42</sup> brings together all existing centres for clinical genetics within a collaborative platform designed to support the implementation of next-generation sequencing with routine patient diagnostics. In an effort to identify bottlenecks and challenges beyond the technology itself that need to be overcome to make actual diagnostic use of next-generation sequencing a reality, the CGD is currently running a simulation of the complete diagnostic procedure with patients with cardiovascular disease. The results of this pilot study will be presented in September 2012.

At the Mayo Clinic Center for Individualized Medicine in the United States of America, an ambitious programme of discovery, translation and clinical application has been initiated in an effort to establish the foundations for personalised medicine<sup>43</sup>. The approach is centred around five translational programmes: biomarker discovery, clinomics, epigenomics, microbiome and pharmacogenomics. In each area, the emphasis is on linking data to clinical findings and treatment response in an effort to develop precise diagnostic tests and tailor therapy to individual patients. The translational programmes are supported by core infrastructure, notably a biobank that will soon act as a comprehensive repository for samples from 50,000 patients and extensive bioinformatics support. However, the approach being applied at the Mayo Clinic Center for Individualized Medicine encompasses wider considerations, such as

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Sequencing. *Nature Biotechnol* 2012; 28(1): 1.

42. <http://www.genomics.nl/Research/Public-Private%20Partnerships/CGD.aspx>

43. <http://mayoresearch.mayo.edu/center-for-individualized-medicine/index.cfm>

41. Gathering Clouds and a Sequencing Storm: Why Cloud Computing Could Broaden Community Access to Next-Generation

standardisation of data collection and processing, bioethics programmes in areas such as risk assessment and communication, data security and privacy, ownership of research findings, educational and administrative infrastructure, and ICT solutions. As such, the experiences of the Mayo Clinic may provide an early proof of principle, not just for data collection and integration but also for the wider implementation of personalised medicine.

#### 4.3.2 The next 10 years – building interaction networks

During the next phase of technological development in personalised medicine, it will be necessary to integrate standardised data from large samples such as patient cohorts within the context of phenotypic and environmental data. Healthcare professionals will demand a very high level of precision in the interaction networks that are built but the technology used to achieve this must not result in a substantial increase in response time.

A new technological challenge at this stage will be the development of methods to measure and quantitate the functional state of molecular systems. The ability to obtain data on factors such as protein phosphorylation state and localisation, enzyme-substrate interactions, and markers of cell activity will be a crucial step in the transition towards real-time analysis of dynamic physiological networks.

The complex algorithms arising from this technological integration will also need to be validated in the clinic and their cost-effectiveness, acceptance by stakeholders and integration into healthcare systems demonstrated. A key concern here will be to define the most appropriate study designs to test potentially relevant findings. Core considerations will be how to distinguish between pathology and simple variation based on complex interaction data, how to assess the impact of targeted interventions and how to model their overall cost-effectiveness in the population. These questions will require solutions not only from ICT and bioinformatics but also from social and clinical research.

It should not be forgotten that technology solutions require trained professionals to develop and implement them. At this stage in the development of personalised medicine, then, the need for interaction networks can be understood to refer not only to complex biological information but also to human resources. Thought must therefore be given to the training of technologists and also to the intellectual and communications infrastructure that supports cross-disciplinary interaction.

#### 4.3.3 The next 20 years – measuring dynamic networks *in vivo*

Once the clinical utility of complex, integrated models has been demonstrated, the demand from the healthcare profession will be for real-time monitoring of individual health state, remote sensing, and rapid integration of information into *in silico* models. This will require non-invasive technologies, such as nano devices, novel communications solutions to relay information, and also algorithms that feed into appropriate user interfaces and alert the citizen or healthcare professional to relevant change. If these goals are achieved, it will be possible to apply individual preventive and corrective measures in real time and thereby ensure the continued health of citizens.

#### 4.3.4 Projections for technology (Figure 2)

### 4.4 Integration

A core element in the transition towards personalised medicine is the integration of information from multiple data sources. The challenge will effectively be to generate technological solutions that can process the output from multiple core technologies. It is only by providing these sorts of integrative platforms that we can hope to move from a traditional disease model towards a systems-based mechanistic approach to health and disease.

#### 4.4.1 The next five years – discovery

The initial phase in developing an integrated approach to personalised medicine will be discovery. Clearly, before true integration can be achieved the core elements must be refined and validated. Thus, 'omics technologies must be consolidated and advances made in areas such as epigenetics, environmental sampling and characterisation of the microbiome at the interface between organism and environment.

Discovery must feed forward into a prototype model that will form the basis for future integration. This model will need to take into account all available 'omics technologies. However, it will also need to provide a template onto which additional inputs such as imaging data and contextual information on environmental conditions and lifestyle can be added. It is this prototype model that will need to provide the proof of principle for integration.

Harmonisation will once again be essential in preparing the ground for integration. As with harmonisation of sampling protocols and data generation, attention must also be paid to factors such



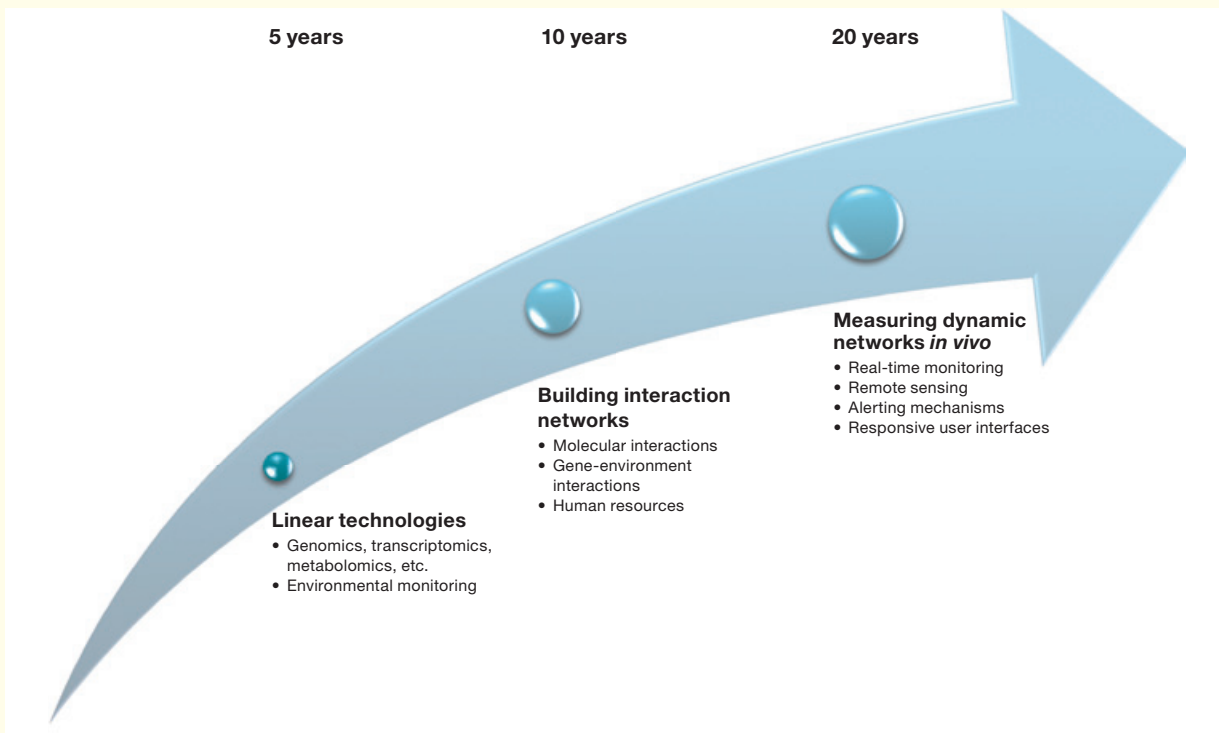


Figure 2. Projections for technology

as compatible terminology and cross-disciplinary and even cultural communication. Europe-wide frameworks will be needed to ensure the consistent use of terms, for instance, as well as continued accessibility of all relevant information. Similarly, user interfaces must ensure effective communication irrespective of the location, language, or culture of the user. This is likely to be a particular concern for citizen-level interfaces.

#### 4.4.2 The next 10 years – validation

Once a prototype model for integration of technologies has been developed, the next step is obviously to validate the model. This process should not be confused with the validation steps that will also be needed for individual biomarkers and technologies. It is to be hoped that those initiatives will precede validation of integrated models, or at least run in parallel. To provide a proof of principle for integration, a simple objective will need to be defined, such as the ability to model the response of a cancer cell to treatment. However, the focus at this stage is not on the specific clinical application but rather on obtaining proof of concepts and creating the conditions for refinement of the model and integration into European frameworks.

#### Box 5: The virtual liver network – a model of integration?

The challenge of integrating data into reliable models of a defined biological system is currently being taken up by the Virtual Liver Network, a large-scale research initiative funded by the German Federal Ministry for Education and Research<sup>44</sup>. The core goal of the project is to generate a model of human liver physiology, morphology and function through the integration of data at multiple organisational levels, from subcellular events to whole-organ physiology. The outcome will be a modifiable platform with which to analyse unmet medical needs and provide key insights into health and disease using systems biology rather than reductionist data. Integration is not only a data issue for the Virtual Liver Network, however. The network comprises 70 research groups throughout Germany and is in the process of establishing international links. Thus, the experience of this initiative is likely to provide useful insights into the coordination of activity across multiple centres that is likely to be an increasingly common feature of personalised medicine.

A core element in building and validating the prototype model will be to define its purpose. For instance, is it to provide on-going feedback on individual health or to support diagnosis and treatment of specific problems? This question highlights the need for on-going consultation between stakehold-

44. <http://www.virtual-liver.de/>



Figure 3. Projections for integration

ers in personalised medicine, particularly citizens (not only patients) and the healthcare profession.

Before implementation can begin, the appropriate infrastructure and reference datasets must be established. This is in part a technological challenge, as the core ICT facilities must be generated in order to process data from multiple sources and generate a meaningful output. However, the utility of the output is critically dependent on understanding the needs of stakeholders and being able to demonstrate the benefits of the new technologies. This is not merely a question of validation. It is also a communication and education issue, and it is likely that tools such as e-learning platforms will need to be developed for a variety of purposes.

#### 4.4.3 The next 20 years – implementation

Implementation of integrated models will present new challenges. In particular, the need for continued monitoring of health status will drive developments in nanotechnology. Beyond individual monitoring considerations, however, there will also be a requirement for systematic, longitudinal data generation. Cohorts and other large-scale data sources will need to meet rigid standards for data collection, processing and annotation. Thus, harmonisation and development of frameworks for sharing of information are once again critical to the success of personalised medicine.

## 4.5 Key enabling factors to develop the technological support for personalised medicine

### 4.5.1 Systems approach

Personalised medicine has the potential to go far beyond targeted diagnosis and therapy. By developing truly integrated models of health status over the life course of individuals, we may be well positioned to take a systems-based approach to extending the healthy lifespan of citizens. Key enabling factors in achieving this goal will be an increased understanding of ‘healthy’ phenotypes and contextualisation of health outcomes based on environmental data. This is predicted to provide a platform for community-stratified medicine and will radically redefine our approach to individual and community health. Early steps to facilitate the development of a systems approach will be the ability to sample environmental and lifestyle inputs more effectively and link them to individual health records and other relevant data sets<sup>45</sup>.

### 4.5.2 Harmonisation

Harmonisation is recognised as a key enabling factor across all of the domains considered. If samples are not collected, stored and classified according to

45. Brand A. Public Health Genomics and Personalized Healthcare: a pipeline from cell to society. *Drug Metabol Drug Interact* 2012; 27(3): 121–123

similar procedures, the potential for cross-referencing and integration across databases and systems will be seriously compromised. Likewise, differences in analytical protocols or data handling can profoundly affect the information generated from the same samples. In other words, the quality of the input determines the quality of the output. This is the ‘garbage in, garbage out’ problem. Consideration should be given to enforcing the harmonisation of protocols in all newly initiated studies and gradually introducing harmonisation in existing cohorts and related initiatives.

Datasets relating to patients and their representations differ substantially from those obtained in a research setting, irrespective of whether they are generated in healthcare settings or by patients

themselves. Given the overlap between healthcare and on-going research in personalised medicine, the different types of information need to be matched, as inconsistent representation could hinder both the use of patient data for research and the translation of research findings into the healthcare arena. For instance, a ‘clinical statement’ describing an adverse event associated with drug therapy should have the same semantic representation irrespective of whether it is intended for research or clinical purposes<sup>46</sup>.

46. Shabo Shvo A. Meaningful Use of Pharmacogenomics in Health Records: Semantics Should Be Made Explicit. *Pharmacogenom* 2010 11(1): 81–87.

### Box 6: Data from outside the clinic – patients and citizens as producers and end users of data in personalised medicine

As we move towards the era of personalised medicine, the distinction between knowledge producers and knowledge recipients is becoming less rigid. Patients are now taking advantage of new media and ICT opportunities to organise themselves not just to share experiences and support but also to exchange data on health status and outcomes. The company PatientsLikeMe, for instance, has established an electronic platform with the goal of helping patients to “share and learn from real-world, outcome-based health data”<sup>47</sup>. Patients who register with the site can share information on symptoms, quality of life, treatments, specific disease variables and other factors. These data are then integrated to generate a highly flexible output that links treatments to specific symptoms and outcomes, for instance, or disease course to lifestyle variables, etc.

In essence, PatientsLikeMe functions as a patient-led electronic health resource. However, it also serves as a resource for research. On the one hand, it provides a tool linking patients to registered clinical trials in which they might be eligible to participate. Perhaps more striking, however, has been the use of PatientsLikeMe as a platform for self-organised trials. A recent report in the journal *Nature Biotechnology* described how PatientsLikeMe had been used to analyse the effect of lithium on disease course in a group of patients with amyotrophic lateral sclerosis<sup>48</sup>. The study used algorithms to reduce the potential for bias in the analysis and found that the results were consistent with those obtained in subsequent randomised trials. Such studies not only demonstrate the potential of new ICT solutions to accelerate clinical discovery but also the power of citizen agency and solidarity, as no such ap-

47. <http://www.patientslikeme.com/>

48. Wicks P, Vaughan TE, Massagli MP, Heywood J. Accelerated Clinical Discovery Using Self-Reported Patient Data Collected Online and a Patient-Matching Algorithm. *Nature Biotechnol* 2011; 29(5): 411–414.

proach would be possible without the willingness of patients to share their data.

