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INNOVATION and PATIENT ACCESS to PERSONALISED MEDICINE

Report from Irish Presidency Conference March 20th/21st 2013

The European Alliance for Personalised Medicine brings together healthcare experts and patient advocates on major chronic diseases to improve patient care by accelerating the development, delivery and uptake of personalised medicine and diagnostics. The aim is to promote alignment among diverse views and priorities, and to bridge the gap between lay and professional perceptions of innovation. It is an ambitious agenda, but one that can help transform healthcare and the quality of life for Europeans, by ensuring that European medicine is at the forefront of putting science at the service of citizens.

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Executive Summary

Major advances in healthcare are just around the corner, with a wealth of new possibilities promised for European patients and society through the increased adoption of personalised approaches to medicine. Personalised medicine looks at health information from single patients, using the new and detailed information now becoming available through advances in science and technology. It could provide better prevention and treatment and a more efficient and cost-effective healthcare system.

But if the potential is to be realised, changes will be necessary in the way medicines are developed, regulated, and rewarded. Greater collaboration will be needed across a wide range of actors in healthcare. And systems will need to catch up with science. This report summarises some of the catching-up that has to take place. It reflects contributions from stakeholders and conclusions from the conference "Innovation and patient access to personalised medicine", which took place in Dublin on 21st and 22nd March under the auspices of the Irish EU Presidency. It also emphasises that the changes needed require early engagement from researchers, patients, policy-makers, regulators and payers. The essential changes are needed in the following areas:

Research

- more multidisciplinary research, with closer collaboration between drug and diagnostic developers, clinicians, biologists, biostatisticians and information and communications technology.
- infrastructures that can support large screening platforms to identify target populations, and that provide relevant IT tools such as simulation or computer assisted decision.
- increased basic and collaborative pre-competitive research into biomarkers
- additional funding for international academic clinical trials in all disease areas.
- ICT that can support lifelong monitoring and deliver meaningful information on risk prediction, molecular and physiological phenotyping, treatment outcomes and monitoring in a form that supports clinical decision-making.

Regulation

- simplified, harmonised and more predictable regulatory procedures across Europe, so as to reduce unnecessary costs and administrative burdens and to promote international clinical research.

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- closer dialogue among decision-makers and manufacturers from early in development and along the life-cycle of products, to better identify requirements and reduce duplication.
- adapted regulatory pathways to assist with the efficient translation of new therapies from the lab to the patients and support for their timely access to targeted medicines.
- benefit and risk to be evaluated on real life data, with patients, policy makers and payers as active participants in the process.
- acceptance of observational studies, making use of harmonised and standardised data on all available patients from clinical registries to demonstrate effectiveness.
- coherence in legislation relating to authorisation of medicines and diagnostics, data protection, the use of specimens, or medical devices.

Incentives for innovation

- new methods for calculating the benefit and risk of medicines and companion diagnostics, taking account of benefits to society.
- revised systems for assessing, investing in and rewarding the new technologies that will put personalised medicine within reach.
- a new reimbursement model, using managed entry agreements and value-based pricing, with more coordination among authorities on measurement of efficacy and effectiveness.
- faster procedures for bringing new medicines to patients.

Making better use of data

- seamless access to medical data, wider sharing, and data protection rules that recognise the merits of research and re-use of data and safeguard personal privacy through apt consent arrangements.
- faster take-up and wider use of new technologies and mechanisms for data capture and data processing.
- standardisation of data and quality of data, to permit integration and interpretation of information from multiple sources and link findings to specific outcomes in individual citizens.
- greater use of sophisticated analysis methods and mathematical modeling approaches to create robust models of disease that help develop targeted therapies.

Education

- initiatives to provide formal educational approaches within industry and among regulators on the required statistical science.
- investments in resources and know-how, to widen awareness and ability amongst physicians in the use of companion diagnostic/drug therapies, and to ensure

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sustainable career paths for trained professionals.
- teams of competent personnel in hospitals and labs to permit efficient and rapid biomarker testing and allow drug/diagnostic combinations to benefit patients.
- creation of the intellectual and communications infrastructure to support cross-disciplinary interaction and training for ICT and healthcare professionals.
- promotion of health literacy among patients and the public, and provision of credible information about benefit and risk of diagnostic and therapeutic interventions.

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Foreword

by Tonio Borg Commissioner for Health and Consumer Affairs

Personalised medicine is a promising concept. As patients are divided into groups based on their individual, biological, genetic and genomic characteristics, medical interventions are tailored to those patients' needs. Hence, this new approach can help reduce the risk of undesirable adverse reactions, and at the same time make medicine more effective. Personalised medicine is an innovative, efficient and patient-centred alternative to the one-size-fits-all medicine. And it also yields a maximum return on healthcare investment - a valuable argument for decision-makers in times of austerity.

Ensuring patients' access to safe, quality treatment lies at the very heart of our European policies, and personalised medicine is part of our plans for the future of European healthcare. We are currently improving the legal framework for clinical trials and medical devices, which will benefit personalised medicine. Once adopted, the new Regulation on Clinical Trials will facilitate multi-national trials. This is critical for the testing of personalised medicine, which often requires cross-border clinical trials to meet the necessary target population. The proposed Regulation on Medical Devices will reinforce the current regime for in vitro diagnostics in order to ensure an appropriate level of safety and performance specific to those tests.

Finally, the EU Network on Health Technology Assessment enables Member States to exchange information on scientific developments and achievements, thereby reducing duplication of efforts.

The move towards personalised medicine is an evolutionary process. Although some personalised medicine treatments are already available on the European market, there is still a long way to go to turn personalised medicine into a widespread approach to illness.

This is why I wish to congratulate the European Alliance for Personalised Medicine, and to reiterate our support for their relentless work. By fostering cooperation between all stakeholders, they help create the right conditions for personalised medicine to be taken up and to be easily accessible to patients.

Together, we can make science deliver better for European patients.

Tonio Borg
European Commissioner for Health and Consumer Affairs

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1. Personalised medicine and the innovation agenda:

An integrated approach with the patient at the centre

Personalised medicine starts with the patient. In practice, rather than having a unique treatment for each individual person, patients are sub-divided into groups based on their "molecular make up", i.e. using biomarkers. By this stratification of patients, medical interventions can be tailored to be more effective in a particular group of patients. Personalised medicine most frequently refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and stratified prevention. It may also involve imaging and other technologies.

This rapidly developing science-driven approach to health care has potentially very high benefits for patients, clinicians and health care systems alike. Advantages may include the ability to make more informed medical decisions; a higher probability of desired outcomes thanks to better-targeted therapies; a reduced probability of adverse reactions to medicines; a focus on prevention and prediction of disease rather than reaction to it; earlier disease intervention than has been possible in the past; and improved healthcare cost-containment.

The Commission Communication of 2008 on a Renewed Vision of the Pharmaceutical Sector remarked that "With the emergence of new technologies like pharmacogenomics and patient-specific modelling and disease simulators, personalised medicine is now on the horizon. In the long term, doctors may be able to use genetic information to determine the right medicines, at the right dose and time. This field is already affecting companies' business strategies, the design of clinical trials and the way medicines are prescribed".

Personalised medicine is being taken into account to some extent in recent EU legislative initiatives, including the proposals to update rules on medical devices and on clinical trials, and the new pharmacovigilance regime. But medicines and the corresponding diagnostic devices at the heart of personalised medicine are still subject to distinct regulatory frameworks. Similarly,

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legislation for patients to directly report adverse events - which could facilitate integration of pharmacogenomic data into medical care - will require an informed patient. At the same time, while linking adverse-reaction reporting to pharmacogenetic studies could boost development of a knowledge base and help identify factors that increase the risk of adverse events, adequate provision will be needed in data protection legislation.

2. Data privacy and consent

Conclusions:

- the creation of a legal framework for personal data processing in scientific research and regulation that exploits technology to strengthen data security and to ease access and consent, allowing re-use and secondary use of data

- international transfers of personal data for biomedical research purposes where appropriate privacy accountability mechanisms have been implemented.

- new levels of trust between the research community and participants and patients

- elimination of silos of single-use data and removal of country-specific gridlocks

- equal treatment of all health research data, including genetic information

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The development of personalised medicine depends on easier circulation of personal health data for scientific research purposes – with, of course, appropriate safeguards.

Combining abundant and intricate health data with innovative analysis strategies in a multidisciplinary setting can generate powerful models of complex diseases, and lead to new forms of diagnosis, treatment and prevention. But this implies circulating and sharing personal health data among data experts and medical specialists who can, together, derive the most apt interpretation and extend understanding. At the same time, a society conscious of the importance of personal rights as well as of the importance of personal health legitimately demands a balance between the circulation of data and data privacy. Without adequate resolution of this innate tension, the benefits of personalised medicine will be delayed and perhaps lost. So all stakeholders - especially patients, research participants, healthcare professionals and the public - should be engaged in exploring the best balance between these distinct priorities.

Inappropriate regulations impede cooperative research - particularly across borders - and prevent researchers from mining existing archival data that could lead to new discoveries. Current data privacy provisions may require destruction of data, prohibit use of genetic data, prevent cross-border access, or require explicit consent for re-use. The increasing demands from regulatory authorities for evaluation of medicines in real-life settings require continued access to personal health data.

Unnecessarily complex data protection rules impede biomedical progress. The issue is how to achieve the best possible harmony between distinct regimes and systems of governance that can foster biomedical innovation while respecting individuals' rights to data privacy. Some of the barriers to data circulation are cultural, some are regulatory, and some are simply the consequence of insufficient technical methods for obtaining consent, or the absence of appropriate legal frameworks for obtaining, safeguarding and disclosing data. Arrangements for consent can go a long way towards resolving this tension. Patients are also becoming more alert to the possibilities of allowing sharing of their data. A better understanding, based on trust, between data subjects (and the public) and users of data will make it possible to put data to use for the benefit of healthcare in general as well as for individual patients.

For more details, see the annex, page 32: "Mission: easier circulation and sharing of personal data, appropriately balanced with personal privacy"

3. Moving research results into health systems:

Innovative translational models

Conclusions:

- a new business model that can benefit patients, society, industry and healthcare budgets

- support for public-private partnerships that promote multi-stakeholder collaboration

- regulatory and legislative change that reflects the realities of science and of citizens' needs

- incentives for business models that ensure early patient access to health innovations

- more systematic engagement of all stakeholders, including patients

Science has led to major advances in the understanding of the role of genomics in diseases, in the discovery of biomarkers, in the development of new statistical methods and in the invention of dynamic tools for collecting real-world effectiveness and safety data. The opportunity exists to move beyond the current symptom-based approach to diseases.

But to create effective new methods of diagnosis, treatment and prevention, scientific evidence must be translated into patient access. The current R&D and regulatory processes are ill-adapted, and need adapting to a new understanding of disease biology. Promoting

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innovation will require organisational change to move more efficiently from science to R&D, with greater certainty from product development to product authorisation, and more rapidly from authorisation to patient access.

This means permitting adapted pathways to assist with the efficient translation of new therapies from the lab to the patients. Adaptive pathways can better address patients' needs and support timely access to targeted therapies. This approach harnesses statistical methods and improved IT systems from multiple data sources in the 'real world' in a way that improves patient outcomes and closes the efficacy-effectiveness gap. It analyzes a given therapy's impact on clinical pathways in treatment and diagnosis, which can reduce overall costs to payers.

Benefit and risk need to be evaluated on the basis of real life data, and economic models will need to evolve to provide incentives for innovation with patients, policy makers and media as active participants in the process. Dialogue and collaboration will be necessary between regulators, payers, industry, researchers, patients and healthcare systems. It is no longer inconceivable, for instance, that payers could play a bigger role in participation in research projects.

Europe's research landscape remains too fragmented. A lack of critical mass in many research centres means not enough patients, biological materials, technological resources or competences. Wider collaboration and better infrastructure would help: technical platforms for genomics and other specialty disciplines, screening facilities for new pharmaceutical agents, biobanks for tissues and biofluids, quality-assured patient registries... So too would better resources, for prospective validation of biomarkers that may be predictive for treatment, networks on biostatistics, epidemiology and outcomes research.

Integration along the research continuum would make it easier to bridge basic/preclinical research and clinical research in early translational research. In late translational research, clinical results could be more closely linked to innovations in the health care systems, incorporating outcomes research more systematically, and profiting from the broader human perspective that patients' experience and expertise can bring.

For more details, see the annex, page 40: "Mission: Provision of incentives for effective development of products that are capable of selecting the correct targets for the right recipients"

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4. Diagnostics/medical devices and imaging

Conclusions:

- focused, transparent development pathways for diagnostics and imaging biomarkers at the development stage, in a framework of clear, harmonized rules applied across the EU

- formal regulatory acknowledgement of the significance of companion diagnostics, wider recognition for medical imaging, and standardisation of imaging biomarkers

- investments in establishing and expanding biobanks, and interoperability between '-omics' biobanks and imaging databases

- greater incentives and allocation of time and resources to developing diagnostics, and coordination of reimbursement for medicines and companion diagnostics

- closer research collaboration between industry and academia, and between pharmaceutical and diagnostic manufacturers

- a clinical trials regime that can allow for late-stage biomarker research, such as with adaptations of informed consent to allow re-use of samples

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High quality diagnostics, both companion diagnostics and imaging, are fundamental to personalised medicine, which relies on accurate and reliable diagnostics for making the correct molecular diagnosis, and for identifying the 'right drug' for the 'right patient'. Errors in diagnostics can impact patient care and outcome.

Developing an accurate and reliable diagnostic can be as hard as developing a therapeutic with a positive benefit-risk ratio. Finding a predictive bio-marker is difficult. Development of companion diagnostics is dependent on availability of clinical data and tissue samples to provide clinical evidence. Working with co-dependent technologies for therapies and companion diagnostics presents challenges of complexity and lack of coordination among different sponsors and distinct processes for authorisation and reimbursement. In particular, the costs of developing a companion diagnostic can be high, with little certainty over eventual agreement on its reimbursement status.

At the same time, the rapid evolution of science - together with the limited level of data exclusivity - means that today's innovation can rapidly be superseded by tomorrow's variation. Tests rarely enjoy market exclusivity, and although heavy investments are required to generate clinical evidence, the results can be reproduced without delay and at lower cost by 'fast follower' developers.

In parallel, action should ensure effective introduction of imaging biomarkers into routine care; structured validation processes are needed to replace the current bottleneck of reliance on long and resource-intensive clinical trials. And medical imaging and the emerging field of radiogenomics merit more focused attention.

The EU IVD legislation under discussion should establish the right balance for companion diagnostics, to ensure both clinical effectiveness and patient safety, and at the same time to promote innovation and early patient access.

For more details, see the annex, page 51: "Mission: greater attention to the role of diagnostics and imaging in personalised medicine"

5. ICT tools

Conclusions:

- collaborative research into patient-friendly new technologies for data capture, analysis and sharing

- effective arrangements for data-sharing across different institutions, communities, and contexts

- ethical frameworks to safeguard privacy and greater transparency over health data re-use

- mechanisms for involving citizens

- adequately trained ICT and healthcare professionals

- legislation to balance data access with data protection

Novel technologies are essential to realise the vision of personalised medicine, and the move from a traditional, symptom-based disease model towards a systems-based approach to health and disease that relies on the data-rich characterization of individuals and disease stages.

The basis is large volumes of data - in genomics, epigenomics, proteomics, metabolomics, lipidomics, and other 'omics technologies and environmental (including lifestyle-related) and other datasets, from imaging and physiological monitoring. Collecting, integrating, analysing and interpreting this information from across a range of platforms requires new approaches, so as to be able to predict individual risk, the course of disease, treatment response, and the likelihood of adverse events in individuals. Interpreting different datasets and linking the findings to specific outcomes in individual citizens cannot be achieved through a linear approach: the

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functioning and cooperation of different sub-sets within the system in a dynamic manner has to be grasped - understanding the system in flux.

Technology developments will be required to support non-invasive lifelong real-time monitoring of individual health that can collect and analyse clinical and patient-reported outcomes, going beyond electronic health records and mobile phones that can cut costs and delay, and reducing redundancy in recruitment of trial subjects and collection of specimens.

The data themselves will be valuable only if they are of sufficient quality and sufficiently standardized to be portable and reusable across different contexts and sectors. The shift is from generating large datasets ('big data') to achieving meaningful insights from combining different datasets and looking at long-term longitudinal datasets ('long data'). And technology must deliver information which can serve in risk prediction, molecular and physiological characterisation, treatment outcomes and monitoring.

The ethical and privacy issues that arise with the use and reuse of personal data require an appropriate legal framework and with adequate arrangements for consent, constructed on the basis of trust developed between the health and research communities and citizens, and encouraging large numbers of people to contribute biological material and personal data for analysis. Commercial interests can also be an issue, since pharmaceutical and diagnostic companies could restrict access to important information unless a robust framework for pre-competitive public-private partnerships is established.

For more details, see the annex, page 65: "Mission: facilitating the wider introduction of personalised medicine"

6. An informed, engaged and empowered patient

Conclusions:

- general public health campaigns

- specific campaigns to broaden awareness of personalised medicine

- recognition of patients' rights to seek information about care options

- education that improves health professionals' ability to involve patients

- support for patient organisations

- IT tools that acquaint health professionals with the characteristics of each patient

Personalised medicine will deliver its benefits through greater implication of patients in treatment decision-making and health management. It offers patients the chance to be not merely passive recipients of care but participants, partners and even guides in their own health care. Involving patients in treatment-related decision making is in line with the increasing acknowledgement of patients' right to autonomy and self-determination.

Success will require higher levels of health literacy among patients and the wider population, as well as readiness - and skills - among healthcare professionals to engage more closely with patients in discussing treatment issues and options. Patients who are able to seek knowledge, to understand what is being communicated, and who can judge what is appropriate to their own situation, as well as follow treatment regimes precisely, are always more likely to have better

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health outcomes. In personalised medicine, this active engagement is all the more important, with patients often acting with healthcare professionals as co-producers of health to secure the best outcome possible. It is a shift from the patients' passive role in paternalistic medicine, to an active role in participatory medicine. But levels of health literacy vary widely across and within countries, and need to be raised. Patient groups have an important role in increasing literacy and empowerment.

Successful deployment of personalised medicine will also require broad support for the concept from the public. Awareness of personalised medicine is currently low among the general public, and is not much higher among patients and caregivers. But there is some evidence of support for the need for doctors to discuss the potential of personalised treatment with cancer patients, and a sense that there is not enough information available to patients about new treatment options like personalised medicine. Surveys reveal some public support for being tested for personalised medicine even in the face of the possibility that it would not be of benefit. Similarly, there is broad support among surveyed subjects for sharing their own medical records to help themselves and other patients - although there is substantial concern about the risk of misuse of electronic records, and of business or government benefiting unduly from such information or from personalised medicine. Patient organisations have a powerful voice and could be strong advocates for personalised medicine.

There is an important role for health professionals in ensuring easy access to information, speaking in a plain, clear language, and providing room for reflection and transparency about options and alternatives.

For more details, see the annex, page 72: "Mission: greater implication of patients in treatment decision-making and health management"

7. Clinical trials

Conclusions:

- innovative research methodologies and trial designs that are endorsed by regulators and payers

- improved collaboration between academia and industry

- greater support to public-private partnerships

- formalisation of a risk based approach

- clinical trials rules that simplify and speed trial authorisation, taking account of the new paradigm that personalised medicine introduces

- harmonized legislation and reduced costs and administrative burdens

- public funding for high-quality investigator-driven and academic international clinical trials

Moving personalised medicine towards wider acceptance and use will depend largely on a new approach to complex international clinical research involving highly selected patient populations, the collection of human biological material, and the use of large databases for bioinformatics.

