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Conference report
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Part 1 - Introduction
Personalised medicine is on the frontier of healthcare. It involves the use of molecular diagnostics to identify which patients are most likely to respond to specific medicines so that these medicines can be administered to them more effectively and with fewer side effects.

The potential of personalised medicine is huge. If patients receive only those medicines that are best suited for them, health outcomes for society as a whole will improve. And healthcare systems across Europe will save money. But for this to happen, there will need to be an unprecedented level of cooperation amongst the many stakeholders in the European healthcare system. This includes the research community, medicines and diagnostics manufacturers, regulators, health technology assessors, doctors and other health professionals, including those in public health, and of course, patients.

Personalised medicine poses a multitude of challenges. With the mapping of the human genome, a wealth of information has been generated about how humans differ from one another and how an individual’s genetic make-up can influence his or her susceptibility to disease and response to new treatments. Genomics is only one of the new disciplines, called ‘omics,’ that seeks to define and explain the mechanisms of the human body. Proteomics, or the large-scale study of proteins, is another. There is also epigenomics, transcriptomics, metabolomics and metagenomics, just to name a few. Basic science is putting forward new theories about the causes, treatments and possible cures for disease at breath-taking speed. How can this explosion of knowledge be put to work for better healthcare?

In order to address these challenges, the Health Research Directorate of the European Commission organised a series of workshops on personalised medicine in 2010, culminating in a two-day conference in Brussels, Belgium on 12-13 May, 2011. The objective of the conference was to identify the challenges that will need to be addressed in order to make personalised medicine a reality.

Some of the challenges identified by the workshops included:

- The need to better understand disease mechanisms;
- The need for harmonised methods for the handling and storage of tissue and data for use in biomarker development;
- The need for regulatory clarity as regards the qualification and validation of biomarkers as well as the approval of diagnostic tests;
- The need for a faster uptake of validated ‘omics’ technologies in clinical practice and;
- The need for better training of healthcare professionals in the application of personalised medicines.

At the conference in May, these issues, and others, were discussed by experts from industry, academia, clinics, regulatory authorities, health technology assessors and patient groups. Altogether, there were six sessions and two plenary sessions with keynote speakers. They covered basic research and development; biomarkers; tests in humans, the regulatory
approval process; the post-approval processes, and the patient and practitioner perspectives.

The following report is a summary of these discussions. It is organised into four parts. Whereas Part 1 is the introduction; Part 2 summarises the presentations by speakers at the conference plenary; Part 3 is a summary of the six subject-oriented sessions, and Part 4 is the conclusion. A list of challenges is presented at the end of the summaries of the plenary speeches and at the end of the summaries of each of the six sessions.

The conference programme, presentations and speaker biographies can be consulted online on the personalised medicine pages of the European Commission’s health research website:

Part 2 - Plenary Sessions
Mrs Draghia opened the plenary by declaring that society faces very significant healthcare challenges. Although there have been huge gains in human health in recent decades, progress has been uneven. Not all patients respond to the most common medicines and among those who do, there can be adverse reactions. An estimated 5-7% of all hospital admissions are caused by adverse medicine reactions. Meanwhile, it has become more costly and time consuming to develop new treatments. And the rate of failure of medicines in development is high.

Demographics is also playing a more important role. With older people constituting a greater proportion of the population, the cost of healthcare is rising. Well-informed patients are putting higher demands on healthcare systems, yet governments are under pressure to contain costs. Set against these challenges are new opportunities. There has been an avalanche of new ‘omics’ and molecular information following the sequencing of the human genome. Translating these ‘omics’ from basic to clinical research can deliver a better understanding of human health and disease. This in turn can yield more innovative approaches to the prediction, prevention, treatment, and even cure of disease. Ultimately, this should make healthcare more effective.

Personalised medicine embodies these goals in that it aims to better predict, prevent and treat or cure disease by understanding the individual characteristics of each patient. The process of developing a personalised medicine starts with basic research into a disease. It then moves into the development of tools that can stratify patients who may be eligible for new treatments. Prospective treatments are developed and tested in human trials. If these trials are successful, the therapy is submitted to a regulatory authority for review and approval after which it is priced and reimbursed by a national health authority. Finally, it is administered to a patient.

Each of these steps will require new approaches and new tools and a commitment from all of the stakeholders in the healthcare system to embrace necessary changes. The basic research step will involve understanding the molecular characteristics of disease; the stratification step includes identifying, qualifying and validating biomarkers; the clinical trial step focuses on developing new trial methodologies and being sensitive to ethical considerations; the regulatory step includes a review of both diagnostics and therapies, and the reimbursement step involves the application of health economics in deciding which new treatments should be subsidised. Finally, the patient step means having tests and treatments available in clinical practice. Healthcare professionals will also need to be better trained to administer these new treatments to patients. Personalised medicine is an emerging field which will bring radical change to healthcare. It is at an early stage of development. What is needed now is a long-term structured approach to innovation to bring these treatments into clinical practice.

* Mrs Draghia was speaking on behalf of Máire Geoghegan-Quinn, Commissioner for Research, Innovation and Science, European Commission, who was unable to be present at the conference.
In his address to the conference plenary, Mr Knowles challenged the audience to break the deadlock that exists in medicine development where spending on new medicines is increasing but the number of new, approved molecular entities is declining. Mankind has been enormously successful – some 7,500 medicines are now available to patients worldwide – yet this success is a barrier to progress. This is because we often cannot demonstrate superiority to existing medicines in large diverse patient populations identified as they are today. There will be very few new medicines until we better understand how to reclassify disease at the molecular level.

Molecular biology and imaging are essential to redefine sub populations of patients that will respond to new therapies.

The practice of medicine is changing quickly. For thousands of years, diagnosis and treatment were based on what could be seen, smelled, tasted and intuited. In the last 100 years diagnosis has moved on to include knowledge about biochemistry and cellular processes. Today, diagnosis and treatment incorporate insights into molecular biology and genetics. In the future, patient management must be based on computer analysis of molecular information to identify the optimal or necessary treatments for individual patients. Whereas today, most patients are administered medicines more or less in the same way, treatment in the not-too-distant future will be tailored to selected patient groups defined by their molecular signatures. This is what is known as stratified healthcare, or the use of molecular insights and diagnostic tests to better tailor medicines and manage a patient’s disease. It seems to be an ongoing challenge to bring people who understand human molecular biology together with those who understand the practice of medicine.