Interest in sharing data that can be used to promote individual and collective wellbeing is not restricted to patients, however. Groups such as Quantified Self<sup>49</sup> provide a platform for citizens to collect data about themselves, including lifestyle factors such as eating habits, exercise, etc., physiological variables such as heart rate and blood pressure, and emotional state. The power of these and similar initiatives is their capacity to generate large volumes of data on individual lifestyle, environmental and sociocultural variables, as well as self-reported outcomes, symptoms and quality of life for those with illnesses. The potential for such datasets to be used in the development and implementation of personalised medicine is clear. They might be used, for instance, to generate cost-effectiveness data, or to monitor long-term outcomes of personalised interventions. Furthermore, they could be used to contextualise complex biological data obtained from ‘omics and other technologies. The challenge now is to see how this could be achieved in practice.

Key issues will need to be addressed if platforms such as PatientsLikeMe and Quantified Self are to be integrated into the framework of personalised medicine. For instance, how can data quality and interoperability be ensured? Will efforts to achieve harmonisation of data collection procedures act as a barrier to agency if they are not citizen-led? The emphasis on citizen agency in these platforms reflects one of the core principles of personalised medicine. Consequently, if they can be successfully integrated into the wider framework of the approach, such platforms could provide far more than a powerful data resource.

49. <http://quantifiedself.com/>

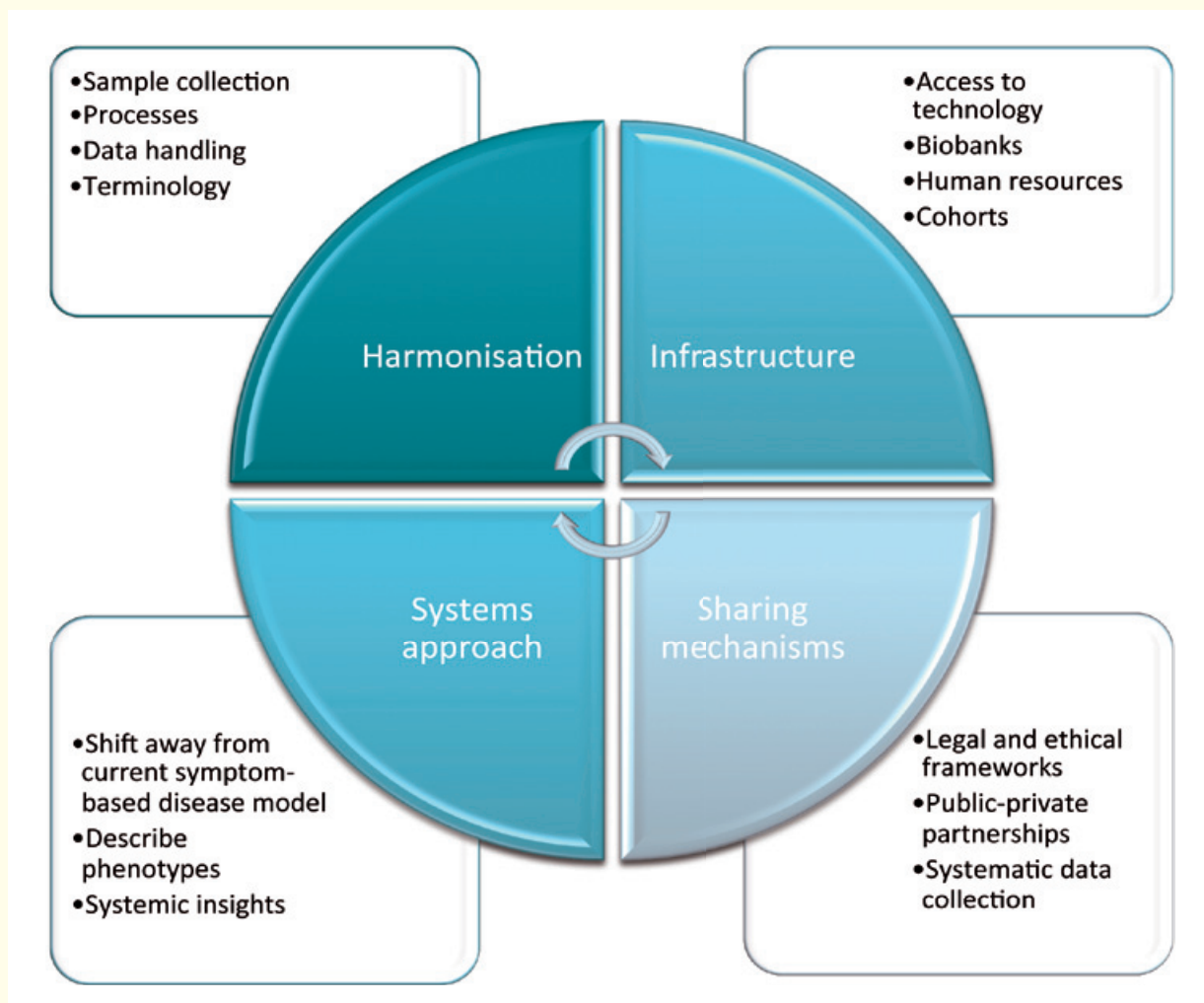


Figure 4. Key enabling factors

#### 4.5.3 Infrastructure

Research infrastructure is recognised to be a key issue at all levels. Resources must be shared to ensure the cost-effectiveness of the large-scale initiatives required to support the development of personalised medicine. Developing a Europe-wide infrastructure will also facilitate harmonisation of protocols and integration and interoperability of data from multiple population samples to refine the models. Likewise, access to physical resources such as imaging technology will need to be sufficiently widespread to allow real-time healthcare delivery and ensure that data can be obtained from varied populations. Shared infrastructure must also take into account human resources to ensure adequate cross-disciplinary education and communication.

#### 4.5.4 Sharing mechanisms

Large-scale integration of datasets poses particular challenges. The willingness of sufficient numbers of people to contribute biological material and personal data to biobanks and other healthcare-related databases will be dependent upon the establishment of

ethical frameworks to protect their privacy and control how information is used. Similarly, commercial interests are often a barrier to data sharing. Thus, involvement of the pharmaceutical and diagnostics industries in the development of personalised medicine could restrict access to important information unless a robust framework for pre-competitive public-private partnerships is established, such as that being developed by Sage Bionetworks<sup>50</sup>. Given the importance of data sharing and collaboration as key enabling factors for personalised medicine (Figure 4), consideration should be given to making compliance with an appropriately structured data-sharing agenda a requirement of funding for new initiatives.

Appropriate sharing mechanisms will also be critical to the future of electronic health records and other personal data. For these to be truly effective in personalised medicine, they will need to cross-institutional, interoperable and longitudi-

50. <http://sagebase.org/>



nal, ultimately over the patient's entire lifetime<sup>51</sup>. Preferably, this type of record should adhere to internationally recognised standards but semantic interoperability should be sought as a minimum. It should also be kept in mind that data sets relating to individuals differ in resolution, from mass and raw data such as whole-exome sequencing or sensor data streams to clinical documents such as hospital discharge summaries or continuity-of-care forms, or patient-generated data from outside the health domain (for instance, see Bhinder *et al.*<sup>52</sup> and Rockwood *et al.*<sup>53</sup>). Ideally, electronic health records should allow key items contained with the raw data to be accessible in a coherent form alongside clinical data. Such representations could be used for purposes such as multiple or repeat analysis<sup>54</sup>, as well as explanation of decisions with the aid of clinical decision-support applications (also for medico-legal reasons). However, flexible sharing mechanisms may be required to achieve such a goal.

## 4.6 Recommendations

### 4.6.1 Data collection and analysis

**Health authorities and public and private research organisations must:**

1. Define rigorous quality control mechanisms for all aspects of data handling, from collection and annotation through to storage and sharing.
2. Agree steps to guarantee the generation of reproducible data based on harmonised protocols.
3. Harmonise approaches to data handling for clinical and research purposes.
4. Ensure that health outcomes data are contextualised based on environmental, lifestyle and other relevant data.
5. Facilitate translational research by ensuring consistent representation of patient data.

### 4.6.2 New technologies and ICT solutions

**Research and development in the public and private sectors must:**

1. Identify which technologies can realistically be moved into the clinic over the next 10 years and communicate with healthcare professionals to prepare the ground for this transition.
2. Identify solutions to the technological challenge of large-scale data storage and transfer.
3. Develop ICT solutions to handle comprehensive biological datasets and convert them into a meaningful output that will inform individual healthcare decisions.
4. Develop ICT solutions to integrate and interpret datasets from multiple sources and link the findings to specific outcomes in individual citizens.
5. Develop *in silico* models to inform clinical decision-making, starting with a prototype model that includes all available 'omics technologies as a proof of principle for integration.
6. Develop non-invasive technologies and novel ICT solutions for real-time monitoring, including:
  - a) Sensors to generate and store real-time information about individual health status.
  - b) Stable biomarkers to facilitate on-going analysis of health status across the life course of individuals.
  - c) Methods to measure and quantitate the functional state of molecular systems.
  - d) Rapid processing of imaging data without loss of precision.
7. Provide ICT solutions that support healthcare professionals in providing straightforward responses to the concerns of patients about future illness, treatment options and opportunities for prevention.
8. Provide ICT interfaces for citizens that facilitate informed choices about monitoring and sharing of different types of data.

### 4.6.3 Evidence base

**Public and private research organisations must:**

1. Define appropriate study designs to test potentially relevant findings.
2. Demonstrate the clinical utility, validity and relevance of all new technologies at the earliest possible stage.
3. Demonstrate the clinical benefit of monitoring biomarkers in asymptomatic, apparently healthy individuals as well as in patients.
4. Determine the implications of making data obtained for diagnostic purposes and monitoring available for research designed to optimise personalised medicine.
5. Improve our understanding of 'healthy' phenotypes.

51. Shabo A. Health Record Banks: Integrating Clinical and Genomic Data Into Patient-Centric Longitudinal and Cross-Institutional Health Records. *Personal Med* 2007; 4(4): 453–455.

52. Bhinder S, Chowdhury N, Granton J, Krahn M, Tullis DE, Waddell TK, *et al.* Feasibility of Internet-Based Health-Related Quality of Life Data Collection in a Large Patient Cohort. *J Med Internet Research* 2010; 12(3): e35.

53. Rockwood K, Zeng A, Leibman C, Mucha L, Mitnitski A. Validation of an Informant-Reported Web-Based Data Collection to Assess Dementia Symptoms. *J Med Internet Research* 2012; 14(2): e42.

54. Shabo A. Integrating Genomics Into Clinical Practice: Standards and Regulatory Challenges. *Curr Opin Mol Therap* 2008; 10(3): 267–272.



#### 4.6.4 Resources

##### European policymakers and governments must:

1. Identify solutions to the cross-border issues affecting the use of electronic health records in an increasingly mobile European population.
2. Ensure provision of the necessary infrastructure and resources to support future integrated approaches, including biobanks and core reference datasets.
3. Ensure widespread access to clinical infrastructure such as imaging technology.
4. Introduce appropriate legal and ethical frameworks to support the sharing of data.
5. Establish the intellectual and communications infrastructure to support cross-disciplinary interaction and training for ICT and healthcare professionals.
6. Support robust frameworks for pre-competitive public-private partnerships in research and development.

## 5.

# What are the disciplinary considerations for personalised medicine?



### 5.1 The challenge of interdisciplinarity

Although the concept of personalised medicine is simple, it will ultimately involve a radical change in the way we approach the health and wellbeing of individual citizens. Furthermore, the factors that will need to be taken into consideration in order to make personalised medicine a reality will vary according to the disease specialty, practice setting and regional context considered. Although personalised medicine might conceivably result in a restructuring of the healthcare profession away from organ-based specialities, its development and initial implementation must work within existing frameworks. It is therefore important that we understand the considerations affecting different disease areas.

Disease specialities such as oncology or cardiovascular disease (CVD) can be understood as individual communities of practice. This means that each specialty might be expected to respond differently to new approaches and technological developments. Attitudes will be defined by the prevailing views within the specialty and influenced by key opinion leaders. A recent example has been the uptake of testing for thiopurine methyltransferase (TPMT) deficiency in patients who are candidates for treatment with azathioprine. Patients with a deficiency in the TPMT enzyme are known to have an increased risk of potentially fatal haematological toxicity. Comparison of the rates of testing for the deficiency among dermatologists, gastroenterologists and rheumatologists in the UK, however, reveals substantial variation among disease specialities, with much higher rates of testing reported

by dermatologists (94%) than gastroenterologists (60%) or rheumatologists (47%)<sup>55</sup>. The observation that those rates parallel the degree to which guidelines in the field advocate the use of testing<sup>46</sup> above highlights the influence of opinion leaders in shaping practice within specialisms.

Attitudes towards new developments are not only influenced by disease specialty, however. Even professionals from within the same specialty are likely to respond differently according to the health system in which they work. For instance, prior to the launch of Herceptin, a drug that targets cells overexpressing the HER-2 receptor in breast cancer, testing for HER-2 status differed markedly among different European countries. Notably, only around 6% of patients with breast cancer in the UK were being tested, whereas in other European countries the rate was closer to 40%. According to studies of the views expressed by physicians in the UK, this low rate of testing reflected a general attitude and even a scepticism regarding the approaches used in other countries<sup>56</sup>. Thus, despite widespread international communication between members of an important disease specialty such as oncology, views will also be strongly influenced by local cultures.

Another opportunity for discrepancies to arise is in the views expressed by commentators and policymakers compared with those directly involved in patient care or research. There is ample evidence

55. Fargher EA, Tricker K, Newman W, Elliott R, Roberts SA, Shaffer JL, *et al.* Current use of pharmacogenetic testing: a national survey of thiopurine methyltransferase testing prior to azathioprine prescription. *Journal of Clinical Pharmacy and Therapeutics* 2007; 32(2): 187-95.