The classical approach to clinical trials cannot capture the necessary data adequately. Now that subgroups of patients are being identified within a broad disease category via prognostic or predictive biomarkers, these scientific advances in diagnostic refinement and stratification have to be incorporated into the format of clinical trials. The legal framework in Europe needs adapting, not only to permit easier access to smaller groups of subjects, but also to recognise the validity of results from trials much smaller than the classic randomised approach. And

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adequate methodologies and infrastructures that support large screening platforms are needed to ensure quality of the research and reliability of evidence.

This can succeed only if there is greater collaboration among many partners - industry and academia, statisticians and patients, but also regulators. Smart but robust clinical research methodologies need to be endorsed by regulators and payers. Progress will frequently mean the use of new technologies for data capture, direct data entry, and real-time response, across smaller multi-centre trials in several countries. Wider support will be needed, to multidisciplinary research, and to public-private partnerships. And clearer and more harmonised regulation will be vital - with the shape of the Clinical Trials Regulation now under discussion taking on crucial significance.

Wider harmonisation will ease the process, and help to lower costs and administrative burdens. A new paradigm could introduce a risk-based approach, and bring translational science and elements of health technology assessment into clinical trials, with greater public support for trials.

For more details, see the annex, page 81: "Mission: To ensure a responsive regulatory environment that responds to the needs of all stakeholders whilst ensuring patient safety, with the end result of ensuring development of treatments for patients."

8. Health technology assessment:

Securing patient access to personalised medicine

Conclusions:

- better understanding among HTA bodies of the specificities of the -omics technologies

- adaption of assessment methodologies to take account of new ways of developing evidence

- integration of the concepts of overall economic value and equity into HTA

- wider input from stakeholders into HTA bodies' methodologies, and clarity over the patient role within the HTA structure

- an EU-wide HTA standard method to support developments in personalised medicine, and greater cross-border sharing of expertise among HTA bodies

- closer alignment of the assessment of therapies and companion diagnostics

- advice and support on how to prepare for HTA requirements

- early engagement in terms of dialogue and advice with the HTA agencies

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The emerging discipline of health technology assessment faces new challenges from the specific characteristics of the -omics technologies and of personalised medicine. While the aim of HTA is to identify the greater value of a medicine, there are limitations in practice to the applicability of HTA methodologies to personalised medicine. Procedures often lack methodological flexibility, inadequately capturing the patient evidence and experience, and suffer from excessive bureaucracy and high fixed costs. They often fail to take account of trial designs capturing real clinical benefit, and many typical HTA approaches can delay the identification of clinically important genetic variants. They also frequently display scepticism over the possibility of drawing general conclusions from evidence derived from treatment tailored to the patient. Methodologies used in assessing companion diagnostics and associated treatments are also often inconsistent.

Effective evaluation of the medical, social, economic and ethical issues of products in a systematic, transparent, unbiased, robust manner will promote safe, effective, health policies that are patient-focused and obtain best value - whether at the time of launch or on the basis of use in real-life circumstances.

At present the attitude - and divergent conclusions - of many HTA bodies adds to the unpredictability and uncertainty that handicaps the development of personalised medicine. Different recommendations currently emerge across countries for the same drug and indications, sometimes because the requests for evidence differed, sometimes because agencies appraised the same evidence and address the clinical uncertainties in different manners, and sometimes because they employ different economic models. Smaller companies - many of which are important drivers of personalised medicine - encounter difficulties when confronted with HTA requirements, and the consequence is often delayed - or failed - market access. These factors make it even more urgent for HTA bodies to make effective re-use of HTA information from one member state to another, to reduce duplication of work and provide consistency across territories. Specific consideration should also be given to the role of patient and public involvement in the process.

The inclusion of HTA in the proposed update to the EU Transparency Directive is welcome, as a clear recognition that Member States are moving closer to value-based pricing in their systems. But regulators need to move away from a focus on short-term solutions to the broader concept of overall economic value.

For more details, see the annex, page 90 "Mission: healthcare resources allocated to development and utilisation of personalised medicine, through acceptance of its long-term cost-effective benefits".

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9. Innovative payer models

Conclusions:

- pricing and reimbursement procedures that take account of the potential of personalised medicine by including patient relevant outcomes

- the inclusion of the concept of reward for innovation in pricing and reimbursement systems

- closer collaboration with reimbursement authorities from early in the drug development process

- harmonisation and streamlining of data requirements and processes between regulators and pricing and reimbursement authorities

- strengthened and better-integrated data collection systems at national and EU level

- coordinated assessment and reimbursement mechanisms for drugs and companion diagnostics

- further exploration of adaptive licensing and managed entry agreements

Innovative payer models are essential to obtaining the benefits of personalised medicine. European drug development and market access models are no longer appropriate.

Pricing and reimbursement decisions are currently made largely at the time of launch on the

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basis of evidence from randomised clinical trials. These evaluate merely the average effect of a medicine and set a price for each dose prescribed, irrespective of the effect on individual patients. Since personalised medicines can target narrower populations of patients which are more likely to respond to the treatment, payers should have an interest in pricing and reimbursement models that allow them to pay only for those patients that respond positively to a treatment. But at present, authorities are labouring under uncertainty about how to measure the value of innovative products, and their decisions reflect this.

A response to uncertainty is available through the staggered approach to market access envisaged by adaptive licensing, in which a product is allowed earlier market access but under carefully controlled conditions, and its authorisation - and its price and reimbursement status - are progressively modified in the light of greater knowledge from wider use. Another avenue is the use of managed entry agreements, under which a manufacturer and a payer or provider establishes specific conditions for reimbursement of a medicine. These can be a useful stepping stone towards the development of new pricing and reimbursement models. Early contact between authorities and companies can help build trust on which new approaches can be based.

Pricing and reimbursement authorities often have no mandate to reward innovation, and the context they operate in usually divorces them from broader considerations of overall healthcare spending. As a result, their decisions fail to take account of the added value that personalised medicine offers. In consequence, the incentive for the development of personalised medicine is reduced.

In addition, pricing and reimbursement authorities frequently demand supporting information that has already been supplied - but frequently in response to differing requirements - during the product authorisation process. This imposes a time-consuming and expensive administrative burden on companies, and creates unnecessary duplication and delay. It also risks confusion among the conclusions reached by diverse official bodies. Data exists widely at national and EU level, but is not always adequately collected and integrated, often leading to imperfect decision-making.

For more details, see the annex, page 97 "Mission: to effect a paradigm shift in pricing and reimbursement to recognise the societal value of a medicine."

10. Education and training of healthcare professionals

Conclusions:

- provision of continuing professional development and training activities

- adapted curricula for undergraduate, post-graduate and specialist education

- training systems that provide for interprofessional collaborative practice and produce interdisciplinary professionals

Healthcare professionals cannot be expected to adapt to new ways of approaching patients and coping with new technology unless they are suitably trained. They are being asked to move beyond traditional reactive medicine towards proactive healthcare management, employing screening, early treatment, and prevention, and to classify and treat disease in a new way, interpreting information from across sources that blur the traditional boundaries of individual specialties.

Professionals prescribing, dispensing and administering medicines will need to be confident of the science behind targeted therapies, including greater understanding of the immune system and molecular medicine, and knowledge of the mechanisms of action and interaction of targeted therapies, as well as common adverse events. Communication skills with patients will also need to be developed. It will be necessary for professionals tailoring individual care to adopt a holistic approach to patients, taking account not only of individuals' genetic characteristics,

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but also of family history, social circumstances, environment and behaviours.

It is equally important to develop training for the many other professionals whose disciplines are essential to the successful development of personalised medicine - in bio-informatics, statistics, or mathematical modeling for example, to promote the shared understanding and collaborative development of the tools for personalised medicine. Employers, professional organisations, certification entities, regulatory agencies, and others will have to be involved in effecting the necessary changes.

While it is important to ensure training for those professionals who are currently practising, a broader shift is needed so that education syllabuses are adapted too, to prepare the next generation of researchers, physicians and nurses. Curricula should be transparent, and transferable between countries. This is true for healthcare professionals, but also - if the necessary interdisciplinary approach is to be achieved - for other professions whose contributions and collaboration will be increasingly necessary as personalised medicine develops.

For more details, see the annex, page 104: "Mission: promoting a shift among clinicians and other healthcare professionals away from traditional reactive medicine towards proactive healthcare management, employing screening, early treatment, and prevention"

11. Public-private partnerships

Pioneering personalised medicine research with the Innovative Medicines Initiative

Conclusions:

- increased open collaboration in multidisciplinary research partnerships that cross sectors and borders and stakeholder groups

- wider support for neutral brokers to ensure equity and quality in partnerships

- adventurous approaches to the development of new medicines, in which partnerships can play a crucial role.

The challenges to be overcome in developing personalised medicine are numerous and difficult. They include the wide heterogeneity of disease, a lack of predictive biomarkers, clinical designs and regulatory processes that are outdated, the determination among public authorities to contain healthcare spending, and the inadequate incentives for companies. Only a shift in mindset among the stakeholder communities can overcome these challenges.

Identifying the different and distinct diseases that are currently considered to be one disease and developing the appropriate tests to diagnose them and the treatments to tackle them requires a large-scale research and innovation effort involving all key players in the drug development process. Public-private partnerships are a valuable model for driving personalised

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medicines research forward, as they bring together experts from academia, research centres, the pharmaceutical industry, small and medium sized enterprises, hospitals, regulators, and patient groups.

The Innovative Medicines Initiative (IMI), as the largest public-private partnership of its type, is an example of how a neutral broker can promote that shift. By bringing together both private industry and the public sector - in the form of the European Commission - it is able to foster large-scale industry collaboration and engagement with the scientific community. It can catalyse open innovation. It can facilitate intellectual property agreements. It ensures the excellence of the partnerships and projects established. And it promotes the active involvement of patients, regulators and payers.

The outcomes are an increased probability of success and earlier patient access. Public-private partnerships contribute to move personalised medicine forward by addressing key scientific challenges, developing tools to translate scientific advances into regulatory guidelines, considering new pathways to accelerate patient access to innovative therapies.

For more details, see the annex, page 109: " Mission: promoting a new, open, more collaborative environment for drug research and development in Europe to help drive personalised medicine to deliver more of its potential benefits".

EAPM Members and Observers

Cancer-Related Organisations
European Cancer Patient Coalition (ECPC)
Organisation of European Cancer institutes (OECI)
EUROCAN Platform
E-Cancer Medical Science
European Society of Medical Oncology (ESMO)
European Oncology Nursing Society (EONS)
ECP Biobanks
European Haematology Association (EHA)
European Society for Pathology (ESP)
Cancer Research UK
European Organisation for Research and Treatment of Cancer
European Association of Cancer Research

Institutional Related Observers
DG ENTER, DG Research, DG SANCO, MEPS

Payers
Association Internationale de la Mutualité
European Social Insurance Platform

Other Disease Organisations
European Association of Urology (EAU)
European Patients Forum
EPDA
European Kidney Health Alliance
International Diabetes Federation
EURORDIS
European Brain Council
European Society of Cardiology
European Respiratory Society

Medical / Academic Organisations
European Science Foundation
Karolinska Institute
European Society of Radiology
Institute for Public Health Genomics (IPHG)

Industry
EDMA, EuropaBio, Eli-Lilly, Pfizer, Novartis, Amgen, Merck Serono, Genomic Healthcare, Roche

Associations
European Hospital and Healthcare Federation
European Association of Pharmaceutical Wholesalers
Pharmacy Group of the EU

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INNOVATION and PATIENT ACCESS to PERSONALISED MEDICINE

ANNEX TO THE REPORT

Report from Irish Presidency Conference March 20th/21st 2013

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Mission: easier circulation and sharing of personal data, appropriately balanced with personal privacy - Data privacy and consent

The development of personalised medicine can occur only if easier circulation of personal health data is allowed for scientific research purposes – with, of course, appropriate safeguards.

Personalised medicine looks at health information from the single patient, including the genetic and phenotypic characteristics, to determine which treatments will be most safe and effective for the individual. In addition to tailoring treatment to individuals' needs, another merit of personalised medicine is that it allows better awareness of trends and susceptibilities among defined populations and sub-groups of population, thus permitting not only diagnosis and treatment, but also much more effective prevention.

Analysis of personal data is also an important public health tool that governments used to quickly identify, remedy or prevent the spread of adverse events in certain populations when they are first reported. In addition, personal data shapes healthcare policies, which are based on information about the costs and benefits of interventions. In short, personal data has a profound and often understated impact on many aspects of healthcare.

Understanding intricate health data is challenging, but when abundant heath data is combined with innovative analysis strategies in a multidisciplinary setting, powerful models of complex diseases emerge. This implies circulating and sharing personal health data with a wide range of data experts and medical specialists. Together, these professionals can derive the most apt interpretation from the data and extend the work of others. Such a community-based approach has proven successful in other areas of science and technology (such as information technology and astronomy) and could be applied to biomedical research. Given however the legitimate attention to data privacy in a society conscious of the importance of personal rights as well as of the importance of personal health, a balance must be struck between the need for circulation of data and the need for data privacy.

All stakeholders must be engaged on how to obtain the best balance between these conflicting priorities, and how to achieve the best possible harmony between distinct regimes and systems of governance. The current country-specific gridlock around data protection must be broken,

and a transparent regulatory and governance framework be developed to support improvements to personal and global health while respecting the individual's right to control personal data. Arrangements for consent can go a long way towards easing this dilemma. But the nature of those arrangements will be critical to their effectiveness in allowing adequate circulation and appropriate use of personal data. Therefore the options that might be entertained for such arrangements also need to be discussed.

The case for data circulation is clear.

Medical discoveries rely on the ability to safely and effectively collect and analyse personal data concerning patient treatment and outcomes. Without personal data, scientists would lack insight into the causes of certain conditions and diseases, and could not develop suitable curative and preventative measures. In each of the steps in the scientific process – i.e., an observation leading to a hypothesis, followed by testing and then confirmation – the ability to effectively collect, analyse, and re-analyse patient information is crucial. The ability to sustain and expand on scientific innovations also depends upon the continued availability of the data, which in biomedical research means access to personal health data. In many cases, novel biomarkers emerge midway through a study, or after it has closed, and rapid re-analysis of existing data is vital to promptly get this new knowledge into personalised treatments. Furthermore, discoveries must be reproducible and validated by independent experts, and for this they need access to the data.

Using personal data is also critical to public health, and healthcare efficiency. The development of new medical interventions demands extensive testing to ensure patient safety and effectiveness. Moreover, health authorities are increasingly demanding the evaluation of the effectiveness of medicines in real-life settings, which requires continued access to personal health data.

Financial considerations are also prompting the investigation of novel and potentially more cost-effective and efficient models to biomedical research. For example, the use of electronic medical record data as a source of readily available research data eliminates the need for costly and lengthy active new recruitment, and drastically reduces collection of redundant specimens and data.

Today, availability of data and material are often prerequisites to achieve publication or to secure continued funding. This emphasis on transparency through data circulation results in a rapid exchange of information. This, in turn, promotes scientific integrity and treatment safety, and encourages the expedited translation of scientific research results into applicable treatments or technologies to improve health.

Data circulation is vital for scientific integrity, treatment safety and research efficiency. Ensuring continuous and seamless access to medical data is crucial for medical research and

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innovation. However, complex data protection rules are a major regulatory constraint and an impediment to biomedical progress toward achieving personalised medicine. Updating these EU rules should take account of the impacts for individuals' health and global healthcare. The right to privacy and the right to health must both be protected in the reforms that are implemented. In this context, the current proposal of the European Commission for a General Data Protection Regulation merits examination.

This needs the involvement of all stakeholders - patients, research participants, healthcare professionals and the public.

Regulators must create an appropriate legal framework that empowers individuals. The rules must not inhibit biobanks, retrospective clinical research, collaboration among communities and experts worldwide, or other activities central to the development of personalised medicine. The EU's proposed data protection regulation addresses many of these issues, including those raised by the cloud. The Commission communication on the cloud[1] clarifies the important question of applicable law by ensuring that a single set of rules would apply directly and uniformly across all 27 Member States. This "will be good for business and citizens by bringing about a level playing field and reduced administrative burdens and compliance costs throughout Europe for businesses, while ensuring a high level of protection for individuals and giving them more control over their data". The proposal facilitates transfers of personal data to countries outside the EU and EEA while ensuring the continuity of protection of the concerned individuals, insists the Commission, which adds that it is "important that Council and Parliament work swiftly towards the adoption of the proposed regulation as soon as possible in 2013".

A number of safeguards already operate to ensure the protection of personal data when these are collected specifically for research purposes. When personal data is collected directly from an individual by a healthcare provider or clinical research organization, the patient is often informed of the scope of the data to be collected, the purposes for which it will be used, and the length of use or storage. The patient is often asked to provide explicit, opt-in consent to the collection and use[2]. In addition, professional standards govern the use and disclosure of

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1   http://ec.europa.eu/information_society/activities/cloudcomputing/docs/com/com_cloud.pdf

2   The scope of a consent to use personal data may vary. It can be limited to one individual clinical study or it may cover future research on the disease in question. Healthcare companies seek to provide patients with the information they require to make informed decisions regarding the use of their medical information and biospecimens. This is true in the research context. In the healthcare delivery context, the situation is a bit more complicated, with some jurisdictions taking the view that explicit, opt-in consent is a pre-requisite to providing healthcare (except in emergency situations) and other jurisdictions taking the view that because of the nature of the doctor-patient relationship, consent should not be used as a basis for processing of personal data in the healthcare delivery context. In these latter jurisdictions, there is always implied consent (except in emergency situations where consent is presumed), but there may not be express consent.The EU Article 29 Working Party has previously explored the limits of consent in the health care context. For example, with respect to electronic health records, the Working Party has opined that "free consent means a voluntary decision, by an individual in possession of all of his faculties, taken in the absence of coercion of any kind, be it social, financial, psychological or other. Any consent given under the threat of non-treatment or lower quality treatment in a medical situation cannot be considered as 'free' ... Where as a necessary and unavoidable consequence of the medical situation a health professional has to process personal data in an EHR system, it is misleading if he seeks to legitimise this processing through consent. Reliance on consent should be confined to cases where the individual data subject has a genuine free choice and is subsequently able to withdraw the consent without detriment." The EU Data Protection Directive itself permits Personal Data to be Processed without consent where it "is required for the purposes of preventive medicine, medical diagnosis,

personal data. For example, physicians are subject to an oath of secrecy; similarly, clinical researchers are subject to Good Clinical Practice standards. Independent ethics committees review research protocols (a document that describes the objective(s), design, methodology, statistical considerations, and organization of a study) and assess the privacy risks to individual data subjects. These safeguards effectively protect data privacy. But they are ill-adapted to ongoing cross-disciplinary collaborative research efforts, such as community-based projects like the DREAM projects, that foster collaboration and harness the power of worldwide experts to improve and accelerate knowledge through shared data and methods. Such efforts are hindered by current regulatory barriers designed for a one-site, one-time, one-use data analysis approach. Yet significant progress is seen when such challenges are allowed to take place[3].