‘We create a story about a medicine that is partly right. But the story is sometimes much bigger,’ Mr Knowles commented. Metformin, for example, is an approved medicine for Type 2 diabetes. But recent research has indicated that it may also have a potential in cancer. Similarly, Herceptin (trastuzumab), may also be effective in colorectal cancer patients over expressing HER2, in addition to its approved indication in breast and gastric cancer. Herceptin, the world’s first stratified protein therapeutic, has been successful in treating women with human epidermal growth factor Receptor 2-positive (HER2+) breast cancer by targeting cells expressing an excess of these receptors. However, the usefulness of the treatment could be even greater by making better use of molecular diagnostics to identify other patients with other different cancers that over express HER2. This principle can be applied to all cancer treatments which have a molecular marker predicting response.

What then, is the way forward? The first step is to use molecular signatures to redefine disease and use this to identify patients likely to respond to treatment. This is already becoming accepted practise in medicine development. Under this new approach, patients would be ‘stratified’ into subgroups according to their biomarker profile and likely response to a specific treatment. Even more valuable is the next step in which patients receive personalised novel combination therapies based on the molecular pathology of their specific disease. Each combination may only be very efficacious in one in 1,000 patients, but this
could lead to actual cures.

Concluding, Mr Knowles said all stakeholders should support new ways of redefining disease and applying the new molecular biology tools to define optimal treatment. It is important to create a better understanding of the value of molecular diagnostics both to cost effective health care and better patient outcomes in Europe.

**Challenges :**

1. Fund more and better studies aimed at re-classifying human disease at a molecular level; in particular conduct studies involving very well defined patient samples.
2. Fund studies on novel clinical trial designs using prospective observational studies in order to show how better decisions based on molecular data lead to more cost-effective and much better outcomes for patients.
3. Change the way in which patient information is generated in clinical practice to enable evidence to support change in treatment practices.
4. Encourage a shift from companion diagnostics for each therapy to an approach that uses the molecular definition of what combination of therapies is suitable for each individual patient.
5. Encourage novel partnerships and collaborations to achieve the above, for example by bringing biologists and clinicians together.
6. Require researchers that receive public funds to define the patient populations in their studies as a prerequisite for receiving funding.
Axel Ullrich

Professor and Director, Department for Molecular Biology, Max Planck Institute of Biochemistry, Germany

Axel Ullrich drew on his experience as initiator of the original Herceptin project at Genentech (now Roche) to explain how the first personalised medicine for cancer was discovered, and how science has moved on since that time.

Herceptin is a monoclonal antibody and the first targeted therapy to be approved for human use anywhere in the world. It targets the human epidermal growth factor Receptor 2 (HER2) protein which is over-expressed in some women with breast cancer. As a Genentech scientist in 1985, Dr Ullrich and colleagues cloned the first full-length human HER2 gene. Two years later, the Genentech team and a team from the University of California at Los Angeles linked HER2 over-expression with the more aggressive types of breast cancer. They found that about 25% of all breast cancer tumours contained an amplified HER2 gene.

In 1990, Genentech scientists synthesized Herceptin by humanising a mouse antibody targeting HER2. Two years later, the company received regulatory approval to start the first Herceptin human trials, and in September 1998, the medicine was approved by the US Food and Drug Administration (FDA). The FDA also approved a diagnostic that had been developed separately to identify patients that would be eligible for Herceptin treatment.

Since the Herceptin approval, scientists have learned even more about the human genome, and this is likely to change the approach to cancer in the future. It is now known that there are 10 million genetic determinants in the human genome and these account for the differences among individuals. In recent years, attention has focused on germ-line alterations, in addition to somatic gene mutations in trying to understand the progression of certain types of cancer.

J Bange and colleagues reported in 2002 that a single nucleotide change in codon 388 of the fibroblast growth factor receptor 4 gene (FGFR4) is implicated in the progression and poor outlook for certain cancers, including breast cancer.

A study published in 2010 (A Single Nucleotide Change in the Mouse Genome Accelerates Breast Cancer Progression, Cancer Research, 15 January 2010 70;802) confirmed this finding in mice. The study showed that the Arg385 codon (which corresponds to the Arg388 in humans) on the FGFR4 gene in a mouse model enhanced the progression of breast cancer. The study therefore validated FGFR4 R385/R388 as a prognostic marker for breast cancer and as a candidate target for individualised cancer therapy development, Mr Ullrich said.

Genetic information should therefore be used in the diagnosis of patients, and not just in the classification of the tumour itself.

**Challenge:**

1. Continue studies into the human genome and into the development of new prognostic biomarkers.
Mr Dalli highlighted the potential of personalised medicine to provide solutions that are, from the outset, better tailored to different patient groups than the so-called ‘one size fits all’ medicinal products of today. By offering personalised medicines to patients, healthcare providers can avoid trial and error and reduce adverse reactions. This offers the potential for major benefits to patients and to the healthcare system as a whole. At the moment, this potential is largely unexploited. Efforts by academia and industry need to be stepped up.

The current EU regulatory framework for pharmaceuticals, coupled with detailed scientific guidance documents, ensures that all new products meet standards of quality, safety and efficacy before being launched onto a market. This applies equally to personalised medicine. But there is a clinical trial aspect. For example, does the defined or limited patient population for a personalised medicine pose additional challenges in the conduct of clinical trials?

Mr Dalli said that industry must have a framework which allows it to organise clinical trials in the European Union across borders in an efficient manner. This issue will be considered in the forthcoming revision of the Clinical Trials Directive (Directive 2001/20/EC). Likewise, the forthcoming recast of the medical devices legislation is an opportunity to ensure that diagnostic medical devices used in the context of personalised medicines offer the appropriate level of quality and safety, he said.

The Commissioner said it is hoped that the costs for personalised medicine can be offset by efficiency gains. But even with possible efficiency gains, it will be a challenge for policymakers to reconcile high prices with the growing demand for healthcare from an ageing population, and against a backdrop of economic and budget austerity.

Health Technology Assessment (HTA) provides a methodology for addressing the uptake of health technologies. But the HTA bodies in the EU need to cooperate so that the information generated by one HTA body can be used by another. A successful uptake of personalised medicine in Europe requires that HTA methods take into account the specificities of the new technologies.