56. Hedgecoe A. *The politics of personalised medicine: pharmacogenetics in the clinic*. New York: Cambridge University Press, 2004.

of how information can become distorted through misrepresentation of published research, inflation of claims and selective reference to research findings<sup>57</sup>. An example from personalised medicine is the hype that developed around the use of APOE4 as a predictor of treatment outcome in patients with Alzheimer's disease. While many reviews and commentaries cited this as a landmark finding that provided a proof of principle for pharmacogenetic approaches, researchers appeared to be less convinced and many believed that the finding was simply false<sup>47</sup>. The impact of this cannot be underestimated, as it has the potential to undermine the confidence of important stakeholders in the process, leaving them feeling that they are not represented by those responsible for policy and decision-making.

The challenge for personalised medicine is clearly one of how to achieve cross-disciplinary consensus that allows specific challenges to be addressed in each context, be it regional, organisational, or disciplinary, while ensuring that the foundations are laid to allow a truly personalised approach to healthcare to be established. A useful starting point in this endeavour is to explore the issue from the perspective of individual disease specialities. We have therefore looked at three disease areas expected to have quite different perspectives on the goals, challenges and prerequisites for personalised medicine, namely cancer, CVD and rare diseases.

## 5.2 How is personalised medicine understood?

### 5.2.1 Optimisation

Optimisation of the healthcare process is a core feature of personalised medicine across disease specialities. However, the nature of the optimisation will vary according to the field in question. In fields such as cancer, numerous pharmaceutical interventions have already been tested and approved for use. Their effectiveness depends on a number of factors, however, and in many cases a single drug is found to be inadequate. The role of personalised medicine will therefore be to facilitate the identification of optimal treatment combinations and to reduce the likelihood of adverse events. To achieve this, two types of information will be required. It will first be necessary to obtain a detailed description of both the biological makeup of the individual and the molecular characteristics of the disease, and often also relevant information on lifestyle and other

environmental factors. This information will then need to be linked to data on treatment response and outcome. Thus, complete genomic profiles will be combined with other 'omics data and detailed phenotypic descriptions to provide the foundation for decision-making. The complexity of this task is staggering, since the management of even simple conditions can be strongly influenced by the presence of comorbidities and other patient variables.

In disease areas such as CVD, optimisation of drug treatments will seek to increase the benefit-to-risk ratio and enhance treatment response. In this disease area, however, optimisation will not apply to pharmaceutical interventions alone. The critical role of lifestyle and diet in CVD will most likely lead to an emphasis on monitoring, education and lifestyle intervention as part of the framework for personalised medicine. Improvements in our ability to obtain reliable readouts of existing measures such as blood pressure, fasting glucose and cholesterol would themselves be predicted to have tangible benefits for cardiovascular health. Furthermore, dynamic readouts of many simple markers would provide on-going feedback as to the effectiveness of prevention and adherence to exercise and dietary regimens designed to reduce risk. Personalisation must even extend to educational interventions and outreach in an effort to optimise self-care of cardiovascular health in specific social and cultural groups.

In rare diseases, the situation is somewhat different. Not only are treatments often poorly developed or simply unavailable, many conditions remain undiagnosed and diagnosis is often based purely on descriptive symptoms and clinical examination. Optimisation is therefore required at the earliest stages in the process to increase the likelihood and accuracy of diagnosis. By optimising detection, the opportunity for early and more effective intervention is enhanced. Education of healthcare professionals is likely to play an important role in bringing this about. Awareness of rare diseases needs to be raised among the healthcare professions through educational initiatives, guidelines and diagnostic algorithms. It may also be necessary to introduce technology that allows symptom recognition to be automated. Moreover, the symptoms themselves will need to be broken down to generate the more detailed phenotypic descriptions that will support personalised medicine.

### 5.2.2 Integration

A key feature of personalised medicine across disease areas is integration. Yet integration is required at many different levels. Data from multiple indi-

57. Greenberg SA. How citation distortions create unfounded authority: analysis of a citation network. *BMJ* 2009; 339: b2680.

viduals must be integrated in order to determine the range of factors that can generate a given disease phenotype and indeed the different disease mechanisms involved. In rare diseases, for instance, the pathogenic mechanism responsible for *retinitis pigmentosa* can vary according to the underlying mutation, even when the mutation involves the same gene<sup>58</sup>. The same is true for cystic fibrosis in which many genetic variants exist that influence the functionality of the CFTR16. Comprehensive biological descriptions will be required to understand the range of phenotypes that occur within a given disease entity across the course of the disease. Similarly, biological profiles will need to be integrated with environmental, nutritional and lifestyle data obtained across the life course of individuals in order to achieve the complete descriptions necessary to support the vision of personalised medicine.

Although integration of multiple data types from multiple individuals is a defining feature of personalised medicine across disease areas, it is perhaps best exemplified by cancer. Here, virtual patients are being used to integrate 'omics data and other data types in order to rapidly identify the most appropriate interventions and provide information on possible side effects, etc. Although the technological challenges are significant, these models may even be able to predict disease course and response to treatment.

The ability to model and predict disease course is not only a consideration following diagnosis. In chronic progressive diseases such as CVD, early detection of physiological changes that, if uncorrected, will result in morbidity later in life is critically important. Dynamic integration of physiological data over an individual's lifetime is thus of equal importance to the integration of static 'omics data in order to predict susceptibility and identify appropriate treatment options.

Integration of static biological data with dynamic physiological data and information on environmental exposure and lifestyle requires that data on a given citizen are accessible from any geographical location. In an increasingly mobile population, personalised medicine will necessitate systems such as electronic health records to ensure that comprehensive data are always available and can be continually updated. This will require a different type of integration in which Europe-wide integrated networks allow on-going collection, storage and cross-referencing of individual information with local environmental data. This type

of integration demands standardised and interoperable platforms in which data can be assumed to have been collected and annotated using similar protocols. Thus, harmonisation of protocols among European member states with appropriate agreements to allow routine sharing will be an additional enabling factor for personalised medicine.

### Box 7: Patients entering the virtual world

Once the foundations of personalised medicine have been laid through the reclassification of disease, the identification of targeted therapies and prevention strategies, etc., we will still be faced with the challenge of making the right healthcare decisions in each individual citizen. Whereas traditional approaches to medicine have attempted to reduce complexity through statistical analysis of shared characteristics in large unstratified populations, personalised medicine attempts to embrace it by considering all of the potentially influencing factors in a given individual. Such an approach presents a major computational challenge if we seek to identify the best course of action to promote health and wellbeing in a given individual.

One solution to the challenge of computing all of the relevant data on a given individual is to use an *in silico* model. This is the approach taken by groups such as the European IT Future of Medicine (ITFoM) project<sup>13</sup> and the US company Entelos<sup>59</sup>. In both cases, reference datasets are used to generate models against which so-called virtual patients can be compared. In the case of Entelos, modelling is used as an approach to non-invasive research, such that virtual patients can be used to predict outcomes and accelerate the drug discovery and development process. The ITFoM project, on the other hand, is focused on the use of *in silico* modelling to generate what is effectively a virtual twin for real individuals to be used in personalised healthcare decisions. Thus, the data from each individual will be overlaid onto a reference model to allow simulations to be carried out in the individual's virtual twin in order to predict disease course, response to treatment and even the effectiveness of preventive measures.

Some of the data used to populate virtual patients will be coded and structured in order to make it easily accessible for *in silico* modelling. However, an enormous amount of useful data is actually generated in natural language. Unfortunately, traditional computing systems have struggled to process this sort of data effectively. Recent advances, such as IBM's Watson computer<sup>32</sup> may begin to solve the problem. Watson is designed specifically to deal with unstructured, textual data. Through complex semantic analysis of that information, it is able to generate meaningful answers to questions posed in natural human language. IBM predicts that Watson

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58. Jacobson SG, Cideciyan AV. Treatment possibilities for retinitis pigmentosa. *N Engl J Med* 2010; 363(17): 1669-71.

59. <http://www.entelos.com/>



will be used to allow doctors to identify the most appropriate treatments and the predicted outcomes for a given patient in real time and is already piloting its use with a large health insurance provider in the United States of America as a tool to optimise therapeutic decision-making and approval.

The volume of potentially useful information that can have an effect on an individual's health and wellbeing is expanding at an unprecedented rate. If we take into account the value of patient-reported data in personalised medicine (see Box 6), the importance of computing solutions such as Watson that can deal with natural language are clear. If these data can be incorporated into or linked with additional biological and environmental data, the potential for using ICT to support personalised medicine appears almost unlimited.

### 5.2.3 Prediction and prognosis

Personalised medicine entails a lifelong approach to healthcare. An important aspect of this approach is the ability to predict the likelihood of disease, the natural history of identified subtypes, the outcome of treatment and the effectiveness of prevention. In rare diseases, it is hoped that personalised medicine will provide a framework for assessing not only risk *per se* but more broadly hazard. In CVD, prediction is likely to be an ongoing process that goes hand in hand with physiological monitoring. In cancer, as in other disease areas, prediction of risk will involve a combination of genetic risk factors, prognostic indicators (such as age and socioeconomic factors), biomarkers and environmental exposures (including nutrition and lifestyle). Recent advances in molecular technologies have enabled rapid progress in the identification of minimally invasive, blood-based screening of biomarkers for early detection of cancer<sup>60</sup>. These can function as aids to clinical diagnosis and prognostic biomarkers to monitor treatment response and stratify patients to receive the most appropriate pharmacotherapy or drug combination. As this sort of predictive information becomes available for different treatments, disease entities and biological contexts, it will be integrated into models such as virtual patients to guide decision-making. In this way, it will be possible not only to tailor therapy but also to take a proactive, pre-emptive approach as seen increasingly in cancer with the use of primary and secondary chemoprevention<sup>61</sup>. Such advances will profoundly enhance the power of personalised medicine as a lifelong approach to healthcare.

60. <http://edrn.nci.nih.gov/about-edrn>

61. Keith RL. Lung Cancer Chemoprevention. *Proceedings of the American Thoracic Society* 2012; 9(2): 52–56.

## 5.3 What are the challenges facing existing disease areas?

### 5.3.1 Biomarkers

Biomarkers are essential to the future of personalised medicine. Their use for statistical prediction of risk and outcome is central to the development of the *in silico* models that will inform the decision-making process. Not surprisingly, the greatest advances in the use of biomarkers to date have occurred in oncology<sup>62</sup>. Nevertheless, there is a need to distinguish between the utility of these biomarkers for research and for treatment. Many biomarkers are currently ignored by clinicians, in part due to their limited utility, and there is therefore a pressing need for biomarkers with improved sensitivity and specificity. In the case of genetic information, it is conceivable that the whole genome will ultimately function as a set of biomarkers with sequencing of individual tumour genomes being used to inform treatment decisions based on *in silico* models. There is some way to go, however, before this becomes a reality.

In contrast to the situation in cancer, very few biomarkers are available for the description of rare disease phenotypes. There are only around 1,000 to 2,000 biomarkers currently identified for around 7,000 to 8,000 known rare diseases<sup>63</sup>. There is a significant need, therefore, for more biomarkers in order to understand the pathogenesis and networks underlying these diseases. The challenge for personalised medicine in this disease area will be to develop an integrated network of information on biomarkers linked to specific phenotypes<sup>54</sup>.

The degree of noise in biological systems can present a serious challenge for the identification of reliable biomarkers. Models must distinguish between informative biological differences and simple biological variation. This may be less of an issue when looking at rare inherited diseases, since they exhibit relatively low biological noise compared to more common complex disorders such as atherosclerosis and autoimmune disease. Rare diseases are also much more genetically stable than conditions such as cancer, where individual tumours can display a high degree of genetic instability. The networking principles that can be developed in the relatively stable and 'noise-free' conditions offered by rare diseases could thus be used to inform approaches

62. Kelloff GJ, Sigman CC. Cancer Biomarkers: Selecting the Right Drug for the Right Patient. *Nat Rev Drug Discov* 2012; 11(3): 201–214.

63. Taruscio D, Salvatore M, Magrelli A, Tomanin R. Predictive Medicine and Biomarkers: the Case of Rare Diseases. *Person Med* 2012; 9(2): 143–146.



for other diseases<sup>64</sup>. A challenge for rare diseases, on the other hand, is the difficulty of defining reference genomes. This highlights a likely challenge for personalised medicine in general. As we increase our understanding of the range of phenotypes encompassed by current disease classifications, we will increasingly be faced with the challenge of clearly distinguishing between health and disease.

In CVD, traditional indicators of disease risk remain the primary source of prognostic information. Many of these classical biomarkers will continue to be relevant in personalised medicine but a greater understanding of their biological basis is needed. Importantly, prognostic factors such as gender and age may be surrogate markers of underlying biological differences. An important challenge will therefore be to identify the true underlying biomarkers of disease susceptibility and to validate the utility of existing prognostic markers. In CVD, there is an urgent need for dynamic biomarkers that can be used to predict events before they occur. Likewise, more biomarkers are required to guide presymptomatic intervention.

Although relatively few imaging biomarkers have been developed to date, they are likely to play an important role in many disease areas. In cancer, for instance, markers are needed for use with technology such as positron emission tomography to allow spatial resolution of cellular events. Such approaches will also be central to the development of non-invasive data collection, which is desirable in all situations and absolutely essential for some. In rare diseases affecting the brain, for instance, routine biopsy is clearly not a valid option, yet nanotechnologies and imaging may make it possible to obtain this information non-invasively. Again, this is a goal for the future of personalised medicine rather than part of its current reality.