The moral foundation of informed consent lies in the essential principle of respect for autonomy. Yet the current implementation of informed consent consists of a simple opt-in participation agreement. It does not empower participants to become active partners in the research process and/or to decide on the fate of their own data. Usually informed consent does not provide for giving any data back to the participant either. It does not include use of the data for future independent validation, unanticipated analysis or to the contribution of the data to a new field of research.   It effectively creates silos of single-use data. So alongside involving all stakeholders in the decision-making and policy process, a parallel exercise will be necessary to inform and alert patients and citizens about the processes of informed consent – and how such processes can be beneficial, for them individually, and for society as a whole. That will make it easier for researchers to obtain appropriate consent for use of data that will conduce to the fuller exploitation of the potential of personalised medicine – a win-win scenario for science and society.

The eMERGE project, organized by NHGRI in the US, has investigated best practices to participant consent, data sharing, returning results to participants and publishing results to scientific journals or community. The lessons from this project, and others like it, should be considered when making regulatory reforms. Participants typically saw sharing of their data as worthwhile. They wanted researchers to respect participants' altruism and to make the most of participants' contributions.   The risks of sharing biomedical personal data was not seen as much different from other normal risks (e.g. normal banking), and 90% of participants gave consent to deposit their health data on the scientific data repository dbGaP. They viewed trustworthiness of the recipient as important and they emphasized the importance of having a choice[4].

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the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject . . . to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy."

3   Sage Bionetworks/Dream breast cancer challenge http://sagebase.org/challenges-overview/

4   Research Practice and Participant Preferences: The Growing Gulf: S. B. Trinidad, S. M. Fullerton, E. J. Ludman, G. P. Jarvik, E. B. Larson, and W. Burke, Science 21 January 2011: 331 (6015), 287-288. [DOI:10.1126/science.1199000

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Consent language should be less about protecting the interest of institutions and more about giving a voice to participants. The consent process must better inform people and allow them to control their data, and must be adapted to modern technologies and regulatory frameworks to take into account the emergence of e-consent processes suitable for telemedicine and/or mobile health applications.

Informed consent forms often "guarantee" confidentiality of the data and state that personal data will not be publicly disclosed in an identifiable form in any research presentations or publications resulting from use of the specimen/data[5]. Yet completely eliminating the risk of re-identification can be difficult or impossible given the extent of data already freely available on public databases. For example, by triangulating free information on the web, it may be technically feasible for those with the requisite skills to infer the identity of some data subjects in a data set from which all direct identifiers have been removed. Furthermore, a requirement to anonymize data can be an obstacle to innovative research. In many fields of medicine and science, it is crucial for researchers to be able to follow the data of particular patients. The traceability of data subjects needs to be an exception in the case of medical data used solely for scientific and public health research purposes.

In the US, health information privacy is governed at the federal level by the regulations adopted under the Health Insurance Portability and Accountability Act (HIPAA). While there are discussions regarding the need to retain some of these identifiers in longitudinal medical research efforts, the HIPAA Privacy Rule establishes a rebuttable presumption that all health information is identifiable. The rule states that a healthcare provider may determine that health information is not individually identifiable only if (i) a statistician determines that the risk that the information could be used by an anticipated recipient to identify a data subject is "very small," or (ii) 18 enumerated identifiers have been removed from the data set and the healthcare provider does not have actual knowledge that the information could be used to identify a data subject (this latter method is known as the "de-identification safe harbor").

The HIPAA de-identification safe harbor alleviates any legal uncertainty around how a data set needs to be transformed in order to be able to be shared or publicly disclosed. Where the de-identification safe harbor would require the removal of some identifiers that are customarily needed for medical research, the statistical certification method provides an important alternative. In combination, these two methods provide a widely accepted framework for acceptable data circulation[6].

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5   Data protection authorities usually distinguish „anonymization" and „pseudonymization." Informed consent forms typically try to draw a distinction between the controls around public disclosure and how the data will be used internally.

6   We do not want to imply that the EU should adopt the HIPAA rules, but a safe-harbor de-identification mechanisms would be helpful in clarifying which "direct identifiers" must be removed prior to sharing data. Of course, the need to retain some of these identifiers in some research must be addressed and a Tiered approach could be proposed : Full de-identification (removal of all 18 direct identifiers) versus partial de-identification (removal of >=15 identifiers (number of identifiers to be determined)

To protect both the right to privacy and the right to health in the reform of the Data Protection Directive, policy makers should recognize key-coding as a measure embedded in the design of clinical research studies. Correspondingly, requirements related to the retention, use and disclosure of key-coded data for research purposes should be distinguished from requirements applicable to personal data. Free circulation for research purposes of key-coded data from which all direct identifiers have been removed [7] should be allowed and the re-use of such data widely allowed without the need to re-contact and re-consent the original study participant. Further, the exercise of the rights of access and rectification of personal data should be directed towards the holder of the key rather than the holder of the key-coded data[8].

Clinical research subjects should be allowed to provide broad consent to the processing of their personal data for secondary biomedical research purposes, such as understanding disease mechanisms and further research concerning the test article[9]. This would help alleviate the difficulty that researchers frequently encounter in predicting outcomes associated with medical testing and treatment, which can make further processing of patient data necessary.

There should be limits to the application of a "right to be forgotten" when it interferes with an ongoing study. For example, once a person agrees to participate in a clinical study, the scientific integrity of the study analysis depends upon the ability of the clinical investigator to accurately track and correlate data about that person, up to the point at which the person either completes participation in the study or withdraws from it, whichever is sooner. Upon withdrawal, no further data about the person is collected; however, it is essential that the data that already has been collected about that person may be retained and analysed. Otherwise the validity of the study may be compromised. The "right to be forgotten" should not apply to key-coded data.

No separate rules should be required for genetic information. All medical data, including genetic data, must satisfy equally high standards of quality and confidentiality. Genetic information is part of the entirety of every individual's health information and does not represent a separate category. Moreover, genetic data is identifiable only to the extent that a reference dataset that directly or indirectly links the data to an identified person is accessible. Thus, genetic exceptionalism is inappropriate. On this point, efforts should be made to educate the public

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7   Subject to caution over the use of 'de-identified' here. The paragraph above talks about HIPAA de-identification, and 'de-identified data' under HIPAA is a term of art. Key-coded clinical trials data would not be considered de-identified under the HIPAA de-identification safe harbor (e.g., dates related to the patient are included in such data sets, and the ,code' itself is generally considered an identifier which is required to be removed under the safe harbor, unless the data is re-coded with a code that is randomly generated). The statistical certification method of de-identification is more research-friendly in terms of allowing important data elements to remain in a data set. Of course, it has the significant disadvantage of requiring data set-by-data set analyses and determinations of what can be permissibly disclosed.

8   When research data is shared among collaborators, they can replace the patient's name and other direct identifiers with a unique random code. This key-coded data should be allowed to circulate among collaborators who are effectively blinded as to the patient's identity, even if one collaborator must retain the ID key to retrieve the pateint's identity. This key holder should be the only one responsible to the patients for any data correction or rectification since it is the only one who knows the patients' iD.   Such dataset is considered identifiable because one of the collaborator retains the ID key . I propose to consider the key-coded dataset as identifiable only by the key holder but not by the other collaborators.

9   Sometimes it will not be possible to get consent, even if broad consent is an option. Therefore an exception is still needed to legitimise data processing.

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about the risks and benefits of genomic research and on the legal framework that surrounds appropriate use of such data. For instance in the US, the GINA act prohibits use of genomic data to discriminate in employment or medical insurance, but does not apply for long-term disability or life-insurance.

International transfers of personal data for biomedical research purposes should be allowed where appropriate privacy accountability mechanisms have been implemented.

Making sense of complex health data requires sophisticated analytical tools and high performance IT infrastructure as well as extensive data storage capacity and communication capability. Internet and cloud computing technologies that allow researchers to collaborate and work efficiently should be leveraged where appropriate. For example, it should be possible to analyse and/or transfer key-coded data on a shared cloud environment that has been certified with respect to processing personal data.   Cloud resources have worked with accredited bodies to develop data security procedures allowing them to process financial, military or government data. The same should be done to allow processing of personal health data.

Success will emerge from finding the right balance. The arguments for data circulation are strong – but so are the arguments for data privacy. So the solution must respect the rights of the individual to data protection, as laid down in the EU Charter, which also specifies that such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law.
To ensure the right balance, all stakeholders must be engaged in the search for solutions – and in particular, representatives of patients and citizens. That is the way to achieve the objective of establishing a fully coherent, transparent, harmonious and robust framework with a high level of protection for all data processing activities in, and outside, the EU.

Action/ changes needed

- create a regulatory environment that resolves complex data protection rules currently impeding biomedical progress
- break silos of single-use data and promote cross-disciplinary collaborative research efforts
- remove country-specific gridlocks on data protection
- allow for re-use and secondary use of data for scientific and regulatory purposes
- no separate rules for genetic information
- acceptance of certified Cloud environments

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Appropriate mechanisms

- adapt arrangements for consent, GCP, ethics
- wider use of technology (electronic medical records, e-consent)
- increased pseudonymisation of data
- recognition of effectiveness of key-coding and distinction of research data from personal data
- limits to "right to be forgotten" and to notifications of breaches of privacy
- international data transfer for biomedical research where appropriate protection mechanisms are in force
- wide stakeholder engagement in search for solutions
- inform and educate patients and citizens about informed consent

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Mission: provision of incentives for effective development of products that are capable of selecting the correct targets for the right recipients - Moving research results into health systems: innovative translational models

Personalised medicine introduces a new era of healthcare that focuses on the individual genomic signature of individuals interacting dynamically in space and time with other health determinants such as environmental and lifestyle factors to create not only a more personalised and stratified approach ("precision medicine") at a much earlier stage to healthcare, but in the end a "truly personalised" or individualised approach.

Certainly, science has led to major advances in the understanding of the role of genomics in diseases, in the discovery of biomarkers[10], in the development of new statistical methods and in the invention of dynamic tools for collecting real world effectiveness and safety data. Conversely, the basic R&D and regulatory process is largely unchanged and, within an unchanged framework, it has simply become steadily more burdensome to develop innovative medicines.

In might be said that the R&D, associated regulatory process, and incentives need to catch up with the science. While the potential for sequentially developing products for several indications has increased, the incentives for doing so are inadequate.

Integrating the new genome-based knowledge and technologies into regulatory pathways (e.g. clinical trials design, statistical analysis, etc.) would in particular require departing from the current symptom-based approach to diseases and turning to progressive development and approval models, which would allow earlier access of patient to valuable therapies and prevention strategies. There is clearly a need for (1) simplification of complex and inflexible regulatory procedures within the current development and regulatory framework, (2) a review of the supportive incentive system(s) in order to improve innovation, and (3) the need for

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10   A biomarker is an indicator of a biological state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. They can be used in the medicines development process as well as for diagnostic, prognostic, monitoring and screening purposes.

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predictability in the European regulatory processes to reduce R&D costs and allow earlier access for patients to innovative medicines.

These changes require early engagement from researchers, patients, policy-makers, regulators and payers. Better integration of patient views in research and regulatory decision making will be key to this process.

Rationale for changing the development model – cancer, a case study

Evidence-based medicine is traditionally built on outcomes of comparative clinical trials. For drug development the evaluation of benefits and toxicities of new pharmaceutical agents starts with early clinical trials to collect basic information regarding doses and toxicity, and continues with randomized clinical trials that evaluate relevant clinical end points and safety. The outcome of a clinical trial in terms of an assessment of clinical efficacy is based on selected patients. At the time of registration of a new pharmaceutical agent, the medicine has been evaluated only under the usual circumstances of healthcare practice. As a result, the available clinical effectiveness data are usually modest. Evaluation of clinical effectiveness and analyses of long-term treatment effects depend on access to quality-assured clinical registries for observational studies.

Increased knowledge of the biological mechanisms behind diseases demonstrates that a conventional descriptive, typically symptom- or pathology-based defined disease can be subdivided in a number of subgroups based on a biological fingerprint. Cancer is a good example. Daily clinical work uses about 200 diagnoses, but increased knowledge of cancer biology shows that each diagnosis contains subgroups. It is anticipated that there are thousands of distinct tumour types. Such diversity significantly increases the difficulty researchers face in studying the disease and in developing appropriate treatments.

The development of new drugs relies on the identification of new disease-specific biological targets. For cancer treatments, the drug targets are generally linked to molecular alterations such as mutations in the DNA - deletions or duplications designed to derange the molecular pathways driving the tumour growth. Since these alterations are specific for subsets of tumours, new anti-cancer agents are effective only for treatment of specific subgroups of patients. Adding to an already complex process, in many cases more than one molecular target must be engaged due to cross-talk between molecular pathways. Further, development of resistance to pharmaceutical agents is a major problem, and in cancer this is due to heterogeneity of the tumour cell population and genomic instability of the tumour cells. Selecting the correct targets for the right participants consequently necessitates innovative and interdisciplinary approaches, involving bioinformatics and systems biology in the clinical research setting.

Future treatments are expected to move towards new types of clinical trial design, such as

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adaptive clinical trials methodologies, where treatment will be modified as biological changes occur in the tumour cells and the tumour cell population. Consequences will be stratification of patients with treatment of specific subgroups, individualised or personalised treatment built on the biology of the disease and normal tissues of the patient. It will not be possible to conduct large randomized clinical trials in this drug development process. It has already been demonstrated that every cancer case is unique, requiring a concept such as "personal utility" and N=1 trials.

However, cancer is just one example. Generally, development of a more predictive and personalised medicine in terms of "truly personalised medicine" is necessary to solve the increasing health care problems related to the main chronic diseases.

With this development, it is possible to foresee increasing problems in achieving an effective drug development process. The traditional conduct of clinical trials and collection of information regarding benefits and risks must be changed. There is also a need to establish new forms of collaboration, linking academic centres, the pharmaceutical industry, regulators and payers, in order to make the drug development process more effective. No single entity has the depth of knowledge and financial resources to effectively collect and mine the biomedical data needed to allow personalised medicine to become a reality. Collaboration and continued access to clinical research data must be encouraged and supported. It is important to identify the relevant technologies and information needed to approach regulatory authorities and support health technology assessment (HTA).

Clinical trials

The Randomised Control Clinical Trial (RCCT) design is now close to 50 years old and has served science well, but in some areas it has almost outlived its utility. There is now broad agreement that the 'classic' RCCT and the 'null hypothesis' approach to analysing data represents only one (and often not the best) approach to establishing efficacy. Using the concept of "personal utility" and providing evidence on the individual level is the approach needed to implement "truly personalised medicine".

With payers and clinicians increasingly focused on effectiveness and outcome data rather than solely RCCT-derived efficacy, it will be important to use the emerging tools of electronic patient records and mobile health solutions to collect and analyse both clinical and patient-reported outcomes ("personal files"). There is also a lack of available formal educational approaches to the required statistical science, both within industry and among regulators. New analyses are not limited to a pairwise approach whose outcome is a list of altered components in a disease. We must understand disease mechanisms and decipher the relations between multiple molecular alterations and disease outcome. Thus we need to pool data from previous experiments and use sophisticated statistical analysis methods and mathematical modelling

approaches to create robust models of disease that serve to develop targeted therapies.

Effective translational research is important to solve health problems related to the chronic diseases. Early translational research bridges basic and preclinical research with clinical research. The time-consuming process from outcomes of clinical research to adoption in the health care systems, late translational research, is an increasing problem. For adoption we need information about effectiveness of diagnostics and treatments as well as health economy evaluations. Clinical trials of today primarily offer information about clinical efficacy. However, for truly evaluating the value of a new medicine we need information of clinical effectiveness, which means outcomes when a patient population or even a single patient is treated. To assemble such data we need implementation of e.g. smart phone technology and quality assured clinical registries. Clinical effectiveness assays are elements of outcomes research, and an important function of late translational research. A limited quantity of data can be used to define clinical effectiveness in the early part of the drug development process, but to evaluate the long-term benefits and risks a complete outcomes registry would be essential. In the era of stratified personalised medicine, randomised clinical trials identify information from selected patients treated in selected centres. Provided a structure for clinical registries is in place, all patients can be used for demonstrating the true clinical effectiveness by the observational study methodology. With the development of personalised medicine, patients for specific treatments will be fewer and therefore new types of collaborations between research centres are mandatory. This is also the case for clinical registries. A clinical registry should be an infrastructure established by a centre, which in the long run needs to be linked to personal files too. Collaboration between centres is necessary in order to build the harmonised registries for compilation of patient data in order to reach an acceptable critical mass. Such registries not only provide access to information that otherwise would be difficult to collect for any one centre; they can reduce wasteful redundancies in clinical research. Moreover, registries promote data quality, oversight for appropriate use of the data, accountability and trust.

Another clear advantage of registries is that they standardize data, thereby making it directly useable. While registries present an attractive solution to improving clinical effectiveness, incentives and rewards must be in place and regulatory frameworks must be designed to encourage rather than impede participation. A project on this topic should involve collaboration with leading independent statisticians, propose clear regulatory guidelines, establish joint training programmes and encourage and monitor pilots.

Collaborative computational approaches to analysing large-scale data have demonstrated their effectiveness in accelerating access to knowledge. In the biomedical field, efforts such as the DREAM challenges, and the Sage Bionetworks DREAM Breast Cancer Challenge, harnessed the expertise of expert computational scientists and biologists worldwide to develop the best model of the disease and find new predictors of the progression of breast cancer. Such challenges are meant to quickly develop the tools that doctors can use to make better decisions regarding treatment choice and to project a patient's likely disease progression. These challenges engage

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statisticians, biologists, mathematicians, machine learning specialists and computational communities to share tools and methods for a common goal. These communities need to discuss with regulators and policy-makers to ensure such approaches are not prevented by out-dated regulatory constraints.

Benefit/Risk evaluation

The benefit/risk assessment in regulatory decision-making is under discussion in settings including: pre-approval data required for conditional approvals vs. 'full' marketing authorisation, qualitative vs. quantitative assessment methodology, and the need for active comparator clinical trials; post-approval data required to maintain the benefit/risk assessment; alignment on data required for regulatory benefit/risk assessment and HTA needs, and in line with health needs assessment (HNA) and health impact assessment (HIA); and communication of benefit/ risk within medicine labels.

For conventional drugs the benefit is based on a heterogeneous patient population consisting of responders, partial responders and non-responders. For personalised drugs, where patients are selected for response and thus only the risk part, a novel methodology for B/R evaluation may have to be developed.

Activities should be conducted jointly with industry, academia, the EMA/regulators and centres with expertise in public health, applied ethics and law, mathematics, statistics and other key disciplines, to establish a new methodology and communicate it to relevant national policy-makers.

Regulatory pathways for adaptive development

A number of models and tools already exist today for evaluating and approving medicines and therapies, none of which, however, has been specifically designed for the adaptive development that would be required by the growing trends of stratified/personalised medicines approaches pr the implementation of "truly personalised" or individualised medicine and healthcare.

Neither the orphan drug approach nor the existing conditional approval are completely suited for this purpose. The current conditional approval, for example, is mainly used as a final option to 'rescue' a medicine that may otherwise not be approved, rather than being used proactively to promote earlier access of important new medicines for patients. This is due to the specific wording used within the relevant legislation (Reg EC/507/2006).

This concern is shared not only by those who develop the prevention and therapeutic agents, but also by regulators and regulatory science specialists. A number of initiatives have looked

into rationalisation of regulatory pathways, e.g., EMA 2015 Roadmap, Newdigs, the Public Health Genomics European Network (PHGEN), and the UK Athenaeum Group. All these initiatives stem from the principle that knowledge of drugs and their optimal use evolves over time. All of them advocate replacing the current system of unique approval moment with progressive management and reduction of uncertainty, and access to new therapies based on a combination of data from randomized clinical trials and observational data describing the safety, efficacy, and effectiveness of drugs in real-world use and access control. Furthermore, initiatives such as PHEN developed European Best Practice guidelines assisting the EU Member States with guidance on the use of personal files and concepts such as "personal utility".