The new ‘omics’ technologies can play an important role in diagnosis and treatment and also in the prevention of illness. The potential for prevention is huge. At the same time, other factors must also be addressed such as poor living conditions and unhealthy lifestyles, Mr Dalli said. This goes beyond pure technological innovation. Mr Dalli made reference to the European Innovation Partnership for Active and Healthy Ageing - which explores innovative solutions for the future.
Mr Calvo described how the French health authorities have set up a national programme for cancer patients under which they can be tested, free of charge, for the molecular characteristics of their particular tumours. These tests take place at any one of 28 regional centers. Once tested, patients can be prescribed with the most appropriate medicine as soon as possible. The programme was set up in 2006 in response to patient demand for access to the latest targeted cancer therapies.

The programme is operated by the National Cancer Institute (Institut National du Cancer) and the Ministry of Health. Laboratories in the 28 regional hubs administer tests after which samples from patient tumours are analysed and their cancers are defined. The approach to tumour classification has changed with the introduction of molecular diagnostics. It is now known, for example, that colorectal cancer consists of at least four disease subsets, each of which corresponds to a particular genetic mutation. The same is true for non-small cell lung cancer which can be characterised by seven different mutations or chromosomal translocations.

The goal of the French programme is to offer each cancer patient access to a molecular test as soon as possible following the regulatory approval of a new targeted cancer therapy. For example, in 2008 the institute allocated €2.5 million for KRAS testing in colorectal cancer. This was not long after regulatory authorities approved Erbitux (cetuximab) and Vectibix (panitumumab) for patients with colorectal cancer with the non-mutated (wild-type) KRAS gene.

Similarly in 2009, the institute allocated €1.7 million to the regions to test patients with activating mutations of the epidermal growth factor receptor (EGFR) in their tumours. This followed regulatory approval of Iressa (gefitinib) for metastatic non-small cell lung cancer in patients with activating mutations of EGFR. Although there is a cost to the government in offering these tests, there has also been a savings on the cost of medicines. Mr Calvo said that EGFR testing for patients with lung cancer has saved €69 million for the health insurance system because only those patients who could benefit from gefitinib have received the treatment. There are now a number of tests in use in France to help predict a patient’s response to the targeted therapies. These range from KRAS mutation tests for colorectal cancer to V600E mutations in the BRAF gene for melanoma.

The institute is now working on improvements to the system. This involves: elaborating guidelines for the detection of mutations in solid tumours before the targeted therapies are prescribed, and implementing an external quality assessment of the 28 centres.

**Challenges:**

1. Explore at EU level whether the French cancer initiative could be applied elsewhere.
2. Set up systems to ensure the continued quality of molecular tests produced in the EU.
3. Work on ways to increasing patient access to new medicines by identifying new biomarkers early.
4. Make greater use of public-private partnerships to implement existing tests and discover new ones.
Elizabeth Ofili

Associate Dean for Clinical Research, Professor of Medicine, Chief of Cardiology and Director, Clinical Research Centre, Morehouse School of Medicine, Atlanta, Georgia, US

Mrs Ofili gave an overview of a personalised medicine trial that is taking place in the US, the first such trial authorised by the US Centers for Medicare & Medicaid Services (CMS), the agency that reimburses medicines for the elderly and people on low incomes. The study, (Warfarin Adverse Event Reduction for Adults Receiving Genetic Testing at Therapy Initiation), is seeking to establish whether genetic tests can help physicians establish a safe dose for warfarin, one of the most commonly prescribed blood thinners in the world. Warfarin is estimated to cause up to 100,000 serious and unnecessary adverse events a year, including many deaths. The cost to human life, and to the US healthcare system is significant. The study is therefore seeking to establish whether genetic tests can improve dosing, reduce adverse events and generate savings for US healthcare.

Specifically, the study will determine the utility of genetic testing in reducing both bleeding and thromboembolism associated with the initiation of warfarin therapy. Participants in the study will be 65 years of age and older, and will have been on warfarin therapy for at least one month. They will be tested for the VKORC1 gene, which correlates with warfarin sensitivity, and the CYP2C9 gene which correlates with warfarin metabolism. The two genes are estimated to account for up to 40% of individual, variable responses to the medicine. The trial has two arms: the standard arm where the warfarin dose will be calculated on the basis of clinical data and the intervention arm where the dose will be decided using clinical data and genotype information.

The 18-month study is expected to enroll more than 7,000 patients at up to 50 sites in the US; warfarin adverse events will be studied at 30, 60 and 90 days from the initial dosing. In addition to the primary endpoint of a reduction of adverse events, the study’s sponsors are also looking for a reduction in INR tests needed to establish a stable warfarin dose. INR is the international normalised ratio, a measure of the effectiveness of blood-thinning medicines.

Mrs Ofili said that for personalised medicine to be widely adopted in clinical practice, reimbursement authorities need to see evidence that the diagnostic tests and medicines are both effective and financially viable.

Challenge:

1. The adoption of genome medicine relies on well-designed prospective studies with clinical outcomes. Further attention should be paid to the scientific rigour and adequate funding for such studies.
Part 3 - Conference Sessions
Session 1: R&D – the basics

Speakers:
Tim Aitman, Imperial College London, UK
Mathias Uhlén, Swedish Royal Institute of Technology, Sweden
Markus Schwaiger, Technical University of Munich, Germany.

Panelists:
Hinrich Gronemeyer, French National Institute of Health and Medical Research, France
Ivo Gut, National Genome Analysis Centre, Spain
Kerstin Lindblad-Toh, Science for Life Laboratory, Sweden

Session Chair:
Detlef Niese, Novartis Pharma AG, Switzerland

In this session, the speakers and panelists reviewed trends in research and their impact on personalised medicine.

Personalised medicine relies on ‘omics’ technologies to help physicians prescribe the right medicine for the right person. The term ‘omics’ is derived from the suffix ‘ome’ and describes the totality of similar objects in biology. Examples are the term ‘genome’ which describes the totality of the genetic make-up of an individual, or ‘proteome,’ which describes the totality of all proteins in an organism. Similarly, the suffix ‘omics’ refers to the biological disciplines which study such objects like genomics, proteomics, epigenomics, transcriptomics, and metabolomics, just to name a few. In 2001, the international Human Genome Project completed a rough draft of the human genome. From this date onward, genome technology has taken off, leading in 2006 to genome-wide association studies, and in 2008, to whole genome and exome sequencing.