### 5.3.2 Complexity

The complexity of the information used to guide treatment and follow-up presents a serious communication issue, particularly in fields such as cancer. Healthcare professionals who are directly responsible for patient care will need to choose which information is communicated to the patient and when. Should patients be informed, for instance, about all of the variables that will be considered in order to identify an appropriate treatment? Should they be made aware of the decision-making process itself or perhaps only have the final choice

explained to them? The appropriate level of information may differ for each individual and, as such, communication may itself need to be personalised. An additional question, therefore, is the degree of autonomy patients might be able to have within personalised care. Is it conceivable, for instance, that some patients will take decisions about their own care based on output from modelling algorithms without the involvement of the physician as an intermediary? The role of healthcare professionals may become increasingly that of translators of complex information to support patient understanding and autonomy. As a result, the relationships between healthcare professionals and patients may ultimately become closer and richer. Such developments could clearly benefit from the support of appropriate low-threshold technological interfaces, psychological support as well as legal and ethical expertise.

### 5.3.3 Technology interface

A key concern in both cancer and CVD is the user interface. In cancer, consideration should be given to how healthcare professionals interact with the technology, using the analogy of a pilot in a hi-tech jet aircraft to explore this question. The technology interface can be used to hide a degree of complexity from professionals responsible for patient care. In this way, it may be possible to streamline patient-care interactions and ensure that neither healthcare professional nor patient is overloaded with unnecessary information. At the same time, the technology interface can be designed to provide additional layers of information to support explanation of diagnoses, treatment decisions and expected outcomes.

In CVD, the design of end-user interfaces will play an important role in determining the effectiveness of self-monitoring. Smartphone applications could be used to provide dynamic readouts of variables such as blood pressure and glucose, as well as to collect additional data on factors that could influence individual health such as lifestyle and diet. Similar technology could be used to inform citizens about dietary choices when shopping, record physical activity, etc. It will be important to remember, however, that self-monitoring is highly dependent upon a person's understanding of the utility of the process and its ease of use, and its uptake is inversely related to its level of invasiveness in people's lives. The effectiveness of simple glucose monitoring, for instance, can vary substantially among patients<sup>65</sup>.

64. Draghia-Akli R. Enabling Personalized Medicine in Europe: a Look at the European Commission's Funding Activities in the Field of Personalized Medicine Research. *Personal Med* 9, 2012; (2): 151–155

65. Fisher L, Polonsky WH, Parkin CG, Jelsovsky Z, Petersen B, Wagner RS. The Impact of Structured Blood Glucose Testing on Attitudes Toward Self-Management Among Poorly Controlled, Insulin-Naïve Patients with Type 2 Diabetes. *Diabetes Research and Clinical Practice* 2012; 96(2): 149–155.

Consequently, technologies such as smartphone monitoring applications will need to be adapted to the patient, as indeed will the use of direct self-monitoring versus physician monitoring on behalf of the patient. In addition, consideration may need to be given to the role of persuasive technologies in personalised medicine<sup>66,67</sup>.

The possibility of using smartphone applications to allow citizens to monitor their own physiology and health status and generate relevant (often long-term) datasets raises important questions about the future role of the physician in the era of personalised medicine. Will it be necessary for physicians to function as gatekeepers for treatment? If sufficiently developed models could provide a direct readout and even indicate the most appropriate treatment, will all citizens need or want a physician to act as an intermediary? On the other hand, many citizens are likely to be dissatisfied with their healthcare being dependent entirely on a technological interface such as a smartphone. The impact of direct human interaction on general wellbeing should also be taken into consideration as part of the personalisation of medicine. It seems unlikely that technological interfaces will replace healthcare professionals in the short term. Nevertheless, in areas such as chronic diseases, many patients may become increasingly able to manage their own pathology and therefore reduce their reliance on healthcare services. Such developments would be predicted to increase patient autonomy and reduce the burden on healthcare resources.

## 5.4 Recommendations

### The healthcare profession must:

1. Initiate large-scale consultation programmes to assess opinion and identify needs among existing disease specialities and across regions and cultures within the same specialty.
2. Identify experiences in existing specialities that could inform practice in personalised medicine as a whole.
3. Define the vision of an integrated, lifelong approach to healthcare in established disease areas in order to inform how personalised medicine will be implemented in the future.
4. Work towards cross-disciplinary consensus on the future of personalised medicine.
5. Work with citizens and patients to define what they need from their relationship with healthcare professionals within the framework of personalised medicine.
6. Work with ICT professionals to design low-threshold technological interfaces that support the interaction between patients and healthcare professionals in personalised medicine.
7. Work with ICT professionals to define how technology such as smartphone applications can be used to monitor health-related and environmental variables and function as a decision-support tool for citizens.
8. Actively inform policymakers and the media of unsubstantiated claims or misrepresentation and support the provision of accurate information in personalised medicine.
9. Promote and participate in the development of Europe-wide integrated networks to facilitate ongoing collection, storage and cross-referencing of individual information with local environmental data.
9. Support efforts to develop an integrated network of biomarkers, including increased availability of imaging biomarkers, linked to information on specific phenotypes.
10. Promote the refinement and integration of existing technologies and biomarkers into the framework of personalised medicine.

66. Lee D, Helal S, Anton S, De Deugd S, Smith A. Participatory and Persuasive Telehealth. *Gerontology*, 2012; 58(3): 269–281.

67. Kennedy CM, Powell J, Payne TH, Ainsworth J, Boyd A, Buchan I. Active Assistance Technology for Health-Related Behavior Change: an Interdisciplinary Review. *J Med Internet Research* 2012; 4(3): e80.

## 6.

# What are the key issues affecting the development and implementation of personalised medicine?



### 6.1 Education

Personalised medicine will have different implications for the various stakeholders in its development and implementation. Health professionals will be called upon to make decisions based on complex biological, environmental and lifestyle information; bioscientists and technologists will need to interact with and understand the needs of the professionals responsible for patient care; citizens will have access to unparalleled opportunities to take responsibility for their own health through active monitoring, prevention measures and even direct treatment choice. In each case, stakeholders will need to be equipped with the requisite skills to participate fully in the future of personalised medicine<sup>68</sup>.

With the introduction of ‘omics data as a common component of patients’ health records, health professionals will need a clear understanding of the principles underlying their interpretation. Technological innovations in the form of decision-support systems can be expected to help physicians in this regard, and it would not be the case that those responsible for patient care would be called upon to interpret data output directly from ‘omics technologies. They will need to be able to critically review the information provided to them, however, and that will require a solid grounding in biological methodology. Statistical interpretation of risk will be a key element, since health professionals will

commonly be called upon to explain risk profiles to patients in a manner that fosters clear understanding and can be acted upon appropriately.

The importance of education in modern biosciences is also reflected in the role of health professionals as participants in the development of personalised medicine. While bioscientists can provide the necessary tools to support personalised medicine, it is the health professionals who must inform them of what is required in the clinic. Consequently, health professionals must be able to communicate with bioscientists and technologists about the tools they need. This principle applies to both groups. Thus, bioscientists and technologists must be sufficiently versed in the principles of medicine to be able to communicate effectively with health professionals.

Currently, the disciplines that inform personalised medicine remain largely separate. Consequently, educational efforts to promote shared understanding and collaborative development of the tools for personalised medicine are essential. The long-term future of personalised medicine, however, is likely to be found in the training of interdisciplinary professionals. Within the biosciences, the challenge is already to produce trained professionals who are adequately versed in biology, mathematics and physics to develop the bioinformatics, imaging and ‘omics tools required to support personalised medicine. Within the healthcare profession, however, the possibility of a shift towards new ways of classifying disease based on systems biology and integration of data from multiple sources, including

68. Carlberg C. The Need for Education in Personalized Medicine. *Person Med* 2012; 9(2): 147–150.

lifestyle information and environmental exposures, will necessitate the training of health professionals with a truly interdisciplinary education. Given the time it takes to train a physician, for instance, let alone that required to plan and establish an in-depth training programme, interdisciplinarity must be considered a long-term goal to run in parallel with short-term multidisciplinary interaction. It is clear, however, that education and training must be made an immediate priority area. If we do not initiate the process now, we will not have the human resources to support the vision of personalised medicine further down the line.

Personalised medicine carries enormous potential not just to offer the most appropriate healthcare options to individual citizens but also to place them at the centre of the process. Efforts to promote and support stakeholder participation (see section 6.2) are dependent upon the ability of those stakeholders to use the resources available to them. In the case of individual European citizens, a key element in supporting participation will be through promotion of health literacy<sup>69</sup>. According to a recent systematic review, “Health literacy is linked to literacy and entails people’s knowledge, motivation and competences to access, understand, appraise and apply health information in order to make judgments and take decisions in everyday life concerning healthcare, disease prevention and health promotion to maintain or improve quality of life during the life course”<sup>70</sup>. Although promoting health literacy goes far beyond health education, it is clear that education will be a critically important element, particularly in ensuring that citizens are able to understand and react to developments such as risk prediction and physiological monitoring. Influencing fields such as genomics in personalised medicine have implications that extend far beyond the clinic. In order for citizens to be active participants in the decision-making process over issues such as privacy of genomic and other personal data, responsibility must be taken to promote an adequate level of health literacy to support participation.

Finally, health literacy and education will also be important issues for policymakers and other stakeholders, such as regulators, health managers, and HTA and health impact assessment (HIA) professionals, who will play crucial roles in imple-

menting personalised medicine<sup>71</sup>. Those whose role it is to support public engagement, establish ethical frameworks, establish public policy, etc. will all need to learn about the relevant issues affecting the field. In practice, this will be a core element of a participatory model of personalised medicine, in which ideas and knowledge from multiple sources lead to cross-fertilisation and strengthening of the framework that supports the future of the approach. Furthermore, those driving the technological and clinical developments that will support personalised medicine will need to engage experts in HTA, HIA, health economics and legal issues to ensure the development of robust frameworks for the future.

### 6.1.1 Recommendations

**European policymakers and educational institutions must:**

1. Provide incentives for the interdisciplinary education of healthcare professionals and scientists from the earliest stages of professional development.
2. Provide training for healthcare professionals, bioscientists, ICT professionals and those with expertise in regulatory and social domains to facilitate collaborative development of the tools for personalised medicine.
3. Ensure adequate training of the professionals and citizens who will use the relevant ICT solutions as they are developed.
4. Establish mechanisms to promote health literacy among European citizens as an impetus to participation.

### 6.2 Stakeholder participation

One of the lifelong skills associated with health literacy is the ability to find and assess health-related information<sup>72</sup>. It is only through access to reliable information that individual citizens can equip themselves with the skills to take greater control of their own health and to participate actively in a system of personalised medicine that benefits both individuals and society as a whole. Thus, access to information is a key factor in efforts to position the patient or citizen at the centre of the healthcare process in

69. Testori Coggi P. A European view on the future of personalised medicine in the EU. *Eur J Public Health* 2011; 21(1): 6-7

70. Sorensen K, Van den Broucke S, Fullam J, Doyle G, Pelikan J, Slonska Z, et al. Health literacy and public health: A systematic review and integration of definitions and models. *BMC Public Health* 2012; 12: 80.

71. Rosenkötter N, Vondeling H, Blancquaert I, Mekel OC, Kristensen FB, Brand A. The contribution of health technology assessment, health needs assessment, and health impact assessment to the assessment and translation of technologies in the field of public health genomics. *Public Health Genomics* 2011; 14(1): 43-52

72. Sorensen K, Brand H. Health literacy: the essential catalyst for the responsible and effective translation of genome-based information for the benefit of population health. *Public Health Genomics* 2011; 14(4-5): 195-200.



personalised medicine. Participation is not only about placing citizens at the centre, however; it is also a practical consideration for personalised medicine. Personalised medicine is a highly data-driven approach and the development of algorithms to support treatment choice, prognostic evaluation and monitoring, for instance, will depend on the opportunity to access information from large numbers of citizens spanning regional, cultural and socioeconomic divisions. Many citizens are already using a wide variety of technological tools (e.g. smartphone applications) to generate and analyse health-related information, some of which could be fruitfully used for research and clinical decision-making. This will require public trust, and thus a core aspect of this endeavour will be a commitment to transparency, accountability and often also solidarity<sup>73</sup>. Only in this way will trust be gained regarding the benefits and safeguards of data provision and sharing. A key consideration will therefore be active support for open public dialogue about the value of personalised medicine and how issues of confidentiality and control of personal data can be dealt with appropriately.

The manner in which citizens access information in personalised medicine is likely to vary. For some, health literacy will need to be supported by education and targeted provision of information, whereas for others, the issue will instead be one of removing barriers and helping to uphold standards of quality and ethical provision of information. One important step towards society-wide participation will be to ensure that information is communicated in an accessible and appropriate manner for each stakeholder group. This principle is applicable at all levels of participation. In addition, to promote participation and agency as a core principle of personalised medicine, communication should endeavour to foster cooperation rather than hierarchical relationships.

Stakeholder participation is equally applicable in the relationship between bioscientists, technologists and healthcare professionals<sup>74</sup>. Primary care physicians and doctors from other clinical specialities, for instance, will need complex data to be presented in a way that facilitates rapid and shared decision-making. To develop appropriate interfaces, technologists will need to engage the participation of healthcare professionals and listen to their needs rather than attempt to educate them on what they *should* be doing. Likewise, the development of technological

solutions for citizens and patients, for instance to support monitoring or decision-making to promote personal health, will require close collaboration between technologists, healthcare professionals, communications specialists and citizens in order to be effective. If appropriate solutions can be developed in this way, it is likely that the role of the state will shift from taking responsibility for individual health towards empowerment of citizens and their communities to take responsibility for their own health. However, this will require a genuine devolution of power and agency to the citizen. Token measures used ostensibly to empower citizens will not be effective if the central aim is merely to encourage them to give up data and intellectual property rights in order that they can be used and exploited by others. It should also be remembered, however, that participation will inevitably be variable and some groups will need to delegate responsibility for their care back to the healthcare profession.

Implementation of personalised medicine, including strategies to facilitate the participation of key stakeholders such as healthcare professionals and citizens will require the support of other stakeholders, namely those able to fund these initiatives. Mobilising support will first require an awareness of the key players in the process. More information is therefore required to identify who the key players are and what their attitudes are towards personalised medicine. As in other areas of personalised medicine, it would be wise to engage the support of health economists as early as possible to evaluate the overall return on investment in personalised medicine. Given the requirement to establish infrastructure and long-term development programmes, it will be essential to establish sustainable economic models.