Whereas regulators evaluate the added value of medicines under perfect conditions, they have to judge the likely added value in real-life facing the reality of (i) deliberate use outside the strict limits of the SPC, (ii) ability of prescribers to identify the right patients and (iii) variations in patients' adherence to therapy. There is however great interest in schemes for managed entry and for continuous follow-up of patient use and outcomes.

Specific considerations for the new regulatory pathways for personalised and medicine and other defined categories of products (e.g. applicability of diseases/conditions/unmet clinical needs, number of trials required, appropriate surrogate endpoints) require further deliberation, in conjunction with adequate incentives on the demand side (pricing and reimbursement approaches) as approval, reimbursement and incentives are integrally related. Accordingly, achieving this objective will require collaboration between the EU Commission, EMA and reimbursement bodies to ensure transparency of the intent and application of the regulatory process and to promote use and reimbursement of medicines approved via a progressive regulatory process.

There has been substantial work via the EMA and think-tanks (e.g. CMR Institute) to define a better, more structured and more patient-responsive approach to defining benefit/risk ratio. There have been instances (e.g. HIV and multiple sclerosis medicines, pandemic vaccines) in which patient pressure and/or the urgency of the situation has resulted in regulatory agencies reconsidering their approach to this balance.

In a related topic, clinicians, health systems, regulators and HTA agencies are increasingly demanding real world data on the performance of medicines. With the advent of mobile health and other tools, the collection of such personal data has become much easier and less expensive. There should be models for use of registries or the mining of electronic health records ("personal files") or claims databases. For these reasons, industry must step up its engagement in e-health initiatives to ensure that these efforts cater to our needs as well. In some cases, these data can offset or replace the need for formal Phase 4 studies, with clear economic advantages for sponsors. Standards are beginning to be established at a national level, but it is clearly advantageous for such standards to be applicable across Europe or even globally.

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The new Directive on Patient Rights in Cross-Border Healthcare is a landmark because it codifies the European Court of Justice jurisprudence on patients' rights to be reimbursed from healthcare in other EU Member States. It also creates a voluntary network of National Authorities with responsibility for eHealth. This network will focus on three key areas: guidelines of a list of data to be included in the patient summary records that can be consulted across borders by health professionals; methodology for the use of medical information for public health and medical research (e.g., HTA for quality assurance purposes); and common identification and authentication measures to transfer data in cross-border healthcare, since the data need to follow the patient/citizen. This Directive provides a common European legal framework for dealing with personal health information and personal files. The Directive is now in the transposition phase. Since the mid-1990's the European Court of Justice had to decide several cases which demonstrated the tensions between the European Union and the competence of the Member States in the field of health. While the Court used principles of competition and consumer protection law to extend the impact of the market freedoms on health, the Treaties after Maastricht confirmed the very limited role of the EU in health policies. In principle the Directive affects only a small proportion of healthcare expenditures in the Member States.

However, it might be of particular importance in the field of personalised medicine and healthcare, since personalised healthcare managing the health of individuals may require health services from other Member States as well. The Directive fosters the establishment of networks of reference, it clarifies the reimbursement rules and it provides patients with better access to information regarding health services in other Member States. Art 13 stresses the access to information and the provision/reimbursement of services which are not provided by the country of residence. In addition, Art 15 strengthens European cooperation in the field of HTA, which can be of further added value for personalised medicine and healthcare. Thus, in principle the Directive implies the creation of a common European health data infrastructure.

Examples of Collaborative models to move forward

EurocanPlatform is a consortium of 23 cancer research centres and five additional cancer organizations. Establishment of the consortium was funded by the European Commission with the intention to build a platform for European translational cancer research and to structure translational cancer research by sharing patients, biological materials, technological resources and competences. In order to improve late translational cancer research a decision has been taken to develop a European structure for outcomes research. Fourteen centres in the consortium have decided to start pilot projects to structure clinical effectiveness assays and outcomes research. The project on clinical effectiveness will be conducted together with the European Hematology Association, and a complete structure for outcomes research will start with breast cancer as a model for other tumour diseases. As a pilot study, clinical effectiveness will be registered for innovative anticancer agents for three solid tumours and three malignant

hematological diseases. The planned structure for outcomes research will have the critical mass for collection of relevant and quality assured data in a relatively short period. An important next step will be to reach agreements between the academic centres involved, the pharmaceutical industry, regulatory authorities and health technology assessment organizations regarding data necessary for evaluations of benefits and risks. With the relevant clinical data it will be possible to make the increasingly complex drug development process more effective.

The Innovative Medicines Initiative (see chapter 11)

The Public Health Genomics European Network (PHGEN) In 2008 the European Commission had asked for the development of European Best Practice Guidelines to support the Member States (and other relevant stakeholders) to more efficiently and effectively work together at the European level in addressing the challenges from emerging genome-based information and technologies, and to prepare for the paradigm shift of personalised healthcare. The Public Health Genomics European Network (PHGEN II, EU Project No. 20081302) fulfilled this task and recently produced the first edition of "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies" (www.phgen.eu). These guidelines will assist all EU Member States, applicant and EFTA-European Economic Area countries with evidence-based guidance on the timely and responsible integration of genome-based information and technologies into healthcare systems for the benefit of population health. On 18 and 19 April 2012, the competent authorities of the EU Member States as well as key European and national organizations and institutions from policy-making, academia, and the private sector – among them the European Medicines Agency – came together to endorse the Declaration of Rome on 19 April 2012, a summary of the "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies".

The next steps for PHGEN will be to ensure the implementation of the European best practice guidelines in European countries through the efforts of the well-established PHGEN National Task Forces. PHGEN is currently working towards a Joint Action in 2014 with the support of the EU Member States. Collaboration between PHGEN and the European Regional Office of the World Health Organization is also being explored and links will be maintained with the European Commission.

Learning-Adapting-Leveling model The core diagnostic/therapeutic segment of the market comprising primarily drugs, medical devices and diagnostics is expected to be worth £26 billion by 2015. Improvements in genome-based technologies are primarily responsible for this staggering growth. The market is pioneered by small to medium enterprises (SMEs) regarded as the true innovators of personalized diagnostics market, contributing significantly to benefits to society, in line with Europe's growth strategy EU 2020.

However, both historically and currently, the timely uptake and implementation of these SME-based genomics-related applications in real time is generally slow and penetration negligible.

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The average time to diffusion in healthcare systems is over 10-20 years even with marketing approval (FDA, CE, etc.). As a result, and given the pace of technological development, by the time a relevant application is integrated into the healthcare system, it is considered less relevant because a more effective and efficient application has become available on the market. Consequently, businesses and patients in need of new and more accurate clinical diagnostics and treatment are at a disadvantage. This increases the burden of disease and becomes a development hurdle for companies, leading to product failure and loss of employment, capital and IP.

Based around this bottleneck of healthcare integration, the unique Learning-Adapting-Leveling (LAL) model was developed at Maastricht University. This model is innovative in bringing together in parallel two never-before connected activities: technology transfer, used by industry to translate academic knowledge, patents and applied research into marketable products, and public health assessment tools including HTA. The Learning-Adapting-Leveling model identifies non-synergy between these two different entities as the reason for the bottleneck of technological integration. The model assesses the feasibility of the developing technology from the start to near the end of the technology maturation process for real-time uptake by healthcare systems and policy guidelines, thereby give real-time recommendations to compensate for any gaps in the process prior to launching the product, and helping to build contact with policy.

This model encourages early-on involvement of stakeholders including doctors, industry, patient groups, investors, insurance companies, HTA professionals, promoting cross-talk and public-private partnership. The model also takes into account and assesses the Value of Information and conducts control analysis of possible gaps according to the ten Public Health Tasks defined by the Public Health Genomics European Network (PHGEN, www.phgen.eu). The model has been officially integrated in the European best practice guidelines for QA, provision and use of genome-based information and technologies developed by PHGEN, FP7s and a few SMEs as well as the EU flagship project ICT Future of Medicine (www.itfom.eu).

Conclusions and Recommendations

Science is driving us towards a world of personalised medicines and therefore a potentially more efficient and cost-effective healthcare system. However, a number of hurdles should be addressed to facilitate this process:

- Translation from basic research to clinical research: This requires open research collaboration mechanisms, including access to data and diagnostics which allow patient stratification. It also requires a supportive European legal framework on research enablers (e.g. on personal data protection, stem cells, etc.)
- Translation from research to development of innovative healthcare products: to incorporate the patient perspective and new sciences/genome-based knowledge and

technologies into a more flexible adaptive development model

- Translation from development to healthcare delivery and access: new understanding of disease biology and earlier patient access under adaptive development would also require changes to the way healthcare delivery and reimbursement of health services are organised
- Incentivising research investments: under current regulatory and healthcare systems, personalised medicine and healthcare is not incentivised, as it would give access to only a small patient population..Reflection should be launched on how to facilitate progress in the field. The PHGEN European Best Practice Guidelines have been developed and endorsed to assist the EU Member States in this process.

Against this background

- Collaborative research to enhance disease biology understanding and generating data in support to new citizen/patient centric adaptive development approaches should be encouraged through public private partnerships under Horizon 2020
- The European Commission should secure consistency of legislation governing research enablers with the objective of moving towards truly personalized medicines using identifiable personal data
- The EC should explore mechanisms for exploiting large data sets "owned" by healthcare systems and research infrastructures, ensuring a balance between citizens' ownership of the personal data and the common good (public health)
- The EC should encourage multi-stakeholder dialogue between research, healthcare systems, regulators, citizens and patients to make progress on citizen/patient centric adaptive development of and access to products, therapies and all kind of person-centred interventions

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Action/ changes needed

- update the basic processes of R&D and regulation to allow evaluation of clinical effectiveness and analyses of long-term treatment outcomes with real-world data
- integrate new knowledge into regulatory pathways
- simplify and speed up complex, inconsistent and inflexible regulatory procedures, also taking account of diagnostics
- review systems to incentivise innovation through novel methodologies for benefit-risk evaluation and reimbursement
- more predictable systems to cut costs and speed patient access
- permit collection and pooling and mining of relevant information on benefit and risk
- more pro-active use of conditional authorisation
- progressive management and reduction of uncertainty in adaptive authorisation models

Appropriate mechanisms

- adaptive clinical trial methodologies, with stratification of patients
- wider research collaboration, particularly through PPPs
- involve bio-informatics and systems biology in the clinical research setting
- early engagement of and collaboration between all stakeholders and many disciplines
- quality-assured and harmonised clinical registries for observational studies
- use of electronic patient records and mobile health solutions, including smart-phones
- improved statistical education among industry and regulators

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Mission: greater attention to the role of diagnostics and imaging in personalised medicine - Diagnostics/medical devices and imaging

Diagnostics, both companion diagnostics (CDx) and imaging, are a frequently underrated yet essential part of the personalised medicine equation. To use an everyday allegory, the diagnostic is the navigation system which describes the path, and the medicine is the vehicle which makes it possible to follow the suggested route. While that might paint an over-simplified picture, it does illustrate the importance of the diagnostic. Yet for many, the diagnostic exists in a black box that is either poorly understood or worse, not even taken into consideration.

Companion and molecular diagnostics play an integral role in personalised medicine approaches, forming a very specific technology particular to personalizing treatment. While personalised medicine is certainly not limited to companion diagnostics, they do form a very specific technology which is particular to personalizing treatment and can thus be used to demonstrate the challenges which other types of diagnostics will frequently face as well. Medical imaging has also been a driver in the development of personalised medicine, since it has always been personalised, assessing the location and severity of an abnormality in an individual, and providing phenotyping biomarkers (morphological, biological, functional, metabolical) in a person-centred approach. adiogenomics is an emerging promising field creating a link between molecular diagnostics and diagnostic imaging.

Development stage

For diagnostic development, ever-expanding knowledge of the molecular mechanisms behind diseases and searching for reliable biomarkers to predict treatment responses will not be easy. It will take time and resources, and even then it is unlikely that there will be one biomarker for every given medicine. Diseases are multi-faceted and may thus be characterized by interactions between several biomarkers, or it may not prove possible to identify a biomarker to stratify patient populations into subsets of responders. In spite of these factors, there are ways to improve the development of CDx, thus making the process more effective and likelier to succeed.

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The scientific challenge

Biomarker discovery relies on basic research as well as on collaborative, pre-competitive research bringing together industry and academia. The public-private partnership Innovative Medicines Initiative[12] serves as a prime example of such an undertaking. Biomarker discovery and diagnostic development would also benefit from a more effective future framework for running clinical trials in the EU: for example, endorsement of Informed Consent Forms which are sufficiently open to allow further biomarker research on patients' samples if new knowledge emerges.

Lack of incentives to invest in diagnostic development

The role of diagnostics in personalised medicine is limited by the lack of incentives for investing in their development. Unlike pharmaceuticals, diagnostic tests rarely enjoy partial or temporary market advantage, much less exclusivity. .Potentially costly innovation, including investments in generating clinical evidence, can be reproduced without delay and at lower cost by 'fast follower' developers - and tests for HER2[13] expression, or those for determining genotypic differences in warfarin metabolism, may serve as examples. Furthermore, many countries do not require regulatory approval for reimbursement, which encourages some test manufacturers to forego investment in clinical evidence altogether, depriving the marketplace of transparent performance data upon which to base choices.

There are therefore often relatively few incentives for a diagnostic manufacturer to invest in the development of a validated diagnostic. A logical consequence is that it is usually a pharmaceutical company which initiates and subsidizes the development of a test linked to a specific pharmaceutical product.

Collaboration between pharmaceutical and diagnostic manufacturers

Developing a companion diagnostic requires effective ways of collaboration between pharmaceutical and diagnostic manufacturers, whose cooperation in the field carries a significant potential for innovation and improvement of products to detect and monitor disease, as well as helping to guide the choice of optimal therapy. With different development timelines and lifecycles, different regulatory and reimbursement pathways, different markets and, in many cases, different customers, both sides need to develop a better understanding of each other to ensure successful collaboration occurs.

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12   www.imi.europa.eu

13   A protein encoded in the ERBB2 gene, whose over-expression has been linked to the development of some types of breast cancer, for which it is now used as a biomarker.

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The regulatory environment

Healthcare products should be safe and fit for purpose, both when used to treat patients and when used in treatment decision making. This requires clear, harmonized rules across the EU which recognize the differences between diagnostics and pharmaceuticals, providing appropriate regulation that combines the imperative of patient safety with rapid access to innovation.

The regulatory system of the EU provides two frameworks that determine the pathways for medical devices and diagnostics involved in personalised medicine. Many medical devices such as those used for cancer screening come under the Medical Devices Directive (future Regulation), whereas most companion diagnostics are (and will be) governed by the framework for in-vitro diagnostics (IVDs), which encompasses diagnostic products such as reagents, instruments and systems intended for use in diagnosis of disease or other conditions. Today's system for IVDs is built largely on a self-certification procedure, placing heavy responsibility on manufacturers. Examples of current obligations include having in place a qualitative manufacturing process, user instructions that are clear and fit for purpose, ensuring that the "physical" features of devices and diagnostics do not pose any danger such as electric shocks. If a product fulfils these and other related control requirements, it will obtain a CE mark.

The higher the risk associated with the use of a product, the stricter is the obligation to carry out clinical studies and to involve a so-called "Notified Body" to assess manufacturer compliance with the requirements. A Notified Body is a private organisation that has been accredited by the national authorities to assess if a device and its manufacturer meets the requirements of the IVD Directive[14], and whose services are paid for by manufacturers.

The current framework, which dates back to the 1990s, is currently under revision. If implemented, the EU Commission's recent proposal for a Regulation on in vitro diagnostic medical devices (Proposed IVD Regulation) will change the way companion diagnostics are regulated.

With CDx becoming one of the most important tools in achieving the goals of personalised medicine, it is an obvious shortcoming that the current framework does not formally acknowledge them. Without a special distinction, they have to fulfil only minimal technical performance requirements and qualify for self-certification. This does not adequately recognise the impact a CDx has on a patient receiving the right treatment (or in avoiding the wrong treatment).

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14   Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices , http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20090807:EN:PDF

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The proposed IVD Regulation addresses this gap. It provides a definition for CDx: 'a device specifically intended to select patients with a previously diagnosed condition or predisposition as eligible for a targeted therapy.' It also classifies IVDs into four risk categories. Based on high patient risk coupled with a moderate public health risk, CDx will usually fall into Class C —the second-highest risk class, and requiring in-depth involvement of a Notified Body[15].

Both the specific identification and the change in classification are a step in the right direction. More rigorous review will help ensure the quality of CDx, protect public health, and promote the economic benefits of PM to the healthcare system. However, the definition should be improved to ensure that this unique class of IVDs, which plays an essential role in guiding treatment decisions with specific pharmaceuticals, is subject to a sufficiently high standard to guarantee patient safety:

- The term 'targeted therapy' is generally perceived as limited to the oncology field; it should be replaced with something broader to take into account other disease areas such as infectious and inflammatory diseases.
- There are cases when a CDx identifies precisely those patients who should not receive a certain treatment as they would not benefit or may even experience severe side effects; the definition should reflect this possibility.
- The definition should also cover the fact that CDx tests can simultaneously identify multiple biomarkers.

Clinical Evidence Requirements

The proposal extends and clarifies the rules for clinical evidence ("the information that supports the scientific validity and performance for the use of a device as intended by the manufacturer"[16]) that IVDs have to follow, with requirements proportionate to the risk class. This is a welcome step to ensure that diagnostics undergo an adequate validation process.

At the same time, the hurdles should not be so high as to make it nearly impossible to introduce a diagnostic. Diagnostics are different to pharmaceuticals, with shorter lifecycles and a very different risk-benefit profile, explained by the fact that they do not interact directly with the patient's body; this means that they may merit different standards of clinical evidence in order to balance the risk-benefit profile and innovation. For instance, in the case of a new CDx, the report of the pivotal drug study should suffice to demonstrate both clinical performance ("the association of an analyte to a clinical condition or a physiological state"[17]) and scientific validity

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15   The general principles of classification, however, will still apply for those companion diagnostic that fulfill the criteria of a class D device and in these instances, they will indeed fall under class D and not class C.

16   Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices, Art. 2 (28).

17   Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices, Art. 2 (29).

("the ability of a device to yield results that are correlated with a particular clinical condition or a physiological state in accordance with the target population and intended user" [18]), without need for further scientific evidence. Depending on the study design, scientific validity could be further augmented with information generated in earlier-phase drug studies or exploratory research.

It should also be stated that such joint clinical trials of pharmaceutical and diagnostic are one, but not the only means of achieving the overall objective of clinical evidence. For example, for follow-on diagnostics, where other manufacturers prepare a new IVD for an analyte that was previously included in an assessed and CE-marked CDx, a sufficiently robust clinical evidence report should still be required. Clinical evidence, however, might be appropriately demonstrated by means other than a full pivotal drug study, such as a retrospective analysis of samples.

Coordination with a Drug Authority for CDx

The current framework regulating IVDs does not provide a pathway specific to CDx; it resembles that for any other IVD, and occurs independently of the registration process for its associated drug. This takes insufficient account of the fact that the drug and the diagnostic depend on each other for efficacy and utility. Change is needed to ensure that a companion diagnostic and its corresponding medicine are assessed in a coordinated way.

The Commission's IVD Proposal contains provisions that would support this. When assessing a CDx, a Notified Body is required to consult either a Member State Competent Authority or the European Medicines Agency (in the case of a centrally authorised drug) on the suitability of the CDx in relation to the drug concerned[19].