Genomics has made several major contributions to personalised medicine, the speakers said. These include the identification of genes linked to the mechanisms causing several rare diseases; the identification of new therapies for rare diseases and the use of genome-wide association studies to identify new drug targets. Genome-wide association studies examine the genes of different individuals to see how much the genes vary from individual to individual.

There are two major classes of inherited disease: Diseases caused by the mutation of a single gene (also called ‘Mendelian’ diseases and named after Gregor Mendel, a 19th century Austrian priest who first described the principles of genetics), and so-called ‘common, complex diseases’ which are caused by complex interactions of multiple genes and gene mutations. The latter include a large number of common disorders, and the underlying genetic and molecular mechanisms of many of those are still poorly understood. To date, about 3,000 disease genes have been identified out of a total of 7,000 ‘Mendelian’ diseases. Priority should be given to identifying the remaining genes, said one speaker.

Marfan Syndrome, a genetic disorder of the connective tissue, is one example where ‘omics’ technologies helped to unravel the genetic and molecular disease mechanisms, and as a consequence of this, to develop therapy targeting such mechanisms. This rare, single gene disorder is caused by mutations in the fibrillin gene. Transforming growth factor beta (TGF-beta) also plays a role in the disease. Understanding the role of the Marfan gene, and using a mouse model, researchers have been able to develop a potential new treatment for this rare, single-gene disease.
Meanwhile, genome-wide association studies are starting to show their value. Thirty years after the discovery of statins as lipid lowering agents, genome-wide association studies have identified SNPs, or single nucleotide polymorphisms, in the enzyme (HMG-CoA reductase) to be a cause of hypercholesterolaemia, or high cholesterol level. The HMG-CoA reductase enzyme is the target of statins. This raises the question: could genomics have helped discover the statin target? Indeed, genome-wide association studies may in future lead to promising new drug targets.

Another ‘omic’, proteomics, studies the structure and function of proteins. These are the building blocks of life. Just as the Human Genome Project has mapped the human genome, so are researchers in Sweden working on a major project to map the human proteome. The Swedish Human Protein Atlas project, funded by the Knut and Alice Wallenberg Foundation, aims to have a first draft of all protein-coding genes in the human body by 2015.

Similarly, research is taking place to understand the role epigenomics may play in further developing personalised medicine. The epigenome consists of modifications of the genome (often through DNA methylation) that can influence gene expression, without modifying the gene sequence itself. Epigenetic modifications, though not part of the DNA itself, can be passed from cell to cell as they divide. The genetic make-up of cells in an organism is identical, yet there are more than 250 different cells in the human body which are completely different in function and fate. The global epigenetic make-up of each of these cell types is distinct and varies with developmental and environmental signalling and with pathological changes, as well as with ageing. Therefore, epigenetics interprets the genetic information in a cell, development, age, and environmental signal-dependent way. Personalised medicine needs to consider such epigenome dynamics. Most interestingly, epigenetic modifications may be influenced by nutrition.

Finally, the role of imaging in personalised medicine was discussed. Imaging has developed very rapidly in recent years to the point where it is now possible to visualise biological and cellular processes using molecular structures as imaging targets. Modern imaging therefore should lead to the earlier and more specific detection of disease. This has not only facilitated surgery, but also makes it possible to study the pathology and disease pathways of certain disease such as Alzheimer’s disease. One of the newest imaging technologies is a combination of positron emission tomography or PET, with magnetic resonance imaging or MRI.

**Challenges:**

1. Make greater use of genome-wide-association studies and other ‘omics’ technologies to improve the understanding of molecular disease mechanisms, and by consequence the search for new drug targets.
2. Develop new animal models to test potential treatments for single-gene diseases.
3. Develop new treatments for single-gene diseases.
4. Explore drug targets identified through epigenomics.
5. Maintain Europe’s lead in the field of proteomics.
7. Support the commercialisation of new imaging technologies. Develop new imaging standards.
8. Make optimal use of mathematics, computer modeling and simulation to translate information from ‘omics’ research into clinically relevant products and technologies.
10. Support and develop standardised data collection and biobanking for disease cohorts.
Session 2: Biomarkers in personalised medicine

Speakers:
Catherine Larue, Bio-Rad Laboratories, France
Charles Swanton, Cancer Research UK
Krishna Prasad, Medicines and Healthcare products Regulatory Agency, UK.

Panelists:
Thomas Beyer, CMI Experts, Switzerland
Magnus Ingelman-Sundberg, Karolinska Institute, Sweden
Alastair Kent, European Platform for Patient Organisations, Science and Industry, Belgium
Andreas Schuppert, Bayer Technology Services, Germany

Session Chair:
Romano Danesi, University of Pisa, Italy

This session dealt with the role of biomarkers in personalised medicine.

Discussions focused on the definition of biomarkers, methods of validation, and their potential use in clinical practice. Other issues raised during the session included the role of imaging in personalised medicine; the need to standardise all aspects of biomarker development, including tissue collection, as well as data management systems. The issues of biomarker qualification and clinical validation were also discussed.

What then is a biomarker? The session adopted a definition formulated by the US National Institutes of Health. This defines a biomarker as a “characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.” Biomarkers can be molecules such as proteins, but more generally they are any measurable and evaluable indicator of a health condition. Hence they can enable the assessment of a pharmacological response to a therapeutic intervention. In a personalised medicine setting, they are the tools that make it possible to identify the "right medicine for the right patient".

The session heard about four types of biomarkers. They were explained as follows:

**Diagnostic biomarkers.** These are markers that can diagnose a specific disease as early as possible. An example is an RNA test for the Hepatitis C virus that can be used four weeks after an acute HCV infection to predict chronic infection;

**Susceptibility/risk biomarkers.** These are markers that can predict the risk of developing a disease. An example is the test for mutations in the BRCA1 gene which can signal a risk for breast cancer;

**Prognostic biomarkers.** These are markers that predict the evolution of a disease, such as whether it is likely to be indolent or aggressive. Prognostic biomarkers can also be predictive. An example is the test for human epidermal growth factor receptor 2 (HER2) which is an indicator of the more aggressive breast cancers;

**Predictive biomarkers.** These are markers that predict the response of a patient to a treatment and the toxicity of that treatment. An example is the test for mutations of the epidermal growth factor receptor (EGFR), which predict a patient’s response to the non-small cell lung cancer medicine, Iressa (gefitinib).
Biomarkers can also be used for:

- Defining disease subsets. An example is the use of the HER2 marker to guide prescriptions of Herceptin (trastuzumab) for metastatic breast cancer;

- Identifying population subsets likely to respond to specific treatment. An example is testing for tropisms in HIV before prescribing the antiretroviral therapeutic, maraviroc. Only patients with exclusively CCR5-tropic HIV are considered eligible for the treatment;

- Identifying patients who are unlikely to benefit from a treatment and may suffer adverse events from it. Examples are tests for the mutated KRAS gene to exclude panitumamab from patients with colorectal cancer, and testing for the HLA-B gene in patients with AIDS because they are likely to have an allergic reaction to the medicine, abacavir;

- Finding patients with high-risk factors in planning risk-reduction strategies for new treatments.