### 6.2.1 Recommendations

#### **Policymakers, health authorities and other public bodies must:**

1. Establish mechanisms across all relevant domains to support citizen- and community-led promotion of health and wellbeing.
2. Promote and support resources that enable citizens, individually and cooperatively, to access, understand, interpret and make use of reliable information that supports personalised healthcare.
3. Define metrics to measure stakeholder participation, particularly among citizens and their communities.
4. Facilitate public dialogue on the value of personalised medicine and the necessary conditions for its success.

73. Prainsack B, Buyx A. *Solidarity: Reflections on an emerging concept in Bioethics*. London: Nuffield Council on Bioethics, 2011.

74. Lal JA, Schulte in den Bäumen T, Morre SA, Brand A. Public health and valorization of genome-based technologies: a new model. *J Transl Med* 2011; 9(207)



## 6.3 Multidisciplinarity and beyond

The long-term vision for personalised medicine could conceivably encompass a complete reorganisation of the healthcare system. The medical profession, for instance, could move away from organ-related specialities and towards system-based approaches. Patient care could involve specialists in personalised healthcare interacting with multidisciplinary teams and decision-support interfaces. In these and other areas we could be looking at an interdisciplinary future involving professionals trained in wide-ranging areas that breach the boundaries of current disciplines. Whether or not such a transition occurs, the first steps must involve multidisciplinary collaboration, which will need to extend beyond medical specialities and the social sciences to include wider disciplines from genomics to social psychology and communication.

Multidisciplinarity can be seen as an organisational challenge. In order for professionals from different disciplines to be able to interact effectively, they must have an appropriate communication mechanism. In many cases, this involves shared physical space in which opportunities for impromptu interactions are maximised and resources shared. Thus, to achieve multidisciplinarity as a first step towards an interdisciplinary future, investment in appropriate infrastructure may be needed. In parallel, efforts will be needed to support a career structure for multidisciplinary and future interdisciplinary professionals. Resource allocation will therefore need to be planned to ensure sustainability if young professionals are to be attracted to a career in personalised medicine. If they feel that investment is likely to be a short-lived, many will choose not to take that path.

### 6.3.1 Recommendations

**All stakeholders in the future of personalised medicine must:**

1. Participate in the generation of multi- and interdisciplinary frameworks, tools and models to link the needs of different stakeholders in achieving common goals within personalised medicine.

**Policy makers and governments must:**

1. Provide the necessary infrastructure to facilitate multidisciplinary interaction in the transition towards interdisciplinarity.
2. Support the development of career structures in personalised medicine.

## 6.4 Infrastructure

The requirement for appropriate infrastructure goes beyond support for multidisciplinary research institutes and training programmes. The data-rich approaches that are likely to define personalised medicine in the future will require sufficient technological infrastructure to support the collection, storage and annotation of data, access to reference information, etc. An appropriate organisational infrastructure will also be required to control harmonisation of data quality and maintenance, etc. Finally, access to technologies such as imaging will need to be supported by a European infrastructure to prevent the generation of inequalities.

One particularly important area for the future of personalised medicine is the use of electronic health records. Given the low uptake of electronic health records across Europe so far, there is currently a massive gap between potential and realisation. Patient records and information held in hospitals and other institutions represent a huge resource that is unexploited at the moment largely due to a lack of organisational, ethical and logistic solutions<sup>75</sup>. Opening up this resource is likely to be a key facilitating factor for the future of personalised medicine. Efforts should be made to learn from experiences such as those of Finland, Sweden, Scotland and the Basque Country in order to define mechanisms to release the enormous potential of electronic health records to support the implementation of personalised medicine throughout Europe<sup>76</sup>.

### 6.4.1 Recommendations

**Governments and policymakers must:**

1. Develop a two-stage plan for the establishment of personalised healthcare:
  - a) A participatory stage designed to establish the system and provide proof of principle.
  - b) An implementation stage in which the system begins to be applied in European healthcare.
2. Ensure the availability of core infrastructure to support data collection and management over the life course.

75. Mair FS, May C, O'Donnell C, Finch T, Sullivan F, Murray E. Factors That Promote or Inhibit the Implementation of E-Health Systems: an Explanatory Systematic Review. *Bulletin of the World Health Organization* 2012; 90 (5): 357–364.

76. Karl A Stroetmann *et al.* European Countries on Their Journey Towards National eHealth Infrastructures. eHealth Strategies Report (n.d.), [http://www.ehealth-strategies.eu/report/eHealth\\_Strategies\\_Final\\_Report\\_Web.pdf](http://www.ehealth-strategies.eu/report/eHealth_Strategies_Final_Report_Web.pdf).

## 6.5 Revised classification of disease

Classification of diseases is central to all aspects of healthcare by serving as a reference point not only for diagnosis but also for research into the aetiology and treatment of different conditions, regulation of therapies, and reimbursement. With stratified and, ultimately, personalised medicine, however, we are facing a progressive subdivision of existing disease entities and perhaps a complete reclassification of diseases according to the molecular pathways and biological systems involved. Current disease classification is largely organ rather than pathway based<sup>77</sup>. For instance, the category ‘breast cancer’ informs us as to the site of the lesion but not its aetiology. In other disease areas, evidence is appearing to support similar underlying processes, such as chronic inflammation, being expressed in different organs, such as the gut or respiratory system<sup>22</sup>. Consequently, as we begin to develop greater insights into the pathways underlying disease, there is likely to be both convergence and separation of disease classifications.

But what is the advantage of reclassifying diseases? First and foremost, obtaining greater insights into the molecular pathways underlying different disease states will facilitate both targeted therapy and improved monitoring, not only of treatment response but also of individual health status as an aid to prevention and proactive management. The goal would be to generate ongoing descriptions of an individual’s phenotype, including all the molecular, morphological, physiological and psychological information that characterises a person in health and disease, and to be able to assess it in relation to environmental exposures, history and psychosocial context in order to identify appropriate preventive or therapeutic measures to promote continued health. Such an approach has a number of core implications.

Any effort to develop a systems-based disease classification based on underlying causative molecular pathways will be critically dependent upon the availability of reference data. This raises the questions of who collects the data, how and where are they stored, who has access to them and how they should be analysed. Such an enormous potential resource containing integrated, cross-referenced data from multiple individuals will be of value to the healthcare system, research and industry alike, as well as to citizens as end users and providers of the information. Its use must therefore be contained within an appropriate regulatory and governance framework that supports a *circle of trust* for the different stakeholders. Changed disease classifica-

tions may also affect social illness identities, which are presently central to most patient organisations. Changes in their identity and organisation may therefore affect the participation of patients as stakeholders in personalised medicine and care will be needed to address the potential for negative impact on those groups.

Regulatory and governance frameworks will not only need to be created to support information repositories. They will also need to adapt to any changes in disease classification that arise from their use. Marketing approval for medicinal products is controlled by indication. Consequently, regulators and technology producers must accept proposed changes to the classification of those indications before they can be used as a basis for treatment or indeed diagnostic purposes. Similar considerations will apply to HTA and reimbursement procedures. Inevitably, reimbursement procedures require coded classifications. The risk, however, is that classifications are not unified and that multiple classifications are introduced for the same condition. Consequently, upcoming opportunities such as the ICD11 revision scheduled for 2015<sup>77</sup> might be used to support future frameworks for the reclassification of diseases in personalised medicine.

### 6.5.1 Recommendations

**Researchers, health authorities and policymakers must:**

1. Define the relationship between phenotypes, patient information and reference data using large-scale networked approaches.
2. Develop systematic algorithms to map disease pathways onto existing disease classifications.
3. Introduce a networked approach to support agreed disease definitions throughout Europe.
4. Take advantage of upcoming opportunities such as the ICD11 revision scheduled for 2015 to promote the introduction of a new disease taxonomy.
5. Ensure that the naming of disease pathways within the new taxonomy allows for continual updating of definitions to support a stable framework for reliable and safe diagnosis.

## 6.6 Revised testing models

Up until now, the gold standard for testing of therapeutic interventions has been the randomised controlled trial. In personalised medicine, however, this methodology may not always be either neces-

<sup>77</sup> <http://www.who.int/classifications/icd/revision/en/index.html>

sary or suitable<sup>78</sup>. Examples are now available in which highly active drugs can be tested directly in small groups of patients selected on the basis of specific biomarkers<sup>21</sup>. Under these conditions, the use of placebo or standard-of-care comparator arms in standard trial designs can be argued to be unethical. Although most of the examples in which specific biomarkers can be used to predict treatment response to a selective drug currently come from cancer<sup>21</sup>, the move towards personalised medicine is expected to result in a large-scale increase in the number of reliable biomarkers available for many different diseases. Consequently, the way we conceive clinical trials may have to change.

One of the implications of a revision of our approach to clinical trials will be the need to define outcomes and develop appropriate statistical frameworks with which to assess them. Indeed, a shift in emphasis may also be required to include the use of modelling as a valid testing method, as is already occurring in health economics. Insights from the development of orphan drugs could be useful for devising more appropriate testing models in personalised medicine. Virtual testing models could also be an important development for N=1 testing in individual patients based on *in silico* modelling. It may also be necessary to move beyond outcome measures based on symptom reduction and survival and include wider questions of quality of life, productivity, etc. Proof of principle to demonstrate that these new approaches really can deliver on their promises will be absolutely critical at all levels.

### 6.6.1 Recommendations

#### Researchers must:

1. Develop appropriate methods to link diagnostic tools to therapeutic and preventive measures across the discovery and development pathway.
2. Rigorously test the performance (precision, reproducibility, specificity) of diagnostics in specific disease pathways.
3. Address the need for novel approaches to obtaining evidence in personalised medicine. This must include the following:
  - a) Clinical trial designs adapted to the data-collection methods and interventions used in personalised medicine, e.g. N=1 trials, adaptive designs and Latin square methodology.
  - b) New statistical approaches to analyse the results of trials assessing personalised medicine.

- c) Consideration of the influence of factors such as age, gender, ethnicity and environmental context on therapeutic response.

4. Develop new, more efficient models to investigate possible prevention strategies.

## 6.7 Regulatory frameworks

Personalised medicine is beginning to place new demands upon the regulatory frameworks that control the licensing of medicinal products. Two particular driving forces for change are the potential reclassification of diseases and the application of new testing models. The linking of drug licensing to specific diagnoses must be adaptable to changes in disease classifications, identification of new diagnostic categories, particularly those based around molecular pathways rather than organs and symptoms, and indeed to healthcare approaches that are not centred on specific diagnoses. Furthermore, personalised medicine may lead to a reduced focus on drug therapies and a move towards nutraceuticals, gene therapy and regenerative therapies that will all need to be supported by an appropriate regulatory framework. In all cases, changing approaches to testing, moving away from large randomised controlled trials, will necessitate agreement on appropriate levels of evidence. Any such agreements will also need to work alongside HTA, as a guarantee of well-informed, transparent and accountable decision-making and reimbursement procedures.

Regulation is not only about licensing of drugs. There will need to be oversight of quality at all levels for the successful implementation of personalised medicine. Patients and citizens will need to have confidence in the quality of testing, for instance, and also in the quality of the information they receive. If there is a move away from healthcare information being handled almost exclusively through physicians and the medical profession, there will need to be guarantees over the reliability and appropriateness of the information provided to citizens, as well as over the lack of conflicts of interest or commercial misuse of the information provided. Care must nevertheless be taken to ensure that regulation does not stifle innovation where this leads to clear improvement in the health and wellbeing of citizens. Changes in the European regulatory framework to support the development of personalised medicine will need to take into account cross-border issues, as the lack of harmonisation makes European approval difficult. However, it should not be forgotten that regional differences within Europe can themselves provide the flexibility to support innovation.

78. Mandrekar SJ, Sargent DJ. Clinical trial designs for predictive biomarker validation: theoretical considerations and practical challenges. *J Clin Oncol* 2009; 27(24): 4027-34.



### 6.7.1 Recommendations

#### Regulators must:

1. Adapt regulatory frameworks to changes in disease taxonomy and the introduction of new diagnostic categories.
2. Develop appropriate regulatory frameworks for non-pharmaceutical therapies and prevention strategies.
3. Establish levels of evidence applicable to new testing methods.
4. Work closely with HTA professionals to ensure well-informed, transparent and accountable decision-making and reimbursement procedures.
5. Establish appropriate regulatory frameworks for the use of networked databases for diagnostic purposes.
6. Take steps to avoid stifling innovation while providing appropriate guarantees of the quality and safety of health-related products and information, particularly when these are accessed directly by European citizens.

## 6.8 Reimbursement models

Reimbursement of personalised medicine is a complex issue. Although many predict a reduction in healthcare expenditure through rational use of targeted therapies, the potential cost of introducing large-scale data collection such as comprehensive ‘omics profiles, biomarkers and imaging data alongside contextual information on environmental exposures, etc., is enormous. In fields such as oncology, for instance, the fastest rising costs may be associated with imaging rather than drug treatments. Furthermore, the reduced numbers of patients who can be treated by a given targeted drug would be expected to increase its cost at the same time as offering greater or even complete guarantees of efficacy. The question, therefore, is how we determine the cost-to-benefit ratio for personalised medicine as a whole and what changes will need to be made to reimbursement models. Perhaps more importantly, how do we factor in very long-term costs and savings for a system intended to be pre-emptive rather than simply reactive? Given these and other questions facing personalised medicine, the need for close collaboration with health economics and HTA specialists is clear.

An urgent question for personalised medicine is whether reimbursement models can be developed to support long-term prevention and early treatment strategies. For instance, will it be possible to take into consideration not only long-term reductions in hospitalisation or late-stage cancer therapy, for instance,

but also indirect costs such as pensions, productivity, etc.? This may require some reassessment of what constitutes benefit, such as ‘non-events’ for preventive measures. In seeking long-term benefit from short-term investment, reimbursement models may also need to overcome substantial political barriers. The complexity of the problem is compounded in Europe by the regional and cultural differences that influence HTA procedures. Although HTA already takes into account many factors beyond systematic reviews and economic analysis, access to data across regional boundaries could hinder adequate analysis on a European scale. Data ownership, cross-border access and privacy are all issues that could influence our capacity to develop workable HTA models across Europe.