When a drug and a CDx are developed and assessed jointly, the drug authority is already involved in the oversight of the clinical trial dossier for the pharmaceutical and its related CDx. This requires further clarity as to which aspects the drug authority will be assessing to avoid duplication and double regulation.

However, in cases where the drug authority has not been involved in the clinical evidence provided for the CDx, for example if the development of a CDx takes place only after the drug's approval, it might be beneficial to involve the drug authority in the CDx assessment process. The scope of this involvement should be clearly defined. Given the drug authority's specific area of expertise, it seems reasonable to limit their involvement to a review of the scientific validity of the CDx[20]. Notably, this would also mean that the drug authority would have a

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18   Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices, Art. 2 (32).

19   Proposal for a Regulation of the European Parliament and of the Council on in vitro diagnostic medical devices, Annex VIII, Chapter 2, 6.2, Annex IX 3.6.

20   This would be similar to the situation in the United States were separate submission for a drug and related CDx are submitted to CDER (Center for Drug Evaluation and Research) and CDRH (Center for Device and Radiological Health) respectively, but CDRH defers entirely to CDER for a review of the CDx clinical utility and ruling whether and how the CDx has been shown to be safe and effective for its intended use and necessary to the proper use of the drug product.

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very reduced role in the approval process of a follow-on CDx, as they already would have been involved in the scientific validity and clinical evidence process for the original CDx. In this scenario, a drug authority would assume a role in assessing the changes to an already validated CDx only if those changes have a significant influence on the intended purpose of the device. The proposal provides an ideal opportunity to resolve any confusion regarding the role of EMA, which will be more likely to provide a review than a national drug authority for CDx.

Since the development time for a drug-diagnostic pair is exceptionally long, taking as much as five years or more, many CDx currently under development will already be affected by the new framework. An early, optional dialogue involving the Notified Body, the drug authority and the manufacturers of both drug and CDx could be a means of ensuring that the regulatory and evidence expectations of both entities can be met by the manufacturers. This could also improve the familiarity of regulatory authorities with co-development programmes so as to support a smooth and informed review. At the EMA, mechanisms for early dialogue with drug manufacturers already exist and could be leveraged to support this goal. For example, representatives from the manufacturer of the device and the Notified Body could be routinely invited to CDx related aspects of relevant Scientific Advice meetings for drugs which will be linked to a CDx, for a targeted conversation about the device.

In-house tests

In-house tests are IVD medical devices that are manufactured and used within the same health institution, such as a hospital laboratory, and are not subject to regulation at the EU level. These are generally employed when suitable commercial IVDs are not available, thus fostering innovation and encouraging research and development in the field. Under the proposal, they will, however, be subject to certain aspects of the regulatory framework, albeit with exemptions. Given that CDx are in the second-highest risk class and subject to what is essentially a Class D conformity assessment – whereby all devices undergo design examination, if they were to be eligible for the same in-house exemption as other IVDs they would be largely unregulated.

Imaging biomarkers

Going beyond the specific example of companion diagnostics – and, in fact, beyond the scope of the IVD Regulation – the case of imaging biomarkers may further serve to demonstrate the relevance of a regulatory framework which guarantees appropriate validation of medical devices and diagnostics.

Medical imaging plays an important role in the era of personalised medicine in particular in the areas of disease prevention, diagnosis, therapy, drug discovery, theranostics, image-guided interventions and drug delivery. Medical imaging has always been personalised, providing an

individual phenotyping with the assessment of the location and severity of an abnormality. In the future it will play an even more fundamental role in personalised medicine and should thus be considered an integral part of the entire "-omics" area.

Using imaging biomarkers to streamline drug, tumour and disease progression discovery represents a huge advancement in healthcare. Imaging biomarkers play a key role in particular in new drug development, as the developments in quantitative medical imaging have offered the opportunity of using imaging biomarkers to speed up the development processes of new drugs.

In order to allow an effective use of imaging biomarkers, adequate validation and standardisation procedures need to be in place. The qualification and technical validation of imaging biomarkers poses unique challenges in that the accuracy, methods, standardisations and reproducibility are strictly monitored. The clinical value of new biomarkers is of the highest priority in terms of patient management, assessing risk factors and disease prognosis.
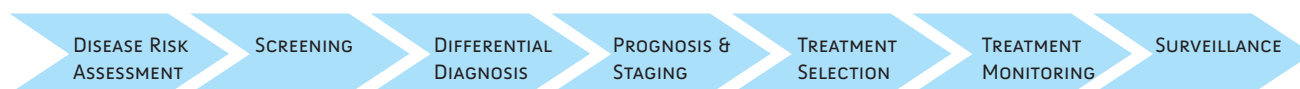
Regulatory processes for imaging biomarkers are very complex at this stage, as imaging biomarkers are not concerned by the CE mark and do not currently fall under the EMA drug approval regulation. They are therefore unlikely to be covered by the EC Directive on in-vitro devices currently under development.

In order to ensure their effective introduction into routine care to the benefit of Europe's patients, structured validation processes are needed that no longer rely on long and resource-intense clinical trials. This bottleneck should be addressed by adopting a facilitated approach that would allow an increased use of imaging biomarkers in clinical trials.

Moreover, there is a strong need to ensure full interoperability between the "omics" biobanks and the imaging databases.

Molecular Diagnostics (MDx)

Besides companion diagnostics, there is a broad class molecular diagnostics that can provide personalised decisions across the course of disease (Figure X - below). These molecular diagnostics assess biological features of patients at a genetic or genomic level and represent personalized result based on biological features of DNA or specific regions or sequences of DNA within the body. Many of these molecular diagnostics are complicated, quantitative and require highly precise methods that often require a centralised lab. These technologies can be catalysts for personalised medicine as they classify disease and identify patients most likely to respond to a particular treatment or services (pharmaceuticals, surgery, radiation, etc), sparing the expense and side effects for those who will not benefit.

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DISEASE RISK ASSESSMENT — SCREENING — DIFFERENTIAL DIAGNOSIS — PROGNOSIS & STAGING — TREATMENT SELECTION — TREATMENT MONITORING — SURVEILLANCE

The promise of molecular diagnostics can be seen across many diseases and clinical settings. Some examples MDx which are commercially available in some countries and include tests which can:

1. Identify which patients are suitable for a heart transplant (Reference: Rosenberg S, Elashoff MR, Beineke P, et al. Multicenter validation of the diagnostic accuracy of a blood-based gene expression test for assessing obstructive coronary artery disease in nondiabetic patients. Ann Intern Med. 2010;153:425–434.)

2. Select which early stage breast cancer patient may benefit from adjuvant chemotherapy (S Paik, G Tang, S Shak et al. Gene Expression and Benefit of Chemotherapy in Women with Node-Negative, Estrogen Receptor-Positive Breast Cancer. J Clin Oncol. 2006; 24(23):3726-3734.)

3. Measures rheumatoid arthritis disease activity by providing single quantitative score tracked over time which can significantly discriminated between clinical responders and non-responders to RA therapy (Curtis JR, van der Helm-van Mil AH, Knevel R, et al. Validation of a novel multi-biomarker test to assess rheumatoid arthritis disease activity. Arthritis Care & Research. 2012; 64 (12):1794–1803.)

An increasing number of molecular diagnostics are being introduced as we better understand the underlying basis of diseases with many new technologies and approaches.

Patient access obstacles for molecular diagnostics

For personalized medicine to reach its full potential, more value needs to be placed on developing well validated, standardized and reproducible diagnostic tools that offer clinically meaningful information leading to better treatment decisions. The two main obstacles for wider introduction and full scale adoption of these tools relate to scientific and market access issues.

a.   Scientific Roadblocks to Early Adoption

The introduction of various biomarkers into clinical practice suffers from challenges in 3 major areas: assessing the complexity of biology, lack of robust studies, and the lack of standardization and reproducibility of currently used tests.

Historically, the development of therapeutically relevant markers has been slowed by

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poor study design, inconsistent findings, and lack of proper validation studies. [Simon, JCO, 2005]. In the literature, you will find many single biomarker studies with positive results without published confirmation studies. Many biomarker studies especially those using high throughput technologies suffer from false positive results and overfitting of data sets. For example, studies which try to correlate genes to the efficacy of a particular treatment or services face significant challenges when more genes are considered because an increasing number of genes will be correlated by chance alone. Therefore, multiple, large studies with homogenous patients populations are needed to develop and validate clinically meaningful biomarkers.

The development of clinically meaningful molecular diagnostics requires robust programs that parallel the requirements found in drug development. The methodology used to validate tests should demonstrate that these biomarkers are analytically validated, clinically validated, have clinical utility, and are cost-effective. A consistent approach for evaluating biomarkers should be considered by central agencies to ensure patient safety and the appropriate use of these tests.

The first step is to confirm that the molecular diagnostic is technically valid, robust and reproducible. Regardless of the technology platform used the molecular diagnostic must be standardized and quality controlled. The process needs to overcome challenges related to items such as pre-analytical issues, heterogeneity of samples, and interpretation of results. There is a need for academia, industry and regulators to be involved in setting up standards and methods to control quality across multiple technologies that are being considered for clinical practice.

One way to clinically validate biomarkers is through prospectively designed studies using archival material from previously conducted clinical studies. These studies differ from retrospective studies that are post hoc analyses or data mining exercises because they require a protocol with a prespecified hypothesis and prospective statistical analysis plan. This approach can facilitate the introduction of new innovative biomarkers with long term follow up. The key to conducting these studies is that clinical trials collect patient material and images to ensure that the most promising biomarkers of the future can be validated at the conclusion of these studies. Accomplishing this requires strong collaboration among clinical study groups, academia, pharmaceutical companies, medical device and diagnostics companies. Another way to validate biomarkers is to incorporate these markers in clinical trials from the beginning.

Once a test is validated clinically, it is important to demonstrate clinical utility or that a test is fit for purpose. The molecular diagnostic should demonstrate that it provides additional information beyond what is currently available and leads to a specific health benefit. If the original test wasn't developed with a specific clinical question in mind, it could fail at this stage because it doesn't offer useful information to clinicians. For

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example, a test that identifies patients likely to become diabetic would be interesting, but the clinical recommendation in most cases would be to modify ones lifestyle -- which wouldn't translate into a treatment change from a patients current episode of care. The test needs to provide useful information in the management of the patient and does guide treatment decisions for physician and patient.

Since many small and midsize companies are developing molecular diagnostic, it will be important that appropriate incentives are established to facilitate development of tests that can be readily offered to patients that fill unmet needs. Fulfilling all the evidence requirements of a molecular diagnostic is significant and requires a substantial investment, so developers of these technologies need a clear pathway to introduce these technologies to European healthcare systems.

b.   Obstacles to Market access of Molecular Diagnostics

There is a need to clarify how molecular diagnostics should be regulated and reimbursed by defining the evidence requirements to ensure the safe use of these advanced diagnostic services.   HTA bodies need to build capacity and knowledge to support the assessment of molecular diagnostics which differs from pharmaceuticals and medical devices. Health technology bodies are typically focused on evaluating quality, efficacy, safety, efficiency, and equity which are not always translatable to molecular diagnostics which are typically evaluated based on analytical validity, clinical validity, clinical utility and cost effectiveness.   A specific evidence framework should be established to evaluate molecular diagnostics and these requirements should be standardized across European agencies. This evidence framework could be integrated into the reimbursement pathways for the various healthcare systems.   The methods used to evaluate the economic value of these tests should be specified by each healthcare system to ensure that the test developers can conduct appropriate studies. Importantly, national and regional bodies need to clarify what is the willingness to pay for diagnostic tests in each system. Molecular diagnostics which support personalized medicine can be more readily introduced if clear regulatory and reimbursement pathways are defined. This field would benefit greatly with from the development of a centralized evaluation framework to determine when a biomarker meets safety, efficacy and quality standards for clinical use and reimbursement.

Once a test is approved for use and reimbursement, there are still challenges in bringing these technologies to market related to how budgets are allocated. Often the costs for these tests are allocated to one budget but the potential savings are seen in other areas of the healthcare system. For example, a test may reduce the use of an expensive treatment, but there may be resistance to use the test because it is additive for the laboratory budget even though the cost savings are significant overall to the healthcare system. These budget silos in many healthcare systems can only reconciled with major

restructuring of the healthcare budgets. In addition, hospital or physician reimbursement can cause barriers to adoption of certain technologies as there may be disincentives to use a test that may reduce a treatment that is profitable to a particular stakeholder.

Education is also needed to enable to use of molecular diagnostics in clinical practice. Since many healthcare professionals have not received formal education regarding genomic medicine, there is a tendency by many not to accept these technologies. There is a specific need to educate physicians on how to assess these diagnostic tools. Since the study designs that validate these technologies are different, physicians need a clear methodology on how to critically assess these tools so they can feel comfortable incorporating them into their clinical practices. Additionally, physicians need appropriate patient educational materials that they can use to enable shared decision making with their patients.

Patient Access

Following CE marking a CDx can in theory be used to guide clinical decision making. In practice, the CE-mark is one, but far from the last hurdle a CDx encounters on its path to widespread availability.

Diagnostic reimbursement

One of the core principles of personalised medicine is that a medication and a diagnostic depend on each other. A lack of coordinated timing in relation to reimbursement approval of a CDx and its associated medicine results in delays for patient access to that medicine. While pharmaceutical pathways for pricing and reimbursement decisions are usually well-defined and have clear timelines attached to them, the same is not true for diagnostics. Diagnostic reimbursement tends to be fragmented, often even within the same country. In many cases, a diagnostics manufacturer is incapable of developing a companion diagnostic alone. Considerable investment from partnerships with pharmaceutical companies is needed to finance many of the clinical investigations involving companion diagnostics, both because diagnostics companies do not have the resources to cover the costs alone and because the current reimbursement framework makes it uncertain, even unlikely, that their efforts will be rewarded.

Lab infrastructure

For a drug/diagnostic combination to be of benefit to patients, biomarker testing must be available in an efficient and timely manner. Hospitals and labs should be adequately equipped with competent personnel and medical technology to be able to deliver on the promise of

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personalised medicine. The French National Cancer Institute, for instance, has successfully set up 28 hospital molecular genetics platforms to provide French cancer patients with routine screening for genetic mutations. While this will require short-term investments to install the necessary infrastructure, it will lead to better care for patients and, in the longer run, is likely to generate cost savings.

Education of healthcare professionals and patients

Since there is a tendency to underestimate the importance of a diagnostic test in treatment decision making, and given that the test is an integral part of a personalised medicine solution, there is a need to shed light on its purpose and characteristics. A patient needs to understand the purpose and benefit of the involved diagnostic tools so as not to perceive them as just another layer of complexity. Educated patients will understand that such a test may be necessary to decide on the right treatment, one that respects genetic differences between people and molecular differences between diseases. Personalised medicine cannot succeed without appropriate awareness amongst physicians as well as a willingness and ability to use such CDx/drug therapies. There is a need for coordinated, interdisciplinary collaboration to ensure that health professionals are educated in the field.

Conclusions

The development of personalised medicines is already challenging in and of itself. Once the difficulties in the development stage have been overcome and a drug-device combination is ready to be used in clinical practice, the package encounters a range of new potential challenges on its way to the market: a lack of coordination between the regulatory pathways for pharmaceuticals and diagnostics, competition for the CDx from other testing methods of uncertain quality, a reimbursement culture which frequently fails to reward the innovative value of a high-quality test, and a frequent lack of understanding related to its importance.

Appropriate regulation can help ensure that scientific and technical advances in biomarker science are reliably translated into safe and effective diagnostic tests that can positively impact patient welfare. Because CDx can direct life-or-death treatment decisions for individual patients, a higher degree of regulation is warranted and welcome. The new provisions in the IVD Proposal are a step in the right direction. Of particular benefit would be provisions to define CDx and their placement in the second-highest risk class.

Also beneficial are the efforts to coordinate the approval process for CDx and their related drugs, for example by involving EMA in their review as necessary. However, more clarity regarding the mechanism of coordination might be needed so that appropriate steps can be incorporated into the long co-development process of a personalised medicine solution. By limiting the involvement of the drug authority in the assessment of the scientific validity and clinical evidence, a duplication of regulatory obligations could be avoided. It would also limit the risk of a medicine's approval being delayed due to lengthy diagnostic review. The EAPM

recommends the development of a guideline on the level of clinical evidence a drug authority might ask for. Regulation is also warranted regardless of the identity of the CDx manufacturer. The decisions driven by a CDx are of vital importance to a patient no matter its origin; for this reason, quality standards should be identical and the same amount of clinical evidence should be required, regardless of whether a test is manufactured by the diagnostics industry or a hospital laboratory.

At the development stage, there is a need for

- Focused, transparent development pathways for diagnostics and imaging biomarkers
- Investments in establishing and expanding biobanks
- More incentives and greater allocation of time and resources to developing diagnostics
- More research collaboration between industry and academia
- More research collaboration between pharmaceutical and diagnostic manufacturers
- More effective clinical trials regime that is sufficiently flexible to allow for late-stage biomarker research, e.g. adaptations of informed consent to allow re-use of samples

Regulation should allow for

- Appropriate, harmonized regulation for all types of medical devices, in vitro diagnostics and imaging biomarkers, balancing patient safety with access to innovation
- Early dialogue between manufacturers and authorities
- Guidance around clinical evidence requirements
- Appropriate clinical and analytical evidence requirements for in-house testing
- Formal regulatory acknowledgement of the significance of companion diagnostics
- Rigorous but proportionate and timely review, duly coordinated with review of corresponding medicine

Market access should be governed by

- **Reimbursement**
  - *Clarity around reimbursement processes for diagnostics*
  - *Shift towards value-based pricing*
- **Coordination of reimbursement for medicines and companion diagnostics**
- **Infrastructure**
  - *Adequate medical technology infrastructure for testing depending on complexity*
  - *Quality initiatives*
- **Education**
  - *Physician education across different specialties*
  - *Patient education*
  - *Public education*

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Action/ changes needed

- formal regulatory acknowledgement of the significance of companion diagnostics, and rigorous but proportionate review, duly coordinated with review of corresponding medicines
- more incentives and greater allocation of time and resources to developing companion diagnostics
- a harmonised EU regulatory framework balancing patient safety with access to innovation
- a more effective clinical trials regime
- coordination of reimbursement for medicines and companion diagnostics

Appropriate mechanisms

- more research collaboration between industry and academia
- more research collaboration between pharmaceutical and diagnostic manufacturers
- adaptations of informed consent to allow re-use of samples
- early dialogue between manufacturers and authorities
- regulation of in-house substitution of companion diagnostics
- adequate medical technology infrastructure for testing in hospitals and labs
- patient education

Mission: facilitating the wider introduction of personalised medicine - ICT tools

New information and communication technologies for detailed individual characterisation of individuals at the molecular level have been, and will remain, crucial in initiating the move to personalised medicine. Personalised medicine cannot exist without advanced technologies, particularly in relation to data generation and handling (Harvery et al., 2012). Further novel technologies will be necessary if the vision of personalised medicine is to become a reality. Genomics, epigenomics, proteomics, metabolomics, lipidomics, and other 'omics technologies, such as analysis of the microbiome, as well as environmental (including lifestyle-related) and other datasets, will be required alongside imaging and physiological monitoring. New technological solutions will be necessary to collect, integrate, and analyse this information. The technology required to support personalised medicine thus faces a massive data-handling challenge. Volume, variety, velocity and value become the four keywords that characterise this massive data-handling requirement. Computations that before took several days can now — with the right ICT setup — take only a few hours. Distributed computing and cloud computing are just a few of the architectures that can ease the burden of processing and analysis by scaling ICT resources as much as the data being processed demands.