Getting more biomarkers validated is both a technical and a regulatory issue. The need for new technology arises because the ‘omics’ disciplines are generating more knowledge. With whole genome sequencing becoming more common, it will be necessary to develop new mathematical and statistical tools to deal with huge amounts of new data. And this data will have to be stored and analysed using common standards. Companies will also require access to well-characterised biobanks. Thus far, no biomarker inventory has been established in Europe.

Regulatory issues arise because there are different procedures in Europe for approving medicines and their companion diagnostics and these procedures in turn, are different from those in force in the US. Nevertheless, the FDA and the European Medicines Agency (EMA) have been working together to qualify biomarkers for use in medicine development. This issue was discussed in more detail in Session 3.

During the session, participants also discussed the potential of imaging techniques for use in personalised medicine. For example biologic features detectable by imaging (imaging biomarkers) can help healthcare professionals predict a patient’s response to a new therapy.

Challenges:

1. There is a need for high throughput screening platforms to identify biomarkers more quickly and cost-effectively; there is also a need for new validation techniques for candidate biomarkers.
2. Tools and methods need to be developed for the functional analysis of cells.
3. There is a need to standardise how specimens are collected within clinical trials, or for routine purposes and how data-sets are analysed.
4. European guidelines are needed for biomarker qualification and clinical validation.
5. Take advantage of new imaging technologies to understand biological mechanisms, including toxicity, at the molecular, whole organ, and whole body level.
6. Standard Operating Procedures (SOPs) are needed for tissue collection and analytical procedures.
7. A Europe-wide biobanking network is needed.
8. The issue of medicine-diagnostic codevelopment should be looked at.
9. Ethically compliant electronic patient records should be developed to inform biomarker research.
Session 3: The tests in human – clinical aspects and clinical research

Speakers:
Anne De Bock, AstraZeneca Plc, Belgium
Munir Pirmohamed, University of Liverpool, UK

Panelists:
Jane Kaye, Oxford University, UK
Denis Lacombe, European Organisation for Research and Treatment of Cancer, Belgium
Cees Smit, Patients Network for Medical Research and Health, the Netherlands
Anne-Mieke Vandamme, Katholieke Universiteit Leuven, Belgium

Session Chair:
Ingrid Klingmann, European Forum for Good Clinical Practice, Belgium

This session dealt with the challenges of bringing biomarker-based medicines into clinical practice.

It featured a case study of a personalised medicine that was approved for marketing in Europe in 2009 for patients with a specific gene mutation – but only after years of trial and error. The medicine is Iressa (gefitinib/AstraZeneca Plc) and it was approved by the European Commission in 2009 for the treatment of adults with non-small cell lung cancer who have mutations of the epidermal growth factor receptor (EGFR) gene. Iressa was the first selective inhibitor of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR). It is thus an EGFR inhibitor. In normal cells, messenger proteins bind to EGFR and activate signalling proteins, leading to cell proliferation. When this signalling system is over-activated, cells can proliferate uncontrollably, leading to cancers such as non-small cell lung cancer.

Iressa was first approved in the US in 2003 by the Food and Drug Administration under an accelerated registration procedure as a single agent for patients with lung cancer who were not responding to chemotherapy. Two years later however, the FDA restricted the label after a follow-up study showed that the medicine delivered no significant survival benefit. AstraZeneca continued to develop the medicine and subsequently found that a subset of lung cancer patients who had a genetic mutation (activating mutations of EGFR-tyrosine kinase) responded convincingly to the medicine. This finding enabled the company to secure its European approval in 2009. The turning point for the medicine was the discovery of these somatic mutations.

The predictive biomarker for Iressa was discovered by an AstraZeneca collaborator about seven years after the start of clinical trials. The product had entered the clinic in 1998. It then took a further 4.5 years of retrospective research to show a significant increase in clinical benefit for those patients identified by the diagnostic test.

The session was told that future developers of personalised therapies will have learned something from this episode and are likely to take a more proactive approach to biomarker development. Developers need to identify predictive markers at the preclinical stage - before the start of clinical development. They should also work with payers and healthcare authorities to ensure that the medicine is targeted towards those patients most likely to respond.

In another presentation, the session heard that evidence of a biomarker’s accuracy is crucial. If more biomarkers are to get into clinical practice, then developers need access to biobanks
to test their hypotheses. Clinical testing was also said to require more harmonisation of ethical and regulatory requirements than exists at present.

While the new targeted cancer therapies are leading the way in personalised medicine, there is also a need to make generic medicines more effective, by better targeting/personalisation. Generics constitute the majority of prescribed medicines for most people in most countries. Yet, with the exception of the warfarin study, there do not appear to be many studies aimed at improving their safety and effectiveness. The issue therefore is, who will fund studies on generic medicines and is there an incentive for diagnostic companies to participate?

It was highlighted that it is a long road from initial research to clinical utility (it is already a long road to reach biomarker validation). Thus, there is a need to manage patient expectations by being candid about the difficulties.

**Challenges:**

1. Develop Europe-wide biobanking.
2. Develop new trial methodologies including adaptive clinical trial design.
3. Promote the development and use of electronic patient records; use these electronic records to inform biomarker research.
4. Provide biomarker studies of generic medicines.
5. Consider the use of all types of biomarkers, not just molecular ones (also functional, imaging, etc).
6. Many approaches (multi-modality) and not just medicines, are needed in achieving personalised healthcare.
7. Standardise insurance requirements for clinical trials in Europe.
Session 4: Towards the market and patients – approval process

Speakers:
Thomas Metcalfe, European Biopharmaceutical Enterprises, Belgium
Marisa Papaluca-Amati, European Medicines Agency, UK
Anne Van Nerom, Scientific Institute of Public Health, Belgium

Panelists:
Deborah Braun, bioMérieux, France
Ian Cree, Queen Alexandra Hospital, UK
Carlo Incerti, Genzyme, Italy
Milan Macek, Charles University, Czech Republic

Session Chair:
Alain Huriez, TcLand Expression, France

This session examined the complex regulatory issues that apply to personalised medicine.