Prioritisation of funding will continue to be an issue through the development, implementation and consolidation of personalised medicine. A key challenge will be to ensure adequate investment in prevention, early diagnosis and monitoring to support future reductions in healthcare expenditure or improved health status for similar financial outlay. Similarly, models will need to increasingly take account of overall cost-effectiveness rather than focusing on individual diseases and their treatment. The issues that currently apply to rare diseases, where large numbers of disease classifications apply to small groups of affected individuals, are likely to become more widely applicable in personalised medicine as common diseases are reclassified into more refined subtypes affecting smaller groups of individuals. As has been found in rare diseases, the small numbers of patients affected by each pathway-specific disease subtype means that the economic return on research investment is likely to be low, along with reduced financial incentive for investment from industry. Reimbursement models may therefore need to take account of overall cost-effectiveness and also ethical and social considerations, including funding to support access to new technologies. Care should also be taken to invest sufficient time and resources to ‘good enough’ technologies as we begin to introduce personalised medicine. In this way, we can ensure that patients obtain benefit at the earliest opportunity.

### 6.8.1 Recommendations

#### Health authorities and reimbursement bodies must:

1. Prioritise HTA for the timely and efficient evaluation of diagnostics, including companion diagnostics.
2. Establish a flexible HTA framework that supports the adoption of technologies that offer



- added value within European healthcare systems.
3. Ensure adequate investment in prevention, early diagnosis and monitoring.
  4. Work towards overall cost-effectiveness evaluations and reduced emphasis on individual diseases and their treatment.
  5. Take account of ethical and social considerations in reimbursement decisions.
  6. Ensure benefit from new technologies is obtained at the earliest opportunity by applying the principle of 'good enough' solutions.

## 6.9 Ethical, legal and social issues

### 6.9.1 Ownership and responsibility

A concern for personalised medicine is who retains control over data collected across the life course of the individual. One possible solution would be for individuals themselves to keep the information in the form of individual health records and other relevant datasets that are accessible through an appropriate technological interface. By shifting the locus of control away from the physician or healthcare system, this may give citizens greater control of their own health and personal information. Such an approach, however, would need to ensure that the right to manage one's own data does not turn into the duty to do so for those who do not have adequate resources (economic or time resources; health or computer literacy skills). In addition, appropriate security and oversight measures will need to be introduced to reduce the risk of data loss.

There is no stakeholder in the current health arena that is capable of sustaining lifetime electronic health records, mainly because it involves intensive ICT efforts, including archiving and semantic preservation over a period of many dozens of years. A possible new approach to this challenge is to change the current legislation of health record keeping so that healthcare providers and clinical trials sponsors are no longer the record keepers. Instead, 'independent health record banks' could be established and be the sole keepers of an individual's health records, objectively serving all stakeholders authorised to access the records. Multiple (and competing) record banks would be merely regulated by European authorities, taking the role of custodians and thus working around the controversial issue of health data ownership. In addition, privacy would be improved by removing the need for globally unique patient identifiers<sup>79</sup>.

79. Shabo, A. Global Socio-Economic-Medico-Legal Model for the Sustainability of Longitudinal Electronic Health Records – Part 2.

Individual responsibility goes beyond control of personal data. Personalised medicine needs to be understood within a social framework and not develop into a form of fragmented individualism. We must therefore ensure that it does not focus entirely on the individual at the expense of understanding the structural and contextual influences on health and lifestyle. For instance, what role does the food industry play in supporting healthy eating or promoting unhealthy dietary choices? Likewise, consideration should be given to the social factors that support or hinder healthy lifestyle choices. Increased emphasis on individual responsibility could lead to a culture of victim blaming. Careful consideration must be given to the risk of marginalising groups by labelling them as simply 'irresponsible' when they fail to follow advice on exercise, for instance, or diet without understanding the social factors that may have a role to play in determining those choices. Healthcare choices must ultimately be understood within their sociocultural context<sup>80</sup>. Perhaps a long-term goal, therefore, is to develop models that allow personalisation not only of disease and its treatment but also of health and the personal decisions that support it along the life course.

Personal identity and notions of collective belonging are another major topic to be considered in relation to personalised medicine. Analysis of traits based on genomic signatures, for instance, cannot be considered to apply only to individual citizens but also to family members who share their genetic heritage. Indeed similar considerations apply to environmental influences within the family setting. An important question to be addressed, therefore, is the extent to which certain information should remain private and the ethical implications of withholding information that could affect the health of one citizen in order to protect the privacy of another.

The relationship between citizen and state is also an important consideration in the era of personalised medicine. Issues will need to be addressed such as whether individuals could be obliged to allow their personal data to be used to develop tools of wider benefit to society. Similarly, will society allow the state to use information on individual behaviour and lifestyle obtained from sources such as CCTV recordings or credit card transactions to increase our understanding of the relationship between behavioural, lifestyle and sociocultural variables and health in individual contexts?

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*Methods of Information in Medicine* 2006; 45(5): 498–505.

80. Buyx A, Prainsack B. Lifestyle-related diseases and individual responsibility through the prism of solidarity. *Clinical Ethics* (in press).

### 6.9.2 Inequalities

Personalised medicine has the potential to improve access to effective, safe treatments for all European citizens. Yet, it also has the potential to introduce or accentuate inequalities. Access to technology is a core issue in this respect. Technology-driven healthcare such as smartphone monitoring could be limited by individual ability to pay for the technology if appropriate measures are not introduced to address that. Furthermore, technological interfaces must be adaptable to end-user needs if we are to avoid the development of a technology divide in which effective healthcare is available only to those able to interact appropriately with the technology. Access to technology is also a concern across countries and regions and reimbursement models developed on a European scale should take these issues into consideration. Importantly, it should be remembered that individual citizens throughout Europe are not merely consumers of healthcare resources. They are also one of the most important resources for personalised medicine through the use of their data to develop and refine algorithms and to assess the effectiveness and safety of interventions. Without ensuring widespread access to personalised medicine, it will be impossible to take adequate account of factors such as race, culture, socioeconomic context, gender, etc. Care must also be taken to ensure that inequalities in research funding among European countries do not lead to differences in the rate at which knowledge is translated into health benefits across Europe.

### 6.9.3 Informed consent

There is a particular concern about the way patients with cancer are informed and recruited to participate in research. The stakes are very high in this disease area as it is an acutely life-threatening condition and there is therefore a different tolerance for treatment efficacy. Acceptance of risk and willingness to volunteer places a greater responsibility on professionals to ensure that patients really are fully informed when providing consent to clinical trials in cancer. All of these factors must be taken into account when building the framework for studies into personalised approaches to cancer therapy. Moreover, many of these issues are relevant to other disease areas and to personalised medicine as a whole. It will be important to remember that consent is not just an issue for clinical trials and treatment but also for areas such as the collection and storage of information and its subsequent use.

Consent ultimately has wide-ranging implications across personalised medicine. As models are developed, refined and updated, it will be essential for agreements to be obtained on the sharing of per-

sonal information. Of particular concern to citizens is the issue of access to identifiable information. New consent models may need to be developed to ensure that information is only shared by professionals for the public good<sup>41,81</sup>. Such models will also need to take into account the nature of the data to be collected. Collection of detailed environmental information to include behavioural and lifestyle data also raises serious privacy issues. Consent models must ultimately act to ensure that individual citizens retain their right to ownership of private information. However, workable frameworks will also be required to ensure that consent, for instance to the use of information from electronic health records, allows for on-going processes and multiple uses of information. The potential of online platforms to provide dynamic and citizen-led solutions should therefore be explored and exploited.

### 6.9.4 Recommendations

#### Legislators and policymakers must:

1. Ensure that the right to manage one's own data does not turn into the duty to do so for those who do not have adequate resources.
2. Guarantee appropriate security and oversight measures to reduce the risk of personal data loss.
3. Investigate solutions such as independent health record banks for the storage and management of personal data.
4. Ensure that the frameworks supporting personalised medicine do not focus entirely on the individual at the expense of understanding the structural and contextual influences on health and lifestyle.
5. Support research into the ethical implications of withholding information that could affect the health of one citizen in order to protect the privacy of another.
6. Initiate widespread consultation on the use of personal data for the wider benefit of society.
7. Support widespread access to personalised medicine to prevent inequality and ensure that factors such as race, culture, socioeconomic context and gender are adequately represented in datasets.
8. Establish appropriate consent models for research and treatment in personalised medicine.

#### Researchers must:

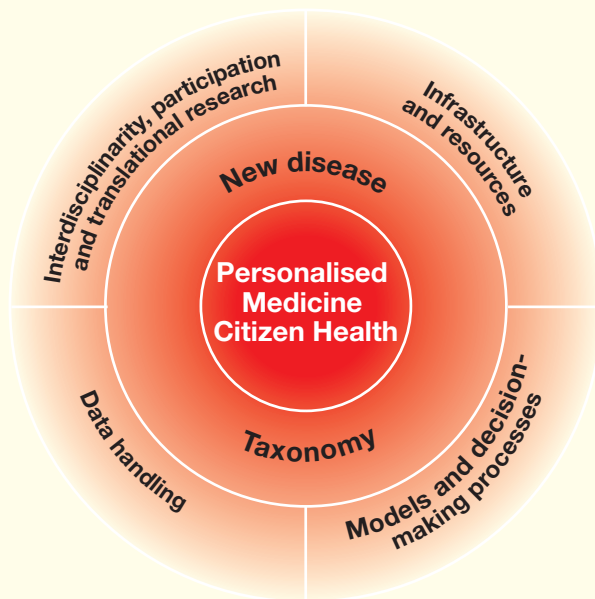
1. Develop models that allow personalisation not only of disease and its treatment but also of health and the personal decisions that support it along the life course.

81. Kaye J, Curren L, Anderson N, Edwards K, Fullerton SM, Kanellopoulou N *et al.* From Patients to Partners: Participant-Centric Initiatives in Biomedical Research, *Nat Rev Genet* 2012; 13(5): 371–376.

# 7. Recommendations



To frame the recommendations that have arisen over the course of the ESF Forward Look on Personalised Medicine, we have adopted a circle model. At the heart of personalised medicine lies the individual citizen, whose health status will be reflected by a new disease taxonomy informed by the multi-layered characterisation of physiological and pathological processes.



To support this new approach to classifying, understanding, treating and preventing disease, we highlight four overarching recommendations:

- 1. Data handling:**  
Comprehensive, accessible and interoperable datasets must be generated to support the development of a new disease taxonomy and allow for its on-going refinement and application.
- 2. Models and decision-making processes:**  
Models and decision-making processes must be revised to reflect a focus on the individual citizen at all levels, from assessment of the safety and efficacy of interventions, through HTA and reimbursement, to diagnosis, treatment and prevention.
- 3. Interdisciplinarity, participation and translational research:**  
Emphasis must be placed on stakeholder participation, interdisciplinary interaction, public-private and pre-competitive partnerships and translational research in order to develop the frameworks that support the vision of personalised medicine and healthcare.
- 4. Infrastructure and resources:**  
Dedicated funding and governmental support must be provided to ensure the availability of core infrastructure, including access to core technology and frameworks for education and training of professionals and the wider community.

These core recommendations are each supported by the specific recommendations identified during the foresight exercise:

## 7.1 Data handling

### Health authorities and public and private research organisations must:

1. Define rigorous quality control mechanisms for all aspects of data handling, from collection and annotation through to storage and sharing.
2. Agree steps to guarantee the generation of reproducible data based on harmonised protocols.
3. Harmonise approaches to data handling for clinical and research purposes.
4. Ensure that health outcomes data are contextualised based on environmental, lifestyle and other relevant data.
5. Facilitate translational research by ensuring consistent representation of patient data.

### Research and development in the public and private sectors must:

1. Identify solutions to the technological challenge of large-scale data storage and transfer.
2. Develop ICT solutions to handle comprehensive biological datasets and convert them into a meaningful output that will inform individual healthcare decisions.
3. Develop ICT solutions to integrate and interpret datasets from multiple sources and link the findings to specific outcomes in individual citizens.
4. Develop non-invasive technologies and ICT solutions for real-time monitoring, including:
  - a) Sensors to generate and store real-time information about individual health status.
  - b) Stable biomarkers to facilitate on-going analysis of health status across the life course of individuals.
  - c) Methods to measure and quantitate the functional state of molecular systems.
  - d) Rapid processing of imaging data without loss of precision.

### The healthcare profession must:

1. Promote and participate in the development of Europe-wide integrated networks to facilitate ongoing collection, storage and cross-referencing of individual information with local environmental data.
2. Support efforts to develop an integrated network of biomarkers, including increased availability of imaging biomarkers, linked to information on specific phenotypes.
3. Promote the refinement and integration of existing technologies and biomarkers into the framework of personalised medicine.

### Researchers, health authorities and policymakers must:

1. Define the relationship between phenotypes, patient information and reference data using large-scale networked approaches.
2. Develop systematic algorithms to map disease pathways onto existing disease classifications.
3. Introduce a networked approach to support agreed disease definitions throughout Europe.
4. Take advantage of upcoming opportunities such as the ICD11 revision scheduled for 2015 to promote the introduction of a new disease taxonomy.
5. Ensure that the naming of disease pathways within the new taxonomy allows for continual updating of definitions to support a stable framework for reliable and safe diagnosis.
6. Investigate solutions such as independent health record banks for the storage and management of personal data.

### Regulators and policymakers must:

1. Introduce appropriate legal and ethical frameworks to support data sharing.
2. Guarantee appropriate security and oversight measures to reduce the risk of personal data loss.