The most critical current issue is not data collection, but how these data can be used to predict individual risk, disease course, treatment response, and the likelihood of adverse events. The current potential for data generation, particularly through 'omics technology, far outstrips current resources for data integration and analysis. One of the biggest challenges at present is to increase our ability to integrate and interpret different datasets and link the findings to specific outcomes in individual citizens. A linear approach is no longer enough: We need to be able to understand the functioning and cooperation of different sub-sets within the system in a dynamic manner: understanding the system in flux. The challenge, thus, is to generate technological solutions that can process the output from multiple core technologies used for various specific purposes. Integrative platforms assuring the interoperability of data as well as technologies are one of the key stepping stones to permit the fundamental move from a traditional disease model towards a systems-based mechanistic approach to health and disease.

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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) brings together all existing genomics centre within a collaborative platform designed to support the implementation of next-generation sequencing as a routine clinical decision making tool in 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.

This also requires that the data be of sufficient quality. And to allow integration of information from multiple sources, the data must be well characterized, standardized, and compatible. In addition, other demands - not just processing power - are placed on ICT by personalised medicine. Storage of the vast amounts of data that are being generated may itself become a limiting factor. And the necessary re-use of personal data presents other delicate issues. Assuring adequate consent of data originators (patients or healthy citizens) is not a straightforward task, given increasing difficulties related to foreseeing future use, and unintended consequences, such as breaches of privacy or confidentiality[21]. The willingness of large numbers of people to contribute biological material and/or 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. The processes of health data reuse need to be transparent with the patient fully informed, and governments must play a seminal role. The cornerstone of data sharing and reuse will be trust, and a trustworthy process for handling citizens' and patients' health data is needed, constructed with the close involvement of citizens.

Also, collaborative settings amongst universities, companies, healthcare providers and other actors require well thought-through governance principles based upon strong data protection principles supported by a high level of security. Privacy and security are key enablers for safe adoption of new health information technologies, minimizing the risk of breaches and other security incidents, building trust, and accelerating adoption and realization of associated benefits.

The technological component of a trustworthy system concerns the design and implementation of ICT tools and services able to guarantee data quality and data security, as well as to provide interoperability, adaptability and scalability. Specific projects funded by the EU and by the IMI initiative, such as EHR4CR, are dealing with such challenges, with

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21   The most relevant and reference for re-identification of individuals in anonymised genetic databases : Gymrek, M. et al. Science 339, 321–324 (2013). For an overview of what the problems related to this are, and how they could be addressed, see Prainsack B, Buyx A : A solidarity-based approach to the governance of research biobanks. Medical Law Review (online first : doi: 10.1093/medlaw/fws040) (2013)

the perspective of defining use cases, tools, technologies and a business model for data reuse. In particular, the EHR4CR business model includes accreditation and certification plans for EHR systems that can be integrated within a system for data reuse.

Data integration overlaps with the concept of data sharing, but the two are not identical. Sharing's dimensions include   (a) vertical sharing between data volunteers and primary researchers; (b) horizontal sharing between data volunteers (increasingly common on web-based platforms such as 23andMe, PatientsLikeMe, Quantified self, etc); (c) horizontal sharing between primary researchers (d) horizontal and vertical sharing between primary, secondary, and tertiary researchers; (e) open source (everything is open to use for everyone, including the public – can be subject to conditions, or not). These different dimensions raise different IT challenges.

Commercial interests too can present barriers to data sharing. The pharmaceutical and diagnostics industries are potential allies in the development of personalised medicine, but could also restrict access to important information unless a robust framework for pre-competitive public-private partnerships is established.

Human resources will also require attention. Technology solutions can deliver results only if there are trained professionals to develop and implement them. Networks are needed not just for sharing complex biological information but also to promote the training of technologists and the intellectual and communications infrastructure that supports cross-disciplinary interaction. And policymakers and educational authorities must create the intellectual and communications infrastructure to support cross-disciplinary interaction and training for ICT and healthcare professionals.

Health professionals and experts on the social, regulatory and ethical dimensions of disease research must work with ICT professionals in design. There is a need for low-threshold technological interfaces that support the interaction between data volunteers and healthcare professionals in personalised medicine. Definitions are also needed of 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. ICT solutions will also be needed to support healthcare professionals in providing straightforward responses to the concerns of patients about future illness, treatment options and opportunities for prevention.

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. The core goal of the project is to generate a model of human liver physiology, morphology, and function through the integration data at multiple organisational levels, from subcellular events to whole-organ physiology. The outcome will be a modifiable platform with which to analyze unmet medical needs and provide key insights into health and disease, using systems

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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 establishing international links. This initiative could provide useful insights into the coordination of activity across multiple centres that is likely to be an increasingly common feature of personalised medicine.

Further challenges can be anticipated as the emphasis in personalised medicine shifts away from patients with clinical symptoms, and towards healthy citizens, with increasing emphasis also being placed on prevention. Technology must become available to effectively deliver meaningful information on risk prediction, molecular and physiological phenotyping, treatment outcomes and monitoring in a form that supports clinical decision-making. Combined genomic and phenotypic analysis will be highly complex, requiring algorithms and mathematical models to provide a clear diagnosis and therapy. Hundreds, or maybe even thousands, of data elements will have to be considered, along with all the factors influencing the individual's condition. It will be necessary to make assessments of current status and risk, and draw up personal plans accordingly for management of the individual's health, risks and diseases. A doctor is incapable of processing so many elements, but ICT can make it possible.

Additional technology developments will be required to support lifelong monitoring of individual health, including more sophisticated use of electronic health records. ICT research needs to explore non-invasive technologies and solutions for real-time monitoring, such as sensors to generate and store real-time information about individual health status, as well as interfaces for citizens that facilitate informed choices about monitoring and sharing of different types of data.

ICT has an essential role in educating, and improving the engagement, different actors in the health domain, including patients and citizens. It can make a crucial contribution both in assuring compliance in complicated therapies, and in lifestyle coaching for prevention and health optimization. In addition, so that healthcare professionals feel comfortable in adopting the new disciplines of personalized medicine, ICT can underpin robust information and communication platforms integrated into healthcare services that can collect and analyze data, assess and interpret it, develop personal plans, follow-up implementation and provide updates and revisions.

The European Commission (Directorate General for Health and Consumers) had asked to develop "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies" to support the EU Member States, Applicant and EFTA-EEA countries as well as other relevant stakeholders to more efficiently and effectively work together at European level in addressing the challenges deriving from emerging genome-based information and technologies and to prepare for the paradigm shift of personalized healthcare in time (Testori-Coggi, 2011). The Public Health Genomics European Network (PHGEN, www.phgen.eu) fulfilled this task and produced the first

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edition of these European best practice guidelines, which have recently been endorsed as the "Declaration of Rome" on 19th of April 2012 by the EU Member States and European and national key stakeholders, including the European Medicines Agency, EMA (Brand and Lal, 2012).

At the same time, the closed circuit thus created can feed science and help in managing disease risk and progression, by identifying new hazards of an environmental and genomic nature. But for this to happen, the tools and processes for data collection and analysis must be standardised across research sites, and research activity at different sites must be integrated to maximise synergies. Scientific research will have to be integrated with healthcare to ensure effective translation.

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22   Harvey A, Brand A, Holgate ST, Kristiansen LV, Lehrach H, Palotie A, Prainsack B. The future of technologies for personalised medicine. New Biotechnol (April 2012) ; doi:10.1016/j.nbt.2012.03.009.

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Action/ changes needed

- new solutions to collecting, integrating and analysing data
- increased ability to integrate and interpret different data sets and link the findings to specific outcomes in individual citizens
- acceptance of data sharing
- acceptance of re-use of data
- attention to prevention and prediction in life-long monitoring
- wider patient and citizen acceptance of technology and of personalised medicine

Appropriate mechanisms

- adequate advanced technologies for generation and handling of data from multiple sources
- standardisation and quality assurance of data
- adequate storage
- adequate ethical frameworks covering contributions of biological material and data
- a robust framework of pre-competitive PPPs to satisfy commercial concerns on data sharing
- adequately trained ICT and healthcare professionals
- adequate ICT support for physicians
- non-invasive sensors of individual health data
- education of patients

Mission: greater implication of patients in treatment decision-making and health management - An informed, engaged and empowered patient

Patients are typically seen only as passive recipients of care. A more desirable model of personalized medicine better enables patients to be participants and guides in their own health care. Patient participation in treatment decision-making is being increasingly advocated as a desirable model especially when patients present with serious illnesses, when there are different treatment options, and when the gains of treatment have to be weighed against possible adverse effects (Robinson and Thomson, 2001). Also, involving patients in treatment related decision making is in line with the increasingly acknowledged patients' right to autonomy and self-determination. Such an approach adopts a bio-psychosocial dimension rather than, or in addition to, a biomedical one. This starts with the attitude that the patient is a person and not merely a body with an attached illness, and it supports sharing of power and of responsibility between the doctor and the patient (Mead and Bower, 2002).

This approach is an integral part of personalized medicine, as both aim at tailoring medical treatment to the individual (physiological and psychological) characteristics of each patient.

Personalized medicine is leading to changes in the medical approach: several research strategies and scientific fields have been more fully developed, such as genomics and pharmacogenetics. In the treatment setting, efforts by academia and industry have been focussed on how to improve diagnostics and prognosis of diseases and how, through the development of predictors of drug response and adverse effects, to improve the safety and efficacy of drugs. For instance, in order to reach customization of patient care, personalized medicine uses genomic information to take advantage of a molecular understanding of a disease. However, other fundamental components of personalized medicine have a relevant role too in deciding about treatment: besides the detailed description of both the biological makeup of the individual and the molecular characteristics of the disease, other patient variables need to be taken into account such as relevant information on lifestyle, cognitive attributes of the patient, and other environmental factors. Indeed, the way in which each patient reacts to his/her illness, decides about treatments, and interacts with health care adds new dimensions to human uniqueness in the same way that genetic information does. Patients psycho-cognitive aspects also need to be factored into the picture by defining a personal profile of how the patient recognises his/

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her specific needs and values, habits and behaviours, hopes and fears, beliefs and cognitive dispositions (P-Five Medicine: Gorini and Pravettoni, 2011). Approaches that exclusively rely on biological and medical information limit their own effectiveness, since psychological dimensions impact on treatment efficacy, as they may interfere with the predictability of treatment effectiveness. For instance, a treatment that was predicted to yield good results because it was perfectly determined by analysis of biomolecular, genetic and imaging data may turn out to be ineffective for an anxious and depressed patient who fails to take the prescribed medicines in the prescribed manner, due to that very psychological distress.

To be fully effective, personalized medicines needs engaged and informed patients who are encouraged to discuss various treatment options and their possible consequences, and then to arrive at an informed determination about the best action. This engagement ensures that patients remain involved in following the various stages of treatment evolution, and that they maintain open channels of communication with their health professionals. The opportunity to be fully informed about one's own disease situation leads to clear understanding of the state of affairs at any time during and after therapy.

Patient engagement

From the patient's point of view, the emergence of personalized medicine in health care translates not only into fewer side effects and better results of treatment, but also into higher engagement in their personalized treatment and management plans, and an increased responsibility to control their own health care.

The possibility of being involved in treatment decision-making is of particular importance in life-threatening diseases, whose treatment course passes through key decision points. In particular, this holds for those illnesses whose treatment options do not lead to clear-cut differences in survival outcome, but which may vary in their impact on the patient's physical and psychological wellbeing (Peters, Hibbard, Slovic, et al. 2007). For instance, for many cancer types, patients who exercise control over decisions regarding their treatment have better outcomes in terms of patient satisfaction and compliance (Gaston & Mitchell, 2005 and Pipe, Conner, Dansky, 2005).

A core aim of personalization is to acknowledge the position of patients at the centre of the endeavour, not merely as receivers of care but actively contributing and participating in the process of care. Such an attitude encourages so called collaborative cognition (Meegan and Berg, 2002), which is the ability to work through complex situations conjointly, resulting in emergent, collaboratively generated ideas which correct misconceptions and increase options, self-efficacy, and learning. This holds not only among the various professionals from different disciplines, who have to interact to deal with all the different information sources, but also the patient.

However, a shared decision process does not imply forcing every patient to assume power and responsibility. Indeed, some patients still prefer to delegate total responsibility for their care to their healthcare professionals: in particular, the elderly, disabled, socially deprived, ethnic minorities or very young patients may choose to do so or be incapable of understanding or processing the necessary information. In such cases, however, patient engagement is still important in that it encourages patients in providing information about their health and wellbeing values, their informational and practical needs, the treatment side effects, and so on. The more engaged is the patient, the more abundant and precise will be the information flow from patient to health professional.

Information exchange and patient-healthcare professional relationship

Health literacy is closely associated with empowerment (Kickbusch & Maag, 2005) because it entails people's knowledge, motivation and competences to access, understand, appraise, and apply health information needed to make judgments and to take decisions in everyday life concerning healthcare, disease prevention and health promotion (Sorensen et al., 2012).

However, the process of involving patients in their care decision implies not only health literate patients, but also a "health literate friendly system" that provides transparent and credible information about the chances of benefit and the risks of harm from distinct medical diagnostic and therapeutic interventions, and that decrease the information and power asymmetry between doctors and patients (i.e. the doctor knows everything, the patient nothing). This means increasing patients' medical information through a language that is matched to their educational level, and allowing patients to effectively state their own preferences and concerns. The information exchange needs to be two-way: the health professional provides information to help explain the clinical situation and subsequent decisions, and the patient provides information on his/her values, preferences, lifestyle, beliefs and previous knowledge about the illness and its treatment (Charles, Gafni and Whelan, 1999). The first type of information flow ensures that all the relevant treatment options are on the table; the second ensures that these can be evaluated by both the healthcare professional and the patient within the context of the patient's specific needs. When this happens, the health professional can create the shared knowledge necessary to consolidate the patient's engagement and to successfully execute the shared decision process.

There is some evidence that good information exchange within a good healthcare professional-patient relationship could be considered as a therapeutic intervention (Mossman, Boudioni and Slevin, 1999) because it helps in preserving or improving the patient's ability to deal with his/her illness, and even in maintaining a good quality of life. This is particularly relevant in the chronic phase of any disease, as it helps to increase the patient's vitality and social functioning, and to reduce the incidence of depression and anxiety.

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A limited level of health literacy, ie a minimal understanding of medical information, may hinder the whole process. Limited health literacy is not only an issue for vulnerable groups such as elderly people or people with low education. A recent study revealed that 47% of the general population faced difficulties in accessing, understanding, judging and applying information to make decisions regarding their health (HLS-EU Consortium, 2012). And several studies focussing on the assessment of the most common conceptualization about cancer found that most people know very little about it. Downs and colleagues (2009) found that, on the surface, many interviewees seemed relatively well informed, talking about risk factors, eating habits, and treatments, for instance using words like "remission." However, further probing showed that many knew the terms, but not the underlying concepts: their mental models were typically incomplete, inconsistent, and error-laden.

When individuals are diagnosed with a serious condition, they have to absorb a series of new details about their illness. To make sense of the new information, and to reason on the details, patients have to integrate the new information with their existing beliefs, which determine what data and what perspectives are examined, acting as a sort of filter through which they can look at the situation.

Several difficulties may arise both when patients have misleading existing beliefs or "knowledge", or none at all about their illness. In the former situation contrasting and inconsistent beliefs lead to the construction of a fragmented and confusing overall picture, making people feel overwhelmed. Thus, patients may retain disparate beliefs, loosely organized around whatever overall mental model of their illness they happen to have (Downs et al., 2009). In the latter case, it is known that patients with low health literacy tend to have poorer health status, tend to be less likely to adhere to prescribed treatments or to comply with self-care plans, and are likely to experience more drug and treatment errors (Institute of Medicine, 2004). So the comprehension of medical terms is fundamental to patient engagement, and achieving a greater ability to understand medical terms in the population is integral to improving the health of disadvantaged populations (Coulter & Ellins, 2007). For instance, from 40% to 60% of medical information provided by health practitioners is forgotten in a few minutes after it is heard, and these percentages increase in old age; furthermore, not all the information "remembered" is correctly recalled (Kessels, 2003).

Knowledge also confers confidence: patients are more likely to trust their capacity to make decisions when efficiently informed (Henderson, 2003). Hence, limited health literacy is a public health challenge, which should be taken into account by health professionals and decision makers when improving patient empowerment.

Health professionals' role in informing and engaging patients within a personalized medicine context

The role and degree of patients' preferred involvement in care decisions, as well as the volume of information desired, depends upon psychological, cognitive, social and cultural characteristics of each patient, as well as upon the characteristics of the healthcare professional-patient relationship (e.g., Harris, 1998). Such an observation explains why empowering patients is not easy. In order to incorporate patients' preferences in clinical decisions, and considering that patients' communication styles vary from patient to patient (influencing the physicians' behaviour), the physician should:

- recognize the patient's health literacy;

- monitor and facilitate patients' understanding of diagnosis and of therapeutic strategies;

- provide information about different treatment options, the possible benefits and risks and the rationale for diagnostics and pre-emptive testing;

- assess patients' decision-making needs (e.g., decisional conflicts, values, willingness to participate/not participate in the decision process, family/social support and resources);

- monitor and facilitate patients' ability to communicate preferences, values, lifestyle.

These are complex talents which allow the healthcare professional to ascertain whether the patient is sufficiently knowledgeable and confident to construct informed preferences.

What can health professionals do to improve health literacy and the possibility of patients to understand their disease? Given that it is the responsibility of health professionals to speak to patients in an easily understandable language, several strategies have been proven to be effective in improving the comprehension of medical terms (for a review: Sudore and Schillinger, 2009), such as well designed written information used as an adjunct to professional consultation (McPherson, Higginson, Hearn, 2001); websites (Gustafson, Hawkins, Boberg et al., 2002); and targeted mass media campaigns (Grilli, Ramsay and Minozzi, 2002). However, in public health campaigns, other professional figures, such as nurses and community pharmacists have a crucial role in increasing the comprehension of medical terms, and in spreading key healthy lifestyles messages. Lifestyle messages such as eating a healthy diet, taking regular exercise, stopping smoking and reducing alcohol intake are particularly relevant in that they both improve general health and might reduce the risk of developing heart disease, diabetes and different types of cancer, as outlined in the European Code Against Cancer[23].

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23   European Code Against Cancer (2003), available at: http://www.cancercode.org

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Clear and extensive information provision leads both to a good understanding of one's illness, and to an easier joint decision-making and a deeper patient engagement. These aims are easier to accomplish when information is given both in oral and in written forms, although frequently patients' primary preference is for such information to come in spoken form from their health professional (Raynor et al., 2007).

Health professionals should also be aware that an information overload may be negative, in that patients may try to reduce the cognitive effort required to process all the information by oversimplifying complex situations (for instance not appreciating that both high risk and high benefit coexist: Epstein and Peters, 2009). As a consequence, information overload, or unwanted details, could diminish the logical consistency of patients' thoughts, and even drive patients away from engagement and from participating in decisions (McCaul, Peters, Nelson and Stefanek, 2005). In this regard, several research projects have shown a high variability of information desires among patients: there is a substantial variation among patients about:

- the ideal amount of information (in fact, the majority of patients, but not all, want to be extensively informed);

- what type of information is considered relevant and therefore important;

- for what purpose the information is needed. (Jenkins, Fallowfield and Saul, 2001)

In addition, patients particularly want information about medicines, firstly to help decision-making, and then for ongoing decisions about the management of those medicines (Raynor et al, 2007). In this respect, community pharmacists may provide expert information about medicines, medical devices and other pharmacy products – for example relating to prevention and management of side-effects, pharmacological interactions and instructions on how to take the medicines to avoid medicine error and improve adherence. Patients value such focussed information about medicines (Raynor et al, 2007), and they prefer an approach to information tailored only to specific patient groups (Dickinson et al, 2012). Community pharmacists may also give advice on medicine-medicine or medicines-patient interaction, assist patients in self-management of their disease, and direct more serious or new cases to the most appropriate health professional or health service. Several research groups have shown that community pharmacists have a significant impact on motivating individuals to see a physician for follow-up care. Their role is therefore key, as people with chronic diseases visit their community pharmacists more frequently than any other healthcare professional.