Some of the complexity relates to the structure of Europe’s regulatory system. Here, medicines with companion diagnostics fall under two regulatory systems: there is a pathway for pharmaceuticals, and there is another pathway for medical devices, which include diagnostics. Under the EU pharmaceutical legislation, innovative medicinal products are as a general rule subject to authorisation by the European Commission in a centralised procedure, following a scientific assessment at the European Medicines Agency in London. Diagnostics (including companion diagnostics/biomarkers), on the other hand, are reviewed under a decentralised system involving independent European notified bodies. By contrast in the US, the Food and Drug Administration assesses and approves medicines and diagnostics under one roof. To what extent should the European system move towards the US model? Or should Europe keep its hybrid model? This issue was discussed, but no conclusion was reached.

Personalised medicine is also about the use of molecular tests in medicine development. Here, many issues are common to both Europe and the US. Issues discussed included how biomarkers can be used to stratify patients in a trial, what types of adaptive trial designs are possible and what clinical endpoints are appropriate, i.e. can biomarkers be used as surrogate endpoints for personalised medicine trials? Whether regulators should allow the use of retrospectively-generated data to validate the clinical utility of biomarkers was also a topic of discussion.

The EMA is already tackling some of these issues through its Innovation Task Force and its scientific advice procedure. Companies can meet with the task force to discuss methods for characterising and validating biomarkers. And they can meet with scientific advice teams to discuss all aspects of medicine development. The agency also arranges about 400 scientific advice sessions per year; an increasing number of these sessions are devoted to personalised medicine development. The EMA has also set up a procedure for qualifying biomarkers for use in clinical trials.

Two pieces of European legislation that affect personalised medicine are under review at the European Commission. The first is the Clinical Trials Directive (Directive 2001/20/EC) and the second is the Directive on in vitro diagnostic medical devices (Directive 98/79/EC). A presentation at the session focused on the revision of the in vitro diagnostic medical devices directive. During a recent consultation on proposed revisions to the directive, an overwhelming majority of respondents supported a move to a risk-based classification system.
based on the GHTF (Global Harmonisation Task Force) system. This would mean classifying devices according to their risk, according to some defined classification rules.

Participants generally supported the hybrid approach. But a representative from industry told the meeting that his peers were looking for closer interaction between the medicine and diagnostic regulators during the development phase of personalised medicines.

Panelists commented on the need for standard operating procedures for pathology and radiology laboratories across Europe and for better accreditation procedures. Others called for “an improved framework for regulatory decisions” and for more patient involvement. Finally, a participant noted that information from post-marketing studies could usefully be fed back into the regulatory process to inform the trial designs of future personalised medicines.

**Challenges:**

1. European clinical testing laboratories (both industry and hospital based) require clear regulatory standards and a stable reimbursement environment. Guidance is needed on which clinical endpoints are considered to deliver patient and societal value; guidance is also needed on innovative clinical trial designs and for the use of retrospectively generated data sets.

2. More investment is required in translational medicine, especially in applied molecular profiling and imaging technologies.

3. A uniform quality framework and delivery infrastructure that maximises patient access is needed for companion diagnostic testing in Europe.

4. More unified and coordinated accreditation procedures should be established for European clinical testing laboratories.

5. There should be a more focused and coordinated effort to use patient registries, patient biological samples, and patient outcome data in a targeted personalised medicine development programme with results published in a timely manner.
Session 5: Uptake in healthcare – post-approval process

Speakers:
Richard Bergström, EFPIA, Belgium
Katherine Payne, University of Manchester, UK
Anna Bucsics, Austrian Social Insurance Institutions, Austria

Panelists:
Angela Brand, Maastricht University, the Netherlands
Finn Børlum Kristensen, National Board of Health, Denmark
Mirella Marlow, National Institute for Health and Clinical Excellence, UK
Clare McGrath, Senior Director, HTA Policy, Europe, Pfizer, UK

Session Chair:
Tim Kievits, PamGene, the Netherlands

What is the value proposition for personalised medicines to companies, to payers and to patients? The answer to this question is not necessarily the same for all three players. In this session, representatives from industry, from a social insurer, and a health economist all spoke about the challenges ahead.

For industry, the key issue is finding a way to derive information about patient benefit following the prescribing of a personalised medicine. The assumption is that insurers will most likely pay for a therapy if they know it will be cost effective. But few healthcare bodies are today able to measure patient outcomes for molecularly-targeted therapies. These bodies are also not yet equipped to assess composite, eg medicine-devise, products from multiple suppliers. For both large and small pharmaceutical companies active in the area, personalised medicine also requires finding innovative business models to secure funding and ensure a viable return on investment.

For the health insurer, the key issues are: 1) how to establish the validity of biomarkers 2) how to find out whether the level and quality of evidence for a diagnostic is comparable to that for a pharmaceutical and 3) how to assess two interdependent dossiers.

A concern for insurers is that future personalised medicines, like orphan medicines, will be developed for small populations and therefore may be priced very aggressively. This will put pressure on public healthcare budgets.

For the health economist, the key issue is measuring the benefit derived from the use of a gene test, or another molecular diagnostic, in a personalised medicine. The most common measure of health economic benefit is the QALY (quality-adjusted life year), or the measure of disease burden, based on the quality and number of years of life a patient would gain by receiving an intervention. Using this formula, the economist can measure the cost of the new medicine relative to the QALYs gained by looking at responders and non-responders. In theory, the addition of, for example, a gene test should increase the response rate. The question therefore is: do targeted medicines with companion tests both save money and increase QALYs?
Challenges:

1. Research should be undertaken to better measure patient outcomes in the context of personalised medicines.
2. Discussions between medicine regulators, health technology bodies and industry about measuring efficacy/effectiveness should continue.
3. The regulation of the components of personalised medicine (e.g., medicines and diagnostics) should be coordinated. A central role for the European Medicines Agency was mentioned as a possible solution.
4. Research into viable business models to help support the introduction of personalised medicine and related technologies should be initiated.
The most advanced area in personalised medicine is without doubt cancer, but another area where personalised medicine also has been used is for the improvement of treatment outcomes for patients with HIV. Several tests have been developed and are in use for the prescription of HIV/AIDS treatments. But as with most advances, new problems arise. Some of them are technical; others are ethical. The new tests are sometimes difficult to evaluate, and they are expensive. They also raise issues around informed consent. Do patients know with whom the data from their blood samples is shared? And while disease prevention, or even cure, is the goal of HIV/AIDS treatment, is society prepared to reintegrate patients who have recovered from the disease?