## 7.2 Models and decision-making processes

### Public and private research organisations must:

1. Define appropriate study designs to test potentially relevant findings.
2. Demonstrate the clinical utility, validity and relevance of all new technologies at the earliest possible stage.
3. Demonstrate the clinical benefit of monitoring biomarkers in asymptomatic, apparently healthy individuals as well as in patients.
4. Determine the implications of making data obtained for diagnostic purposes and monitoring available for research designed to optimise personalised medicine.
5. Promote initiatives to improve our understanding of 'healthy' phenotypes.
6. Develop appropriate methods to link diagnostic tools to therapeutic and preventive measures across the discovery and development pathway.
7. Rigorously test the performance (precision, reproducibility, specificity) of diagnostics in specific disease pathways.
8. Address the need for novel approaches to obtaining evidence in personalised medicine. This must include the following:



- a) Clinical trial designs adapted to the data-collection methods and interventions used in personalised medicine, e.g. N=1 trials, adaptive designs and Latin square methodology.
  - b) New statistical approaches to analyse the results of trials assessing personalised medicine.
  - c) Consideration of the influence of factors such as age, gender, ethnicity and environmental context on therapeutic response.
9. Develop new, more efficient models to investigate possible prevention strategies.

**Regulators must:**

1. Adapt regulatory frameworks to changes in disease taxonomy and the introduction of new diagnostic categories.
2. Develop appropriate regulatory frameworks for non-pharmaceutical therapies and prevention strategies.
3. Establish levels of evidence applicable to new testing methods.
4. Work closely with HTA professionals to ensure well-informed, transparent and accountable decision-making and reimbursement procedures.
5. Establish appropriate regulatory frameworks for the use of networked databases for diagnostic purposes.
6. Take steps to avoid stifling innovation while providing appropriate guarantees of the quality and safety of health-related products and information, particularly when these are accessed directly by European citizens.

**Health authorities and reimbursement bodies must:**

1. Prioritise HTA for the timely and efficient evaluation of diagnostics, including companion diagnostics.
2. Establish a flexible HTA framework that supports the adoption of technologies that offer added value within European healthcare systems.
3. Ensure adequate investment in prevention, early diagnosis and monitoring.
4. Work towards overall cost-effectiveness evaluations and reduced emphasis on individual diseases and their treatment.
5. Take account of ethical and social considerations in reimbursement decisions.
6. Ensure benefit from new technologies is obtained at the earliest opportunity by applying the principle of 'good enough' solutions.

## 7.3 Interdisciplinarity, participation and translational research

**All stakeholders in the future of personalised medicine must:**

1. Pay attention to the effects of language and terminology used in relation to personalised medicine.
2. Take every opportunity to correct the misconception that personalised medicine refers to genomic prediction alone.
3. Avoid inflated claims about the potential of personalised medicine during early stages of planning and implementation.
4. Participate in the generation of multi- and interdisciplinary frameworks, tools and models to link the needs of different stakeholders in achieving common goals within personalised medicine.

**The healthcare profession must:**

1. Raise awareness of examples in which stratified approaches have already begun to be used effectively in the clinic as precursors of a wider vision of personalised medicine.
2. Initiate large-scale consultation programmes to assess opinion and identify needs among existing disease specialities and across regions and cultures within the same specialty.
3. Identify experiences in existing specialities that could inform practice in personalised medicine as a whole.
4. Define the vision of an integrated, lifelong approach to healthcare in established disease areas in order to inform how personalised medicine will be implemented in the future.
5. Work towards cross-disciplinary consensus on the future of personalised medicine.
6. Work with citizens and patients to define what they need from their relationship with healthcare professionals within the framework of personalised medicine.
7. Work with ICT professionals to design low-threshold technological interfaces that support the interaction between patients and healthcare professionals in personalised medicine.
8. Work with ICT professionals to define how technology such as smartphone applications can be used to monitor health-related and environmental variables and function as a decision-support tool for citizens.
9. Actively inform policymakers and the media of unsubstantiated claims or misrepresentation and support the provision of accurate information in personalised medicine.

### Research and development in the public and private sectors must:

1. Identify which technologies can realistically be moved into the clinic over the next 10 years and communicate with healthcare professionals to prepare the ground for this transition.
2. Develop *in silico* models to inform clinical decision-making, starting with a prototype model that includes all available 'omics technologies as a proof of principle for integration.
3. Provide ICT solutions that support healthcare professionals in providing straightforward responses to the concerns of patients about future illness, treatment options and opportunities for prevention.
4. Provide ICT interfaces for citizens that facilitate informed choices about monitoring and sharing of different types of data.
5. Develop models that allow personalisation not only of disease and its treatment but also of health and the personal decisions that support it along the life course.

### Policymakers, health authorities and other public bodies must:

1. Establish mechanisms across all relevant domains to support citizen- and community-led promotion of health and wellbeing.
2. Promote and support resources that enable citizens, individually and cooperatively, to access, understand, interpret and make use of relatable information that supports personalised healthcare.
3. Establish mechanisms to promote health literacy among European citizens as an impetus to participation.
4. Define metrics to measure stakeholder participation, particularly among citizens and their communities.
5. Facilitate public dialogue on the value of personalised medicine and the necessary conditions for its success.

## 7.4 Infrastructure and resources

### Governments and policymakers must:

1. Develop a two-stage plan for the establishment of personalised healthcare:
  - A participatory stage designed to establish the system and provide proof of principle.
  - An implementation stage in which the system begins to be applied in European healthcare.
2. Ensure the availability of core infrastructure to support data collection and management over the life course.

3. Identify solutions to the cross-border issues affecting the use of electronic health records in an increasingly mobile European population.
4. Ensure provision of the necessary infrastructure and resources to support future integrated approaches, including biobanks and core reference datasets.
5. Ensure widespread access to clinical infrastructure such as imaging technology.
6. Support robust frameworks for pre-competitive public-private partnerships in research and development.

### Legislators and policymakers must:

1. Ensure that the right to manage one's own data does not turn into the duty to do so for those who do not have adequate resources.
2. Ensure that the frameworks supporting personalised medicine do not focus entirely on the individual at the expense of understanding the structural and contextual influences on health and lifestyles.
3. Support research into the ethical implications of withholding information that could affect the health of one citizen in order to protect the privacy of another.
4. Initiate widespread consultation on the use of personal data for the wider benefit of society.
5. Support widespread access to personalised medicine to prevent inequality and ensure that factors such as race, culture, socioeconomic context and gender are adequately represented in datasets.
6. Establish appropriate consent models for research and treatment in personalised medicine.

### European policymakers and educational institutions must:

1. Provide incentives for the interdisciplinary education of healthcare professionals and scientists from the earliest stages of professional development.
2. Support the development of career structures in personalised medicine.
3. Establish the intellectual and communications infrastructure to support cross-disciplinary interaction and training for ICT and healthcare professionals.
4. Ensure adequate training of the professionals and citizens who will use the relevant ICT solutions as they are developed.

## 8.

# Can we predict a timeline for the development and implementation of personalised medicine?



Change management will be an important consideration in the transition towards personalised medicine. The future success of the approach will depend on how effectively we can prepare the ground now. This will require active engagement of stakeholders, development of the necessary technological infrastructure, training of personnel and establishment of appropriate regulatory and reimbursement mechanisms, among others. In all cases, timing will be critical. For instance, stakeholder participation will not be optimal unless early expectations are managed appropriately. Health professionals and others will need to see proof of principle, while citizens need to be confident about the responsible, transparent and accountable management of ethical, legal and social concerns. Similarly, networked diagnostic approaches will not be possible without prior steps being taken to ensure standardisation of data inputs and, indeed, participation of patients willing to share personal data.

In all cases, education and health literacy programmes will need to be planned ahead of time to ensure that all stakeholders can play the roles required of them and indeed benefit from the developments that occur. Furthermore, if we envisage a change in the structure of the healthcare professions away from a primary focus on disease specialities and towards multidisciplinary, patient-centred teams, professionals within the existing structure must be engaged in the process of managing this transition from the earliest stage. Key players in this process could be professional societies.

The further we attempt to look into the future, the greater the level of uncertainty we face. Short-term goals are therefore important to ensure that

concrete steps are taken. A failure to look far enough ahead, however, can leave us unprepared for eventualities and act as a barrier to transformative change. Resource allocation is a case in point. If early interest in personalised medicine leads to diversion of resources away from existing treatments and prevention strategies, it may have negative short-term consequences for public health. The longer-term effect, however, could also be to threaten future acceptance of personalised medicine by creating hostility among affected groups. If the long-term goal is to achieve the full potential of this approach, then it will be essential to establish adaptable timelines that allow both short-term milestones and longer-term goals to be addressed.

## 8.1 Core priorities for the next five years

To ensure the future of personalised medicine and lay the foundations that will support its long-term vision, the following recommendations must be given priority over the next 5 years:

### 1. Data handling:

Without data, there will be no personalised medicine. Existing systems for data collection and storage, particularly biobanks, must therefore be consolidated and agreements reached on how to ensure future harmonisation of data collection and handling throughout Europe.

### 2. Models and decision-making processes:

Data cannot support personalised medicine without being converted into evidence. Priority must therefore be given to defining appropriate

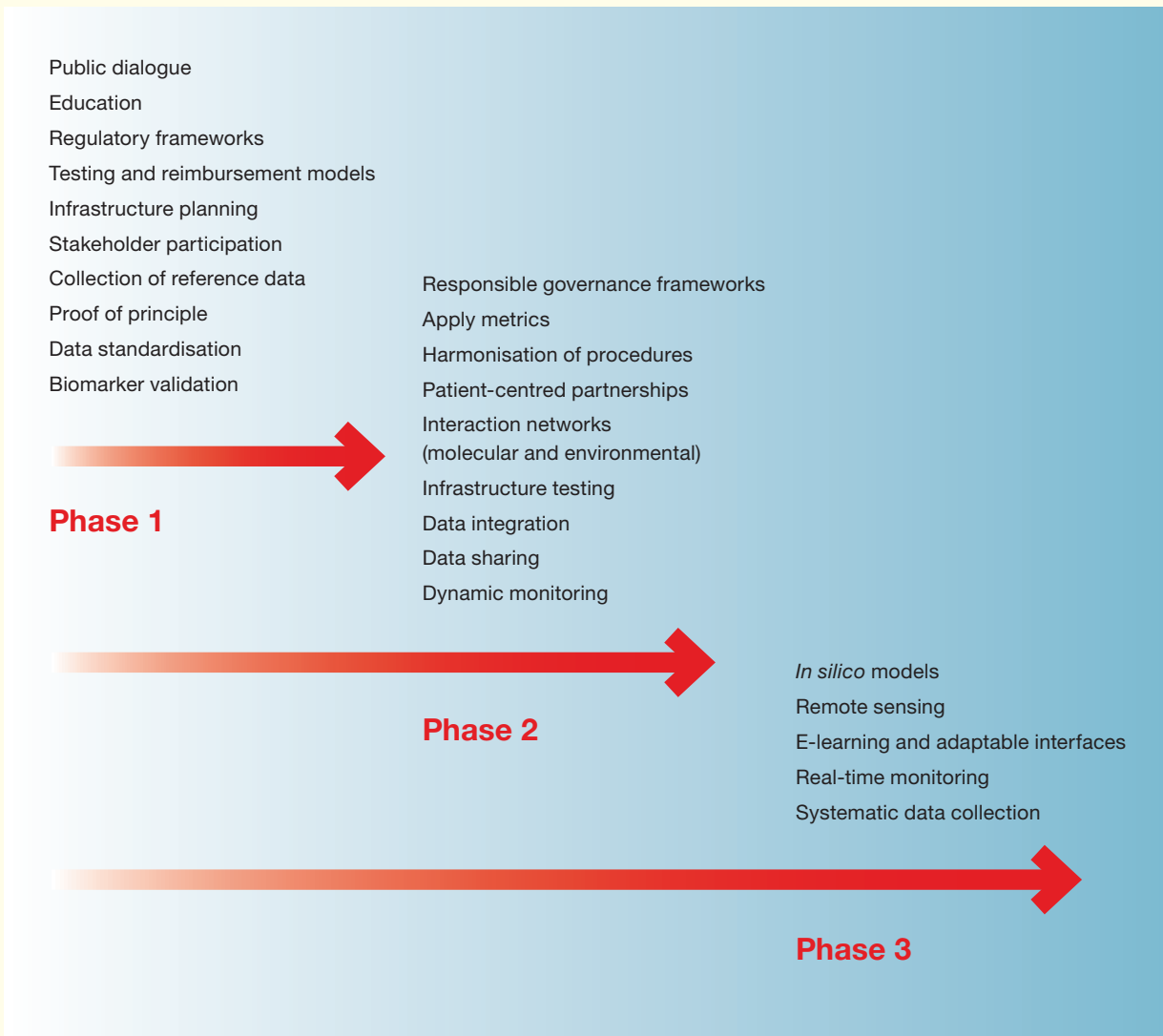


Figure 5. Preliminary timeline for the development and implementation of personalised medicine

mechanisms for the evaluation of data in personalised medicine, especially in terms of clinical trial designs and HTA.

### 3. Interdisciplinarity, participation and translational research:

Professionals and citizens alike will define the future of personalised medicine through discussion and interaction. It is therefore essential that all stakeholders be engaged in wide-ranging consultation processes that facilitate cross-disciplinary interaction and stakeholder participation.

### 4. Infrastructure and resources:

Without dedicated support, the foundations for personalised medicine cannot be established. Funding must therefore be ensured for core infrastructure and education across Europe.