The information exchange between health professionals and patients also covers the chance of benefit and the risk of harm of a given treatment (Bogardus, Holmboe and Jekel, 1999). The optimum methods for expressing such information have not yet been determined but it appears that information on side-effects in numerical form, rather than verbal descriptors, results in a more accurate estimation (Raynor et al, 2007). There is less certainty about the

presentation of benefit information, with some evidence that numerical presentation may hinder comprehension due to frequent misunderstanding of graphs on survival chances, etc. (Hamrosi et al 2012).

The best strategy to communicate risks is ultimately a multifaceted approach that describes both the unwanted outcome and the frequency of that outcome using a combination of techniques, such as qualitative terms, numerical expression, examples from everyday life, and maybe some visual aids such as graphs. The healthcare professional may select which format is most helpful for a given patient, and build the discussion around that (Bogardus et al., 1999). Such a strategy accommodates patients with diverse preferences and abilities for understanding risk information.

A further feature of personalized medicine that health professionals have to address with their patients, in order to maintain the effectiveness of the information exchange and the patients' engagement, is related to the increased emphasis on diagnostics and pre-emptive testing arising from the revolution in genomics and molecular imaging. Indeed, the diagnostic testing necessary to identify the exact disease, and how the patient can benefit from targeted therapies, requires information about the patient's unique physiology, about the physiology, if applicable, of the virus, bacteria, or tumour, and about the patient's ability to metabolize particular drugs. Patients need to be helped in understanding that the path towards obtaining the benefits promised by personalized medicine may require many diagnostic procedures, including for instance more invasive tests. Also, patients need to be helped in keeping and/or increasing their confidence in such diagnostic tests, as reliable instruments for giving correct results — especially when these results are used in making major medical decisions. Health care professionals have also to deal with patients' expectations about an innovative treatment, perhaps hyped by the media or the Internet perceived as of higher quality with respect to traditional treatments. Sometimes, the results of the diagnostic indicate that a particular patient is not eligible for a given treatment. This possibility has to be explained to patients at the earliest moment, certainly pre testing. There is a danger of patients feeling discriminated against because their genetic makeup is "not right". and this might lead to a fracture of the communication between patient and health professionals, and the patient's disengagement. It is therefore important to continuously assist patients in understanding clearly the background of any decision made on their treatment.

Many requests for information posed by patients will be answered by nurses, who in the personalized medicine framework become frontlines of patient care and need. According to the Consensus Panel on Genetics/Genomics Nursing Competencies (2006), nurses will increasingly be called upon to use genetic- and genomic-based approaches and technologies in client care, and therefore they should become knowledgeable about and competent in genetic- and genomic-related healthcare. So the nurse's role is crucial in maintaining good communication with patients, in recognizing the patient's health literacy, in monitoring patients' understanding of diagnosis and of therapeutic strategies, and in facilitating the patients' ability to communicate effectively.

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Healthcare professionals (mainly physicians and nurses) are increasingly required to assess patients' decision-making preferences as wide variations in both preferred and actual roles have been reported (for a review: Tariman, Berry, Cochrane et al., 2010). For instance, whereas patients with advanced cancer mostly express a desire for full information, not all of them wish to actively participate in decision making (Gaston and Mitchell, 2005). Several studies have attempted to determine which factors are associated with a high or low level of desired participation in the decision process: many have shown that higher education level, female sex, age younger than 45 years are associated with patients' preference for a more active role (for a review: Singh, Sloan, Atherton et al., 2010). A review of data from US and Canadian cancer patients found that roughly 50% of cancer patients prefer to have a collaborative relationship with their physician in treatment decision making, and the remaining 50% are split equally between preferring active and passive roles (ibid.).

The PACE Cancer Perceptions Index Survey found that significant percentages of people surveyed want more information and engagement surrounding treatment for cancer. For example, just under 50% of cancer patients surveyed worldwide believe that not enough help in navigating treatment options is available to patients. About four in 10 patients also believed that there is not enough patient involvement in decision making on cancer treatment; in the European countries surveyed, the percentages ranged from a low of 25% in Italy to a high of 58% in Germany who believe that there is not enough patient participation. Four in 10 worldwide also believe that there is not enough specific information about the nature of certain types of cancer available to patients; on this point the European responses ranged from a low of 31% in Italy to 54% in France who believe that not enough information is available. With regard to decision making, the survey found that large and consistent majorities of respondents (75% in France and Germany, 73% in Italy and 72% in UK) believe that patients or their families should be the primary decision-makers about whether a cancer treatment is undertaken to extend a patient's life. The survey also confirms the relatively low level of basic literacy on cancer and personalized medicine. For example, the PACE survey found that upwards of 40% of European respondents (40% in UK, 46% in France, 52% in Italy, and 57% in Germany) believe erroneously that cancer is one disease that manifests itself in many parts of the body rather than hundreds of different diseases. The PACE survey also found that about two out of three people surveyed in the four European countries included in the survey (France, Germany, Italy, and UK) had no awareness of personalized medicine before being presented with the topic in the survey. Once aware of it, large majorities (ranging from 75% in Italy to 91% in the UK) believed that doctors should discuss the potential of personalized medicine with every cancer patient. Large percentages of people (ranging from 42% in Germany to 53% in the UK) maintained that they still would prefer a standard treatment to a personalized treatment for cancer—suggesting that it is awareness and the element of choice that are most important to people, not necessarily a preference for the latest treatment option.

All these results show that most patients do not see themselves as mere recipients of information and therapies, but as increasingly active contributors to the generation and

interpretation of their own medical data. Patients have the opportunity to partner or support the work of healthcare professionals and can feed much useful information to professionals, even when they do not want to participate in the decision process.

Tailoring therapeutic interventions has led to an increased need for additional technological support to process the complex data that has to be taken into account to support the therapeutic decision, and the necessity to effectively communicate the therapeutic rationale to the patient. Fortunately tools to provide clinical decision support designed to improve physicians' decision making are now emerging (Wears and Berg, 2005).

Screening tools may support clinicians in merging and analyzing great amounts of data (the results of biomolecular findings, diagnostic tests, scientific literature, etc.), and also to share such data with other professionals. Consequently, electronic tools are also useful in helping health professionals to provide straightforward responses to the concerns of patients about future illness, treatment options and opportunities for prevention.

But profiling tools may provide clinicians with information about the cognitive attributes of each patient, which will contribute to deeper understanding of expectations, fears, attitudes to risk, and health literacy. This should assist the physician in future interactions with the patient, improving communication efficacy. In parallel, others tools are being created to help patients absorb the information given, and process and use it in subsequent discussions concerning, for instance, therapeutic decisions and follow-up management.

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Recommendations

Health professionals should:
- assess each patient's health literacy;
- pay attention to the terminology used and to its effect on each patient;
- monitor and facilitate each patient's understanding of diagnosis and of therapeutic strategies (taking every opportunity to correct the patient's misconception);
- assess each patient's information needs;
- according to each individual's information preferences, provide details about different treatment options, the possible benefits and risks, the rationale for diagnostics and pre-emptive testing;
- assess each patient's decision-making needs including decisional conflicts, values, willingness to participate/not participate in the decision process, family/social support and resources
- monitor and facilitate each patient's ability to communicate about their preferences, values, lifestyle.

Health professionals may be helped by information technology tools in performing these tasks: screening tools may support in merging and analyzing great amounts of data, and profiling tools may provide information about the cognitive characteristics of each patient.

Action/ changes needed

- transforming patients
- wider health literacy

Appropriate mechanisms

- engaging patients
- adequate information provision tailored to individual needs
- education of doctors

Mission: To ensure a responsive regulatory environment that responds to the needs of all stakeholders whilst ensuring patient safety, with the end result of ensuring development of treatments for patients - Clinical trials

The development of personalized medicine requires complex international clinical trials involving highly selected patient populations, the collection of human biological material and the use of large databases for bioinformatics. The backbone of the clinical research in personalized medicine will be biologically driven clinical trials involving strong translational research components using state of the art technologies such as biomarkers derived from 'omics and non-invasive molecular imaging.

Personalized medicine will require the development of new targeted agents either alone but most probably in combination with approved drugs and/or other therapeutic strategies such as radiotherapy. Personalized medicine will not be sustainable in the current climate given the large attrition rate in drug development, leading to high research and development expenditures and consequently the costs of health care. In addition, the fragmentation of the diseases based on molecular sub-entities (e.g. endotypes) requires international cooperation for screening large patient numbers in order to reaching optimally sized patient populations bearing the alterations of interest. Many drug candidates go into clinical trial without appropriate understanding and documentation of the target biology, which goes some way towards explaining failure at later stages of drug development and the high attrition rate. Moreover, some of the therapeutic agents might have been successful if they had been tested in the patient group most likely to benefit from the drug. Today subgroups of patients are being identified within a broad disease category that map onto optimally selected prognostic and/or predictive biomarkers. However, since the biomarkers and the modelling needs to be validated on large populations, diagnostic refinement and stratification is dependent upon the successful incorporation of scientific advances into clinical trials.

Such a change in the drug development paradigm would need to be supported by adequate methodologies and infrastructures. The quality of the research is crucial since it will ensure that reliable and robust evidence will be generated. Researchers in Europe should benefit from efficient and quality assured research infrastructures which are able to support large screening platforms to identify the target population, as well as relevant IT tools such as simulation or

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computer assisted decision-making.

It is important to ensure multidisciplinarity supporting the collaboration between drugs developers, academia, regulatory agencies and payers. New models of collaboration should be developed allowing Public-Private Partnership following the example of the Innovative Medicine Initiative (developed in chapter 11). The industry should be encouraged to collaborate with academic researchers and Public-Private Partnership should be supported by public bodies. It is critical that the strength of European academic clinical research and the know-how of industry be optimized in such partnerships supported by public bodies to maximize therapeutic advances with control of the risks by optimizing the interactions of the key stakeholders. Performing high quality clinical and translational research requires heavy investments in term of both resources and know-how. Innovative clinical research will rely on the availability of appropriately trained professionals, who need to be trained and rewarded within sustainable career paths. Improvement of the education and career prospects for clinical research professionals is addressed further in Chapter 10.

Regulatory bodies and payers should approve drugs and biomarkers for their effectiveness and the real benefits that they bring to society. More and more drugs are approved with an accelerated procedure based on weaker clinical end-points or surrogate end-point based on the condition that post marketing clinical trials verify the anticipated clinical benefit. Requirements for cost effective new drugs including HTA evaluation and the use of pragmatic/real life data should be elaborated and harmonized at the European level. Dialogue between payers, regulators, HTA bodies, and drugs developers should be initiated early in the drug development process. These aspects are developed in Chapters 8 (HTA) and 9 (Innovative Payers Model).

Without innovative clinical trials in Europe, patients' access to personalized medicine is at risk. Today, the competitiveness of Europe in clinical research is under challenge. Europe is becoming less attractive for drug development than other continents. Europe must be kept on the global map of health research and innovation. This chapter will address the following aspects and propose some recommendations:

- The drug development process must change to accommodate progress in science, with the specific goals of achieving personalized medicine. Smart but robust clinical research methodologies need to be developed and endorsed by regulators and payers.

- Collaboration between academia and the industry for access to innovative agents and sharing know-how is paramount. Such collaboration should be promoted while preserving the independence of academia. Clinical research is a highly resource-intensive activity. Academia should be supported for playing its role. Investigator-driven clinical trials (IDCT) should be better supported by public and private funding to address questions not relevant to the industry but essential for health care providers.

- The legal framework in Europe is hampering international clinical research. Legislations should be harmonized. The related costs and administrative burden should also be reduced.

Optimize the drug development for achieving efficient personalized medicine

The discovery and further validation of targeted treatment or new companion biomarkers will require sophisticated clinical trials designed with a strong translational research component with the ultimate goal to treat the patient at the right time with the right agent or combination of agents. Enabling personalized medicine will require changes in drug development paradigms. R&D should be made more efficient by reducing the attrition rate and meeting patients' medical needs. Methodological challenges must be faced on how to test and to integrate new technologies in clinical research. Modern clinical research is complex and expensive and will require industry to collaborate with academia within new types of partnership favouring multidisciplinarity and the pooling of know-how and resources.

Prioritize biologically sound and multidisciplinary clinical research

In order to reduce the attrition rate in drug development, methodologically robust clinical trials are needed, testing drugs selected on the ground of convincing pre-clinical evidence. Clinical research methodology and drug development approaches should be modeled to take into account the role of the molecular discriminates that predict treatment activity or toxicity. Treatment efficacy can be greatly improved if the biological mechanisms underlying the disease are better known and taken into consideration. Biologically sound and methodologically robust studies will only happen within close multidisciplinary collaboration between the drug developers, the clinician and the biologist. Furthermore, multidisciplinarity also includes the biostatisticians and the developers of information and communications technology (ICT) tools capable of complex modeling. The outcomes of such ICT models will have to be validated clinically.

A big challenge in the era of personalized medicine is the use of combinations of targeted drugs, as in oncology. As cancers may be driven by several pathways, the use of multiple therapeutic agents is now regarded as key to therapeutic success. For pharmaceutical companies, the combination of compounds in early development increases the risk of failure if there is insufficient knowledge about their interactions, whether therapeutic or adverse. Another obstacle to combining drugs is the challenges over data sharing, intellectual property and marketing that are created by the involvement of several companies within one trial. A neutral body like the Innovative Medicines Initiative (IMI) or independent academic clinical research networks may fill a gap to address these issues and help pharmaceutical companies to collaborate in a "non-competitive space". For the approval of agents used in combination, regulators may request evidence that could be

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generated only by sophisticated, time-consuming and expensive clinical trials. Smart but robust clinical research methodology using adaptive design could shorten the trial duration, the size of the studied population and ultimately the trial costs. Modern clinical trial methodologies propose a wide range of adaptive designs that should be selected according to the research question e.g. phase II adaptive design "pick the winner". There is no rule that fits all situations, but the choice of the design should allow the generation of high-quality evidence.

The EAPM is calling for the development of innovative but robust clinical research methodologies to address the complexity of personalized medicine development and endorsed by regulatory bodies.

Promote and support collaboration between academia and the industry

Conducting molecular based clinical trials using classical and historical features is doomed to failure. The conduct of modern clinical research requires major upgrades of both the organization and the infrastructure for performing such trials. Indeed, implementing translational research requires access to human biological and/or complex molecular imaging, which brings new challenges to international multicentre clinical trials for quality assurance and standardization. Special skills are required to build on the new platforms to integrate clinical, biological and imaging data into the decision-making process to mitigate the attrition rate of new drugs and/or decide on molecular sub-entities which will ultimately benefit the introduction of new therapeutic strategies.

Taken together, such changes can be addressed only by new forms of partnership developed between the academic and pharmaceutical sectors, since what is now required is clinical trial infrastructure of multi-talented institutions working under the same standards. Building such infrastructure is beyond the agenda and the timelines of industry, and this task resides in specific academic networks. Pharmaceutical companies would benefit from closer contact with established, leading pan-European academic networks with good track records to facilitate technology transfer. This activity will lead to an increasing number of ties between the pharmaceutical industry and academic institutions. Since this might be interpreted by the public in a detrimental fashion for both industry and academia, the involvement of an 'honest broker' is recommended to ensure transparency and sustainability within these partnerships. One example is the Innovative Medicine Initiative Joint Undertaking supported by the European Commission and the pharmaceutical industry (chapter 11 is devoted the IMI).

The EAPM is calling for more support to Public-Private Partnerships such IMI.

Improve the support to independent academic research

As science becomes more complex, interpretation and understanding of research results are proportionally at a greater risk of deviation. Wide academic consensus operates as a gatekeeper for patients and society. Therefore, the independence of academia towards industry should be preserved. Requirements for independence should be established i.e. the study protocol should be peer reviewed by independent experts, data analysis should be performed by academia or an independent body, academia should control the study database, and academia should be granted the irrevocable right to publish the study results.

An example of an investigator-driven clinical trial in personalized medicine, comparing different drugs, conducted independently by academia in collaboration with pharmaceutical companies, is the clinical trial EORTC 40091 BOS2, evaluating the combination of chemotherapy with angiogenesis inhibitors in 360 colorectal cancer patients with resectable liver metastases expressing the non-mutated KRAS gene. The KRAS status, measured by a companion diagnostic test, indicates whether a colorectal cancer patient will respond to angiogenesis inhibitors.

To be able to play its independent role in public-private partnership, academia needs to be financially supported by public funding. More public funding should be available for performing high-quality international clinical trials. Public funding procedures in Europe should be streamlined and harmonized. To achieve this, a European Investigator Driven Clinical Trials Fund should be created with the mission to fund a significant number of international academic clinical trials in all disease areas every year, through a competitive process targeting scientific excellence and public health added value.

Maintaining quality-assured clinical trial infrastructures is a corner-stone of new European approaches which will help guarantee for patients consistent, long-term and, over time, reliable research. Therefore, academic clinical research infrastructure should benefit from adequate financial support for ensuring their sustainability. Research infrastructure capabilities need to be maintained and skilled and experienced staff retained. Public funding bodies should consider complementing individual project grants with limited core grants. Such financial support should be subject to close monitoring and justified by the excellence and the usefulness of the recipient organization. The duplication of existing research infrastructure should definitively be avoided.

The EAPM is calling for the establishment of public funding mechanisms at the European level for academic research organization covering also the infrastructure costs.

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Improve the clinical research legal framework in Europe

The development of personalized medicine relies on complex research involving patients at the international level, using and reusing data and human biological materials. Such types of activity are regulated by various European and national legislations e.g. the clinical trial authorization, data protection, the use of tissue, medical devices, in-vitro diagnostics, etc. The European framework is complex and heterogeneous. Legislators in Europe need to ensure the consistency of various legislations addressing the obligations of the clinical trial sponsors and the researchers. The European legal framework should support the use of data and human biological material for research purposes at the European level, while safeguarding patients' rights, and promoting pan European cooperation. This section will focus on the authorization of clinical trials (European Commission proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC). Other legal aspects like patient consent and data protection are addressed elsewhere in this document.

Collaboration between stakeholders

The European Commission proposal for a regulation brings several major advances favouring an attractive and research stimulating framework. Key elements of this new framework are described below. However, as several aspects essential to clinical research are not under the direct remit of the Commission (ethics, insurances, regulation of health systems, liabilities, etc.), it cannot be successful without the full support and understanding of all member states and their regulatory bodies. Optimal communication and mutual understanding is therefore essential.

The EAPM urges member states and the Commission to collaborate on these complex and sensitive matters.

Single electronic portal and short timelines

The EAPM welcomes and strongly defends the implementation and use of a single electronic portal managed by the European Commission for clinical trials, without the need to further code data into any of the national systems.

A single list of submission documents in English is also essential.

Coordinated assessment and one approval per member state

The Commission proposes to assess clinical trials in a coordinated way with all general, non-country specific aspects of the trial being assessed by the reporting member state.