Meanwhile, from the clinician’s perspective, the new biomarkers and diagnostics that are meant to improve patient outcomes and reduce adverse events must show "clinical added value". And in addition to searching for new biomarkers, better use should be made of those already existing (eg. those that monitor kidney function at baseline or those that check the organism load of toxic compounds) as there is room for further clinical progress with the tools that we already have.

Another important issue is training. Doctors will need to be trained in a number of disciplines in order to understand and be able to use all the sophisticated tools that will be at their disposal for personalised medicine. And once trained, they should have access to diagnostic and treatment facilities to administer this care in line with the EU principle of health equality and universal access to medicine. The speakers all agreed on the need for collaboration to accelerate the translation of personalised medicine into clinical practice and to prevent disease. Patient involvement in the process is essential. Currently this is not given sufficient attention.

A recurrent issue raised throughout the conference was the need to ensure better collaboration between biologists and clinicians. Such collaborations are necessary to translation of new scientific breakthroughs to clinical applications but do not seem to happen spontaneously and should therefore be encouraged, in particular by research funders. As an example of the cultural differences the review of articles for publication was given. Clinicians often give very low review marks for biological articles whereas biologists give low marks for clinical papers. Efforts should be made to break up such silos of competencies and also to further integrate patient aspects into the early stages of research.
Challenges:

1. Explore what the barriers are to achieve clinical added value by the introduction of personalised medicine approaches.
2. Provide more education and training to clinicians in the use of the new diagnostics, and make sure the required facilities are easily available.
3. Make better use of the biomarkers that we already have before introducing new ones.
4. Get all stakeholders to collaborate in translating research into clinical practice, with an emphasis on patient participation.
5. Explore the social consequences, eg insurance and employment, for patients who overcome a serious or debilitating disease. Are there mechanisms for reintegrating them into society?
Part 4 - Conclusion
The goal of medical practice has always been to provide the best possible care for patients. But this is an evolving concept. Best medical practice is a function of what is known about human disease at any given point in time. In the past, diseases were largely defined in terms of the organs or bodily systems that they affected. Molecular biology has changed this approach because it facilitates an understanding of disease at a cellular level. This represents a paradigm shift in our understanding of illness. Among other things, it means that diseases which we now consider ‘common’ may in fact be a bundle of different diseases. Or that diseases, which we now classify as ‘rare’, may in fact have similarities to one another at a molecular level. Personalised medicine is a description of the way this new knowledge can be captured in medical practice.

Personalised medicine starts with the patient. Using the tools of molecular biology, patients can be sub-divided into groups based on their individual characteristics, or molecular profiles. The molecular profiles make it possible for clinicians to decide which medicines are best suited for which patient groups. This is expected to increase the effectiveness of existing and future treatments as well as to reduce adverse events.

Fine-tuning medical care in this way must necessarily involve improving diagnostic tools such as imaging and genetic tests and integrating them into clinical practice. It also means coming up with new concepts of ‘value’ because the benefits of personalised medicine will be different from those of conventional medicines of the past.

Personalised medicine will require an unprecedented degree of collaboration amongst all of the players in the medical innovation cycle. This starts with the researchers who characterise the disease and elucidate its mechanisms, to the companies that exploit this knowledge by developing new biomarkers, diagnostics and drugs, to the regulators who evaluate and approve them. The chain then continues to include the health technology assessors who establish value, the health authorities who decide reimbursement and the healthcare professionals who administer the medicines to patients. Along the way, a multitude of other players are needed to help the process along.

Many challenges will need to be overcome. For example, the successful uptake of personalised medicine will require common standards for everything from tissue collection, to the management of biobanks, to the collection and analysis of data from clinical trials. It will also require new regulatory approaches, innovative clinical trial designs and a higher level of cooperation among health technology bodies and payers. Industry will need to explore new business models with a further focus on co-operation between different industry sectors and with academia, including public-private partnerships. In addition, healthcare professionals and patients will need to be educated in how to deal with these new personal approaches and ethical aspects, including health equity and solidarity, should be emphasised.

As stated above, we have only just embarked upon the process towards truly personalised medicine. It is clear that a long-term coordinated and holistic approach to innovation is required to bring personalised medicine into clinical practice, and that these challenges will need to be addressed at European, national, regional and local levels.
Some of the key research challenges, grouped into four main themes, are summarised in the list below. A comprehensive list of all challenges identified and discussed during the two-day conference, can be found in the appendix.

**Breaking barriers and speaking the same language**
- Facilitate collaboration between different disciplines from basic to clinical research including biology, mathematics, statistics, pathology and medicine.
- Create interfaces for collaborations and discussions among stakeholders including: basic researchers, pathologists, clinicians, patients, industry, regulators and payers.
- Enable rapid integration of knowledge about relevant novel technologies and new scientific approaches in education and training curricula.

**Generating knowledge and developing the right tools**
- Adapt many research tools for use in clinical settings.
- Set standards for data and sample collection and for analytical procedures together with harmonised, comprehensive coding systems, as well as novel statistical methods and algorithms for analysis of large volumes of complex and heterogeneous data sets.
- Link clinical data with molecular profiles (clinical bioinformatics) and facilitate development of novel algorithms to explore the complex signatures obtained from "-omics" platforms that in the long term can lead to molecular definition of disease in addition to or replacing the clinical definition.
- Translate "-omics" research into clinical applications, starting with rare (monogenic) diseases, and in population cohorts that are gender and age stratified and with a core set of phenotype information on health status including lifestyle data, diets and exposures to environmental and other factors.

**Translation to medical applications**
- Develop new approaches and methodologies for identification and validation of biomarkers.
- Enable identification, qualification and clinical validation of all types of biomarkers (including imaging biomarkers).
- Make better use of biomarkers in existing therapies.
- Facilitate adapted clinical trial methodologies for stratified and/or small populations.