## 8.2 Preliminary timeline for the development and implementation of personalised medicine

(Figure 5)



## Abbreviations

<b>APOE4</b>	Apolipoprotein E (4)
<b>BRCA</b>	Breast Cancer Gene
<b>CFTR</b>	Cystic Fibrosis Transmembrane conductance Regulator
<b>CGD</b>	Centre for Genome Diagnostics
<b>CVD</b>	Cardiovascular disease
<b>EGFR</b>	Epidermal Growth Factor Receptor
<b>EMRC</b>	ESF Standing Committee for the European Medical Research Councils
<b>ESF</b>	European Science Foundation
<b>FDA</b>	Food and Drug Administration
<b>HER-2</b>	Human Epidermal Growth Factor Receptor 2
<b>HIA</b>	Health impact assessment
<b>HTA</b>	Health technology assessment
<b>ICD11</b>	International Classification of Diseases, revision 11
<b>ICT</b>	Information and communication technology
<b>iPOP</b>	Integrative personal omics profile
<b>ITFoM</b>	European IT Future of Medicine project
<b>LESC</b>	ESF Standing Committee for the Life, Earth and Environmental Sciences
<b>PESC</b>	ESF Standing Committee for the Physical and Engineering Sciences
<b>SCH</b>	ESF Standing Committee for the Humanities
<b>SCSS</b>	ESF Standing Committee for the Social Sciences
<b>TPMT</b>	Thiopurine methyltransferase

Annex

**Committee members,  
speakers and participants**

## Committee members, speakers and participants

### Scientific Committee

#### Chairs:

- **Professor Stephen T. Holgate**  
Clinical and Experimental Sciences, School of Medicine, University of Southampton, UK
- **Professor Aarno Palotie**  
Institute for Molecular Medicine Finland (FIMM), University of Helsinki, Finland
- **Professor Barbara Prainsack**  
Centre for Biomedicine and Society, Department of Sociology and Communications, Brunel University, UK

#### Members:

- **Professor Angela Brand**  
Institute for Public Health Genomics (IPHG), Maastricht University, The Netherlands
- **Professor Hans Lehrach**  
Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Germany

### Management Committee

#### Chair:

- **Professor Liselotte Højgaard**  
Chair of the European Medical Research Councils (EMRC), Director, Professor, Clinical Physiology, Nuclear Medicine & PET, Rigshospitalet, Denmark

#### Members:

- **Professor Tanel Tenson**  
Member of the ESF Standing Committee for Life, Earth and Environmental Sciences (LESC), and Faculty of Science and Technology, University of Tartu, Estonia
- **Professor Milena Žic-Fuchs**  
Chair of the ESF Standing Committee for the Humanities (SCH), and Faculty of Philosophy, University of Zagreb, Croatia
- **Professor Rainer Kattel**  
Member of the ESF Standing Committee for the Social Sciences (SCSS), and Institute of Humanities and Social Sciences, Tallinn University of Technology, Estonia
- **Professor Jukka Corander**  
Representative of the ESF Standing Committee for the Physical and Engineering Sciences (PESC), and Department of Mathematics and Statistics, University of Helsinki, Finland
- **Professor Heyo K. Kroemer**  
Deutsche Forschungsgemeinschaft (DFG), Germany
- **Professor Jacques Grassi**  
Institut national de la santé et de la recherche médicale (Inserm), France

- **Professor Francesc Palau Martinez**

Instituto de Biomedicina de Valencia, Spanish Council for Scientific Research (CSIC) and CIBER on Rare Diseases (CIBERER), Spain

### Activities

#### Scoping Workshop

1 July 2010, Brussels (BE)

#### Co-Chairs

- **Professor Carsten Carlberg**  
University of Eastern Finland, School of Medicine, Institute of Biomedicine of the Faculty of Health, Finland
- **Professor Krešimir Pavelic**  
EMRC Standing Committee, Croatian Academy of Sciences and Arts (HAZU), Croatia

#### Participants

- **Professor Rolf Apweiler**  
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### Preparatory Workshop

13-14 January 2011, Luxembourg (LU)

- **Mr Dominic Allen**  
COO, Integrated Biobank of Luxembourg (IBBL), Luxembourg Center for systems Biomedicine, Luxembourg
- **Professor Rudi Balling**  
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- **Professor Dr Olga Golubnitschaja**  
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- **Dr Anna González-Neira**  
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- **Professor Jacques Grassi**  
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- **Professor Adam Hedgcock**  
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- **Dr Jörg Hoheisel**  
Functional Genome Analysis, Deutsches Krebsforschungszentrum, Germany
- **Professor Stephen T. Holgate**  
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- **Professor Heyo Klaus Kroemer**  
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- **Professor Luigi Orsenigo**  
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- **Professor Aarno Palotie**  
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- **Professor Krešimir Pavelic**  
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University of Rijeka, Department of Biotechnology, Croatia
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- **Professor Matti Sintonen**  
SCH Standing Committee, Department of Philosophy, University of Helsinki, Finland
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- **Dr med Kári Stefánsson**  
Founder of deCODE Genetics, Iceland
- **Professor Mike Taussig**  
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- **Professor Peter Wade**  
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### Technology Workshop

19-20 September 2011, London (UK)

- **Professor Rudolf Aerborsold**  
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- **Dr Rolf Apweiler**  
Protein and Nucleotide Data (PANDA) Group, European Bioinformatics Institute, Wellcome Trust Genome Campus, UK
- **Professor Ivano Bertini**  
European Centre for Magnetic Resonance (CERM), University of Florence, Italy
- **Professor Thomas Beyer**  
cmi-experts, GmbH, Switzerland
- **Mr Patrick Boisseau**  
Business Development Nanomedicine, Microtechnologies for Biology and Healthcare Division, Laboratoire d'Électronique et de Technologie de l'Information (LETI), France



- **Professor Angela Brand**  
Institute for Public Health Genomics (IPGH),  
Maastricht University, The Netherlands
- **Professor Carsten Carlberg**  
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Institute of Biomedicine of the Faculty of Health,  
Finland
- **Professor Peter Coveney**  
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- **Dr Falk Ehmann**  
European Medicines Agency (EMA), UK
- **Dr Alex Faulkner**  
Centre for Global Health Policy, School of Global  
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- **Dr Ivo Gut**  
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- **Dr Bärbel Hüsing**  
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Research, Germany
- **Professor Gabriel P. Krestin**  
European Institute for Biomedical Imaging Research  
(EIBIR), Erasmus MC, University Medical Center  
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(President), The Netherlands
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- **Mrs Piret Kukk**  
Fraunhofer Institute for Systems and Innovation  
Research, Germany
- **Professor Ulf Landegren**  
Department of Immunology, Genetics and Pathology  
and SciLifeLab, Uppsala University, Sweden
- **Dr Pierre Legrain**  
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- **Professor John McGrath**  
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- **Dr Peter Mills**  
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- **Professor Francesc Palau Martinez**  
Instituto de Biomedicina de Valencia, Spanish  
Council for Scientific Research (CSIC) and CIBER on  
Rare Diseases (CIBERER), Spain
- **Professor Aarno Palotie**  
Institute for Molecular Medicine Finland (FIMM),  
University of Helsinki, Finland
- **Professor Marisa Papaluca**  
European Medicines Agency (EMA) (for UK) and  
University of Rome 'Tor Vergata' (Italy)
- **Dr Iain Patten**  
Science Writer, Spain
- **Professor Barbara Prainsack**  
Centre for Biomedicine and Society, Department of  
Sociology and Communications, Brunel University,  
UK
- **Professor Timothy Spector**  
Twin Research and Genetic Epidemiology Unit,  
King's College London, UK
- **Dr Ralf Sudbrak**  
Department of Vertebrate Genomics, Max Planck  
Institute for Molecular Genetics, Germany
- **Professor Ben Van Ommen**  
Department of Microbiology and Systems Biology,  
Nutrition and Food Research Institute,  
The Netherlands
- **Dr Stephen Williams**  
SomaLogic Inc, Colorado, USA
- **Professor Kurt Zatloukal**  
Institute of Pathology, Medical University of Graz,  
Austria

## Disease Summit

18-20 October 2011, The Hague (NL)

### Speakers:

- **Dr Karl Freese**  
General Directorate for Health and Consumers  
Public Health, European Commission, Luxembourg
- **Professor Adam Hedgecoe**  
ESRC Centre for Economic & Social Aspects of  
Genomics (Cesagen), Cardiff University, UK
- **Professor Richard Imrich**  
Center for Molecular Medicine, Slovak Academy  
of Sciences, Slovak Republic
- **Professor Barbara Prainsack**  
Centre for Biomedicine and Society, Department  
of Sociology and Communications, Brunel University,  
UK
- **Mr Herman Spolders**  
European Organisation of Personalised Medicine  
(EPEMED), Belgium
- **Mr Daniel Vorhaus**  
Robinson, Bradshaw and Hinson, P.A., Charlotte  
N.C., USA

**Participants:**

- **Dr Michela Bertero**  
Centre for Genomic Regulation (CRG), Spain
- **Professor Angela Brand**  
Institute for Public Health Genomics (IPHG),  
Maastricht University, The Netherlands
- **Professor Carsten Carlberg**  
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- **Professor Jukka Corander**  
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- **Dr Falk Ehmann**  
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- **Dr Beth Greenhough**  
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- **Dr Jörg Hoheisel**  
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- **Professor Jens Kastrup**  
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- **Professor Alexandra Kautzky-Willer**  
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- **Dr Robert Kleemann**  
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Research (TNO), The Netherlands
- **Professor Gabriel P. Krestin**  
European Institute for Biomedical Imaging Research  
(EIBIR), Erasmus MC, University Medical Center  
Rotterdam, and European Society of Radiology  
(President), The Netherlands
- **Dr Linnea Larsson**  
Medical Research Council (MRC), UK
- **Professor Hans Lehrach**  
Department of Vertebrate Genomics, Max Planck  
Institute for Molecular Genetics, Germany
- **Professor Nuria Malats**  
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Spain
- **Dr Karen Melham**  
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Technologies, University of Oxford, UK
- **Professor Colin Palmer**  
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- **Professor Aarno Palotie**  
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- **Assistant Professor George P. Patrinos**  
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Department of Pharmacy, Greece
- **Dr Iain Patten**  
Science Writer, Spain
- **Professor Mario Pazzagli**  
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- **Professor Jasna Peter-Katalinic**  
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Centre for Genomic Regulation (CRG), Spain.  
UPF, ICREA Research Professor
- **Dr Carmel Shalev**  
Faculty of Law, Haifa University, Israel
- **Dr Ralf Sudbrak**  
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Institute for Molecular Genetics, Germany
- **Dr Domenica Taruscio**  
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Istituto Superiore di Sanità, Italy
- **Professor Tanel Tenson**  
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Faculty of Science and Technology, University of  
Tartu, Estonia
- **Dr Rosella Tomanin**  
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University of Padova, Italy
- **Dr Richard Tutton**  
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Lancaster University, UK

**Big Picture Workshops**

13-14 February 2012, Dubrovnik (HR)

**Speakers:**

- **Dr Stephane Berghmans**  
Biomedical Sciences Unit, ESF, France
- **Professor Angela Brand**  
Institute for Public Health Genomics (IPHG),  
Maastricht University, The Netherlands
- **Professor Stephen T. Holgate**  
Clinical and Experimental Sciences, School  
of Medicine, University of Southampton, UK
- **Professor Aarno Palotie**  
Institute for Molecular Medicine Finland (FIMM),  
University of Helsinki, Finland
- **Professor Barbara Prainsack**  
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UK

**Participants:**

- **Dr Wendy Alderton**  
Abcodia Ltd, UK
- **Professor Stefania Boccia**  
Faculty of Medicine and Surgery, Catholic University  
of the Sacred Heart, Italy
- **Professor Helmut Brand**  
Faculty of Health, Medicine and Life Sciences,  
Maastricht University, The Netherlands
- **Dr Koos Burggraaf**  
Centre for Human Drug Research, The Netherlands

- **Professor Carsten Carlberg**  
University of Eastern Finland, School of Medicine,  
Institute of Biomedicine of the Faculty of Health,  
Finland
  - **Dr Hans-Peter Dauben**  
DIMDI, Germany
  - **Professor Jacques Grassi**  
Institut national de la santé et de la recherche  
médicale (Inserm), France
  - **Dr Beth Greenhough**  
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of London, UK
  - **Dr Hinrich Gronemeyer**  
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Inserm/ULP, France
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  - **Dr Adam Heathfield**  
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  - **Dr Tim Hubbard**  
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Genome Campus, UK
  - **Mrs Rebecca Jungwirth**  
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  - **Dr Jane Kaye**  
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Department of Public Health, University of Oxford,  
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  - **Dr Véronique Kiermer**  
Nature Publishing Group, New York, USA
  - **Dr Lars Kristiansen**  
Federation of European Neuroscience Societies  
(FENS), Brussels, Belgium
  - **Professor Adrián Lleren**  
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CICAB Clinical Research Center, Spain
  - **Professor Vangelis Manolopoulos**  
Medical School, Democritus University of Thrace,  
Greece
  - **Mr Hrjove Mestric**  
Croatian Ministry of Science, Education and Sport,  
Croatia
  - **Professor Giovanni Pacini**  
National Research Council Metabolic Modelling  
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  - **Professor Francesc Palau Martinez**  
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  - **Dr Christine Patch**  
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London, UK
  - **Dr Iain Patten**  
Science Writer, Spain
  - **Professor Jasna Peter-Katalinic**  
University of Rijeka, Department of Biotechnology,  
Croatia
  - **Dr Jean-Luc Sanne**  
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Belgium
  - **Mr Duane Schulthess**  
Science/Business, Belgium
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  - **Professor Tanel Tenson**  
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of Tartu, Estonia
  - **Professor Ben Van Ommen**  
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Biology, Nutrition and Food Research Institute,  
The Netherlands
  - **Dr Effy Vayena**  
Institute of Biomedical Ethics, Faculty of Medicine,  
University of Zurich, Switzerland
  - **Dr Joachim Vetter**  
German Ethics Council, Germany
  - **Dr Daniel Vonder Mühl**  
SystemsX.ch, The Swiss Initiative in Systems Biology,  
Switzerland
- Stakeholders Conference**  
**18 April 2012, Rome (IT)**
- Speakers:**
- **Dr Stephane Berghmans**  
Biomedical Sciences Unit, ESF, France
  - **Professor Angela Brand**  
Institute for Public Health Genomics (IPHG),  
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  - **Professor Stephen T. Holgate**  
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  - **Professor Aarno Palotie**  
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- **Professor Helmut Brand**  
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- **Dr Koos Burggraaf**  
Centre for Human Drug Research, The Netherlands
- **Dr Alessandro Buriani**  
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- **Professor Peter Dabrock**  
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- **Dr Hans-Peter Dauben**  
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- **Professor Chris Evelo**  
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- **Dr Stefano Fortinguerra**  
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- **Dr Karl Freese**  
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- **Dr Ingrid Geesink**  
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- **Dr Iñaki Gutierrez-Ibarluzea**  
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- **Professor Adriano Henney**  
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- **Dr Bodo Lange**  
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- **Professor Adrián Llerena**  
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- **Professor Nuria Malats**  
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