**Economic aspects**
- Undertake studies on impact for patients, and on the economic viability of personalised approaches in health care systems.
- Develop methodologies for health technology assessment (HTA); and HTA assessments of personalised medicine approaches taking into account the therapy as well as the predictive/diagnostic tools.
- Carry out comparative cost effectiveness and other pharmaco-economic studies on personalised medicine approaches.
Appendix – List of challenges
Consolidated list of challenges identified at the conference sessions

**Plenary, Jonathan Knowles**

1. Fund more and better studies aimed at re-classifying human disease at a molecular level; in particular conduct studies involving very well defined patient samples.
2. Fund studies on novel clinical trial designs using prospective observational studies in order to show how better decisions based on molecular data lead to more cost-effective and much better outcomes for patients.
3. Change the way in which patient information is generated in clinical practice to enable evidence to support change in treatment practices.
4. Encourage a shift from companion diagnostics for each therapy to an approach that uses the molecular definition of what combination of therapies is suitable for each individual patient.
5. Encourage novel partnerships and collaborations to achieve the above, for example by bringing biologists and clinicians together.
6. Require researchers that receive public funds to define the patient populations in their studies as a prerequisite for receiving funding.

**Plenary, Axel Ullrich**

1. Continue studies into the human genome and into the development of new prognostic biomarkers.

**Plenary, Fabien Calvo**

1. Explore at EU level whether the French cancer initiative could be applied elsewhere.
2. Set up systems to ensure the continued quality of molecular tests produced in the EU.
3. Work on ways to increasing patient access to new medicines by identifying new biomarkers early.
4. Make greater use of public-private partnerships to implement existing tests and discover new ones.

**Plenary, Elizabeth Ofili**

1. The adoption of genome medicine relies on well-designed prospective studies with clinical outcomes. Further attention should be paid to the scientific rigour and adequate funding for such studies.
Session 1: R&D – the basics

1. Make greater use of genome-wide-association studies and other ‘omics’ technologies to improve the understanding of molecular disease mechanisms, and by consequence the search for new drug targets.
2. Develop new animal models to test potential treatments for single-gene diseases.
3. Develop new treatments for single-gene diseases.
4. Explore drug targets identified through epigenomics.
5. Maintain Europe’s lead in the field of proteomics.
7. Support the commercialisation of new imaging technologies. Develop new imaging standards.
8. Make optimal use of mathematics, computer modeling and simulation to translate information from ‘omics’ research into clinically relevant products and technologies.
9. Nurture multidisciplinary research bringing together clinicians and -omics specialists.
10. Support and develop standardised data collection and biobanking for disease cohorts.

Session 2: Biomarkers in personalised medicine

1. There is a need for high throughput screening platforms to identify biomarkers more quickly and cost-effectively; there is also a need for new validation techniques for candidate biomarkers.
2. Tools and methods need to be developed for the functional analysis of cells.
3. There is a need to standardise how specimens are collected within clinical trials, or for routine purposes and how data-sets are analysed.
4. European guidelines are needed for biomarker qualification and clinical validation.
5. Take advantage of new imaging technologies to understand biological mechanisms, including toxicity, at the molecular, whole organ, and whole body level.
6. Standard Operating Procedures (SOPs) are needed for tissue collection and analytical procedures.
7. A Europe-wide biobanking network is needed.
8. The issue of medicine-diagnostic co-development should be looked at.
9. Ethically compliant electronic patient records should be developed to inform biomarker research.

Session 3: The tests in humans – clinical aspects and clinical research

1. Develop Europe-wide biobanking.
2. Develop new trial methodologies including adaptive clinical trial design.
3. Promote the development and use of electronic patient records; use these electronic records to inform biomarker research.
4. Provide biomarker studies of generic medicines.
5. Consider the use of all types of biomarkers, not just molecular ones (also functional, imaging, etc).
6. Many approaches (multi-modality) and not just medicines, are needed in achieving personalised healthcare.
7. Standardise insurance requirements for clinical trials in Europe.
Session 4: Towards the market and patients – approval process

1. European clinical testing laboratories (both industry and hospital based) require clear regulatory standards and a stable reimbursement environment. Guidance is needed on which clinical endpoints are considered to deliver patient and societal value; guidance is also needed on innovative clinical trial designs and for the use of retrospectively generated data sets.

2. More investment is required in translational medicine, especially in applied molecular profiling and imaging technologies.

3. A uniform quality framework and delivery infrastructure that maximizes patient access is needed for companion diagnostic testing in Europe.

4. More unified and coordinated accreditation procedures should be established for European clinical testing laboratories.

5. There should be a more focused and coordinated effort to use patient registries, patient biological samples, and patient outcome data in a targeted personalized medicine development programme with results published in a timely manner.

Session 5: Uptake in healthcare – post-approval process

1. Research should be undertaken to better measure patient outcomes in the context of personalized medicines.

2. Discussions between medicine regulators, health technology bodies and industry about measuring efficacy/effectiveness should continue.

3. The regulation of the components of personalized medicine (eg, medicines and diagnostics) should be coordinated. A central role for the European Medicines Agency was mentioned as a possible solution.

4. Research into viable business models to help support the introduction of personalized medicine and related technologies should be initiated.

Session 6: In the clinic – practitioner and patient perspectives

1. Explore what the barriers are to achieve clinical added value by the introduction of personalized medicine approaches.

2. Provide more education and training to clinicians in the use of the new diagnostics, and make sure the required facilities are easily available.

3. Make better use of the biomarkers that we already have before introducing new ones.

4. Get all stakeholders to collaborate in translating research into clinical practice, with an emphasis on patient participation.

5. Explore the social consequences, eg insurance and employment, for patients who overcome a serious or debilitating disease. Are there mechanisms for reintegrating them into society?
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The process towards personalised medicine, aimed at better predicting, preventing and treating or curing diseases based on a patient’s individual characteristics, is gaining pace in Europe. A long term structured approach to foster innovation in this area and to facilitate the rapid uptake of personalised medicine into clinical practice is therefore needed.

The conference European Perspectives in Personalised Medicine was held in Brussels, Belgium on 12-13 May 2011. It brought together stakeholders involved in all areas of personalised medicine and aimed at identifying key challenges requiring action at European level to progress research, development and implementation of personalised medicine in healthcare.