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This would necessarily need to incorporate the possibility that all other participating countries are able to communicate their position on these aspects to the rapporteur and have these taken into account in the assessment report. In parallel, other aspects of a national/cultural/local nature would be assessed separately by each member state. At issue in this process is that single approval is provided by each member state which embraces all aspects currently covered by the Ethics Committee (EC) opinion and Competent Authorities (CA) approval. The collaboration between different bodies (CA & ECs) on the national level and an optimal mechanism of communication is essential to be able to issue an approval within the timelines specified within the legislation. This essential aspect clearly lies with each member state.

The EAPM strongly calls all member state regulators to urgently make necessary adaptations to their national assessment process.

The payment of submission fees to regulatory bodies can represent significant costs for the trial sponsor. The fee waiver for non-commercial clinical trial has not been addressed in the Commission proposal for a regulation. The payment of fee should be restricted to trials aiming at drug registration.

The EAPM calls on the Commission and the member states to consider waiving fees for non-commercial trials.

Introduction of the elements of a risk based approach

The proposed regulation introduces a risk-based approach, which is a major achievement. The definition of low-intervention clinical trials is created with a reference to standard practice and allowance for additional minimal medical intervention. Low-intervention clinical trials are simplified and granted with shorter timelines of approval, adapted trial monitoring and content of the trial master file, proportionate labeling and insurance requirements. For all other trials the regulation takes a multi-fold approach:

- The nature and extent of the trial monitoring and the content of the trial master file are to be adapted to the clinical trial characteristics;

- Rules on manufacturing and labeling are proposed to be "appropriate and proportionate";

- Insurance for non low-intervention trials is adapted to "the risk of the clinical trial, the potential damage, and the likelihood of the damage".

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The EAPM urges clinical trial testing of Investigational Medicinal Products under the same form as compared to the marketing authorization, but in non-registered indications, should be considered as low-risk.

This should contribute to an overall decrease in the costs of clinical trials while, at the same time, maintaining patient safety and improving and accelerating the establishment of new standards of care.

<u>General simplification of safety reporting and its centralization at EMA</u>
Simplification of safety reporting, and particularly its centralization at the European Medicines Agency, will be a major achievement and should decrease unnecessary administrative workload related to pharmacovigilance while maximizing EU capacity to detect pertinent events in time.

<u>Investigational Medicinal Product (IMP) definition</u>
Regrettably, the IMP definition was not modified in the current Commission proposal for a regulation. The definition of IMP applies not only to the tested medication but also to the comparator, for which the costs may not be covered by the health systems. In reality, the comparator may frequently be the standard treatment that the patient would otherwise have received outside the clinical trial.

The EAPM proposes that to further stimulate research in the EU, all member states should allow drugs to be reimbursed when used in their registered indication or considered as standard treatment in the context of a clinical trial.

Measures proposed to put in place optimal damage compensation for trial participants
The EAPM acknowledges that the new proposal constitutes a radical change in current practice. However, it should be kept in mind that currently clinical trial insurance represents huge costs for sponsors, and if costs are kept as they are, this will lead to further increases in the cost of drugs and inevitably become a burden for health systems.

The EAPM strongly recommends that member states put in place global solutions, which will, at a reasonable cost, guarantee that all patients are indemnified for any damage.

<u>Patient involvement</u>
The EAPM welcomes the mechanism proposed by the regulation for involving patients

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and their representatives in the panel in charge of the authorization of a clinical trial. In addition, patients have an active role to play in the review of informed consent documents and their simplification. Patients are also paramount in the dissemination of information about clinical trials: how to access clinical trials, results from trials. Information about clinical trials should be made more accessible for patients, their relatives and the general public.

Action/ changes needed

- facilitation of complex international trials incorporating scientific advances in studying highly selected populations
- approval procedures for drugs and diagnostics based on benefits to society
- modified trial infrastructure and methodologies, endorsed by regulators and payers
- harmonised approval systems and HTA methodologies
- harmonised CT rules
- member state buy-in to make new EU CT rules work
- introduction of low-intervention trial rules
- simplified safety reporting
- reimbursement of IMPs
- national indemnification sytems for CTs
- greater patient involvement

Appropriate mechanisms

- adaptive trial design
- screening large patient numbers
- collaboration across disciplines in PPPs
- IT tools such as simulation or computer-assisted decision-making
- training and career paths for CT professionals
- better support for independent investigator-driven trials
- effective "gatekeeper" role for academia in all trials
- funding of academic infrastructure
- a European Investigator Driven Clinical Trials Fund

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Mission: healthcare resources allocated to development and utilisation of personalised medicine, through acceptance of its long-term cost-effective benefits - Health technology assessment securing patient access to personalised medicine

HTA is described by EUnetHTA as a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method[25].

In Europe, for phamraceuticals, health technology assessment is used to inform reimbursement decisions on the basis of whether a new technology provides addedvalue compared to existing treatment alternatives. It is used to support (and not replace) resource allocation decisions in healthcare. HTA is described by EUnetHTA a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient focused and seek to achieve best value. Despite its policy goals, HTA must always be firmly rooted in research and the scientific method[26].

There are differences between HTA systems used to support resource allocation decisions. Some build on assessment of clinical added value followed by price negotiation and discussion (such as Germany, France). Others employ cost-utility analysis (CUA), integrating clinical and economic assessment by calculating the cost of interventions against the health benefit gained (mostly expressed in quality adjusted life-years - QALY), and deciding on coverage by the payer/healthcare system according to whether its cost/QALY is below or above a set threshold.

25   http://www.eunethta.eu/about-us/faq#t287n73
26   http://www.eunethta.eu/about-us/faq#t287n73

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There is also a difference between HTA used at the time of launch to inform the first pricing and reimbursement decisions (what EUnetHTA calls 'rapid' HTA), which is based on information collected in clinical trials, and HTA later down the line ('full' HTA or re-assessments), which can integrate more information on the use of products in real-life. Reflection is already taking place on compilation of scientific reviews and assessments into one therapeutic, scientific report that could be made available to the Member States' HTA and Pricing & Reimbursement authorities at the time of Marketing Authorisation, as an additional resource for the Member States. This report might also form the repository for information gained subsequent to the normal clinical development programme – although clearly there are limits to what can and cannot be harmonised in terms of methodologies.

For personalised medicines it is vital to ensure that developments of HTA will support timely patient access. HTA will need adapting to the new R&D paradigm. The longstanding tendency to one-off decision-making at the time of marketing authorisation is starting to give way to more dynamic, progressive approaches, including progressive marketing authorisation and progressive reimbursement.

Substantial efforts are underway at both national and EU-level that aim to create synergies. EU-level actions in HTA can add value if they tackle unnecessary duplication and enable greater clarity, lead to an improvement in standards of methodological and process aspects in HTA, improve predictability, and contribute to better and timely access of health technologies to patients. Methodologies can be further discussed at EU level to arrive at best practices.

But progress would require a commitment by payers to integrate HTA findings into their coverage policies, to avoid a waste of resources. It needs a readiness to exclude other mechanisms that might undermine the approach - such as international reference pricing. If European action can take place at the level of the clinical aspects of HTA, economic evaluation and/or price negotiations must remain at national level. The inclusion of HTA in the proposed update to the EU Transparency Directive is a clear recognition that Member States are moving closer to value-based pricing in their systems.

Regardless of the ever-growing body of research and game-changing new technologies that will make personalised medicine a reality, it will be the ability and willingness of governments, payers and industry to invest in these new technologies that will determine whether patients will have access to these innovative treatments. There is a willingness already, but the issue is to address the related challenges – ranging from overall health budgets to linking treatment with diagnostics.

In a tough economic environment, European Union governments and healthcare providers have been seeking to maximise the value for money that they can obtain from the acquisition of new treatments for patients. Consequently, there is also a large awareness of the limits that can be placed on patients with regards to having to make financial contributions to their healthcare

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needs. Payers are now increasingly likely to deny or severely restrict the use of advanced therapies when there is no clear or exceptional economic value for the broader population as they seek to cut costs and decrease public spending and debt. HTA acts as a mechanism that allows payers to seriously consider whether or not to fund one treatment over another and make it available to the patient that will be most likely to benefit from it. In short, HTA has been devised as a means to ensure a wide choice in which treatments will be offered to which patients, as a means to provide the best possible patient outcomes.

Current models have been based on medicines designed to treat an entire patient population, and the economic value of a specific medicine has traditionally been analysed through a comparison with other treatment alternatives or palliative care. These comparisons are made through the collection of data taken during randomised controlled trials across a broad patient population. In the past, there have been efforts to specifically select sub-groups of patients based on certain conditions, such as age, sex, or likeliness to contract a certain disease, but importantly, these were not constituted with firm scientific evidence or statistically well-sampled within the clinical data, lacking in particular crucial information regarding the molecular and individual patient level.

It can now strongly be argued that the current model of HTA that is prominent across Europe is no longer viable. For instance HTA bodies generally prefer to base their evaluations on randomised control trials (RCTs), but these are not always available for personalised medicines. It is now necessary to adapt this model in order to move away from a sense of urgency which makes the overall process solely focused on achieving short-term solutions, and embrace personalised medicine through a wider concept of overall economic value. It is vital to ensure that regulators across Europe acknowledge the requirement for better coordination and a more standardised approach to assessment.

At the centre of the debate is the fact that choices about whether to fund one treatment or another have to be made. HTA can help decision-makers – and selection of a treatment on the basis of value for money in comparison with other treatments can see the exclusion of more expensive drugs that do not provide value for money if they offer only incremental improvements in clinical benefit.

The promise of personalised medicine

Personalised medicine's principal goal is to confidently and scientifically select patients who have the best possibility of having the stable response to a given treatment. Biomarkers can ensure that data from patients can be used to inform better treatment choices. Through these innovations, medicines will gain a more favourable risk-benefit ratio, thus feeding into better health outcomes, quality of life and utilisation of healthcare resources. The use of safety biomarkers will also help reduce the number of undesirable effects linked to the use of

medicines, by helping to predict which patients are likely to have an adverse reaction to a given treatment.

Personalised medicine also may provide better value for money not only due to improved drug effectiveness. Through more relevant pre selection of patients, a trial would be populated with a much better defined patient population with a higher likelihood of a better therapy response resulting in faster statistical relevant results and an overall lower failure rate of trials. This will result in certain cases in smaller and quicker clinical trials from which patients would benefit through earlier access to the medicine. This would also help to reduce the large investment cost made in developing the therapies.

However, biomarker research and development also brings extra complexity and cost to the performance of clinical trials. Clinical trials are by far the most expensive element of R&D (approximately 40-60% of the investment).

With personalised medicine still in its infancy, clear results on efficiency gains may only arrive in the long-term. However, it is necessary to make policymakers and payers realise that investing now in these advanced therapies and technologies for personalised medicine will see long-term, cost-effective benefits in the future.

Adapting HTA to the new paradigm of personalised medicine - solutions

HTA as it currently stands has not recognised these promising innovations, and still depends too heavily on the increasingly outdated 'one size fits all' model. HTA key decisions are traditionally taken after marketing authorisation. At this time, personalised treatment may not yet have been able to show its full value. There needs to be an expansion of the HTA process for separate valuation of diagnostic kits alongside any new therapy. The development of diagnostic kits for routine use is a crucial part of personalised medicine. It is currently unclear how the diagnostics side of the personalised medicine approach is being valued and how aspects of test validity are taken into account for reimbursement. This makes it difficult for the diagnostic industry to understand return on investments in this area. A standardized HTA approach is needed specifically for this.

With the increasing uptake of PM, the available evidence will be in the form of subgroup analyses of these RCTs (e.g. focusing on one type of patient), which very often are deemed to be insufficiently robust. One of the key issues is whether there are other ways to confirm the plausibility of these benefits, through, for example, clinical expertise, and whether this is acceptable for HTA bodies.

Timely Access to Treatment for Patients
In several cases, personalised medicine approaches will result in smaller patient groups for a particular treatment. In order to advance the development of personalised medicine, for these cases lessons from how Europe has decided to approach the topic of orphan drugs could be

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useful. One solution for reforming HTA that is certainly worth exploring is a more progressive assessment and reimbursement mechanism under which potential personalised therapies for certain diseases are reviewed. Accelerated progressive reimbursement holds that results in clinical trials are often short-term in relation to the natural course of disease progression. Drug assessment might, therefore, be viewed as a continuum, with close interactions between clinical trial sponsors and HTA bodies. A progressive assessment and reimbursement mechanism then becomes the default pathway for certain diseases, provided sufficient dialogue has taken place between patients, physicians, drug developers and HTA bodies.

Finding operational solutions to build a complete understanding of investigational drugs is the responsibility of sponsor companies. Patient benefits are, however, key principles behind any early-access program. It is, therefore, entirely appropriate for patient groups to participate in dialogue with HTA bodies and the drug's developer, explicitly evaluating the benefits and risks of accelerated development.

Non-Adapted Data Requirements and Methods
HTA is typically informed by large-population clinical trial data and tends to provide evaluations based on expected average benefits on large populations. Standard non-personalised comparators lack stratified/personalised efficacy or effectiveness evidences.

In many cases, it is unfeasible to carry out the type of randomized controlled trials that are typical for more common diseases. Flexible and innovative trial designs (including adaptive study designs) should therefore be encouraged, as this could circumvent some of the difficulties of carrying out randomized, double-blind, placebo-controlled studies. Wherever possible, historical data and meta-analyses should also be harnessed to support efficacy claims.

Conventional clinical trial end points are often not available, but overall disease progression rather than overall survival should be considered as a clinical end point for many such diseases. The application of biomarkers can in some cases, such as in various cancers or neuro-degenerative diseases, support reasonable clinical benefit as well as enable faster and more efficient clinical trials.

A dedicated HTA approach to personalised healthcare technologies is needed, in particular:

- Early dialogue and advice, early access if effectiveness is proven, and timely assessment.

- Simpler, individual patient focus, quicker and continuous evidence development and assessment.

- Multiple criteria should be considered in assessing the value of disease treatments, and all value components of personalized healthcare solutions (including societal value and patient equity to access to treatment) should be valued consistently

A survey[27] published in 2012 identified potential hurdles faced by SMEs when dealing with HTA requirements, including lack of understanding of specific requirements and principles of HTA, and lack of expertise in the field. Practical solutions for improving the interaction between SMEs and HTA bodies could include extending SMEs' EMA status to HTA bodies (e.g. free of charge applications) and mentoring programmes.

Conclusion

Many diagnostic and pharmaceutical companies are embarking upon product development projects with the end goal of coupling the use of a therapeutic product to the use of a companion diagnostic test. Regulators encourage this and the payers and HTA assessors now have to determine the value of these therapy-test combinations.

This chapter has sought to map several of the challenges and hurdles for personalised medicine that currently exist throughout HTA systems across Europe. In essence, it is questionable if the conventional models of HTA are able to successfully evaluate new medicines and technologies. Personalized medicine provides the HTA experts in Europe with a new challenge to take into account all factors that will be the result of a greater uptake of personalised medicines.

Concurrently, gaps in the current system that can be targeted for immediate improvement, as well as conversations concerning a more radical overhaul of the entire system, should be undertaken. All relevant stakeholders, from industry (SMEs and larger companies) to regulators, payers, policymakers and patients need to be actively involved in these conversations in order to reach a common consensus and coordination in order to find and agree on the best solutions to achieve these goals.

Recommendations:

- A need to understand the limits of the current HTA approaches for personalised medicine and develop mechanisms such as EUnetHTA to achieve Europe-wide, dedicated HTA standard methods to support developments in the personalised medicine field.
- Involve all stakeholders as earlier as possible in the HTA process with greater respect for the role each party has to play in developing, authorizing, valuing, pricing, prescribing, paying for the therapies and companion diagnostic tests. This especially concerns patients, who decide to undergo the treatments with these innovative products.
- Educate all stakeholders on the implications of new HTA methods in developing therapeutics and diagnostics in this field.

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27   conducted by SFL services for EuropaBio

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Action/ changes needed

- integrated and updated and harmonised approach to HTA, market access and reimbursement
- integration of the concepts of overall economic value and equity into HTA
- flexible CT designs
- wider collaboration across industry, regulators, payers, and patients

Appropriate mechanisms

- progressive assessment and accelerated progressive reimbursement
- patient involvement in HTA
- early dialogue between sponsors and authorities
- multiple criteria for value assessment
- assistance for innovative smaller firms in understanding HTA

Mission: to effect a paradigm shift in pricing and reimbursement to recognise the societal value of a medicine – Innovative payer models

European solidarity-based healthcare systems aim at providing universal access to qualitative care for their population. To enable universal access, health authorities across European countries have set up healthcare systems that protect citizens/patients from the financial burden of accessing healthcare, and in general terms, healthcare is community funded. For medicines, national health authorities in each EU Member State have put in place pricing and reimbursement (P&R) mechanisms by which they define which medicines they should pay for — and how much.

Today's P&R mechanisms have been developed on the model of medicines developed to treat a wide population of patients indiscriminately diagnosed on the basis of their symptoms. Clinical trials looking at this wide population of patients aim at identifying the average effect of a treatment. This means that in real life some individual patients will experience a less than average effect and others will experience an above than average effect. In fact, research shows that efficacy rate for standard treatment ranges between 62% to 25% depending on the disease area[28]. In the current model, P&R levels are established through an evaluation of this average effect, because it is frequently not possible to a priori identify those individuals which will experience an above than average effect. Therefore, 'payers'[29] set a homogeneous P&R level for a medicine at the initial time of launch of this medicine, and subsequently pay for each dose prescribed, irrespective of the level of effect on the specific patient. Whilst payers do recognise that some patients are most likely to benefit from a particular drug and often approve use in specific subgroups of patients only (e.g. specific age group or failure of previous therapy), the limiting factor in moving towards more personalised treatment is the very often limited knowledge about who the most likely to benefit patients are at the time P&R decisions are taken.

Increasingly however, medical advance and the analysis of the molecular basis of diseases

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28   Miller, Ashton-Chess, Spolders et al., personalised medicine (2011) 8 (2), 137-148

29   We will use the terminology 'payers' to refer to those mostly public or quasi-public institutions throughout European countries which support the cost of healthcare in solidarity-based European healthcare systems. 'Payers' take different forms in different European countries.

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enable a stratification of patients, so that medicines can target narrower populations of patients which are more likely to respond to the treatment (e.g. trastuzumab (Herceptin®) for breast cancer patients whose tumoral cells express the human epidermal growth factor receptor-2 surface protein). At the same time, payers are increasingly interested and driving the development of P&R models that allows them to pay only for those patients that respond positively to a treatment. These developments mean that a paradigm shift in P&R mechanisms is needed.

Today P&R levels are mainly defined on the basis of information on average treatment impact from clinical trials, manufacturers' proposed prices, and comparison with P&R levels in other Member States through international reference pricing. These static and heavily administered forms of P&R regulation should be replaced by more flexible approaches that will accompany differentiated views on a medicine's added value, including its societal value, and its contribution to overall disease management and an efficient management of healthcare resources. A new pricing and reimbursement (P&R) model is needed to enable:

- Better collection of data on the effectiveness of treatments
- Appropriate assessment of this data to determine the value of treatments
- Translation of the recognized value in P&R levels

A new pricing and reimbursment model - smarter data is needed

Increasingly, approaches to manage entry of new medicines, commonly referred to as managed entry agreements (MEAs), are used in a number of EU Member States. A MEA can be defined as an arrangement between a manufacturer and payer/provider that enables reimbursement of a medicine subject to specified conditions. Although combinations are possible, there are two main groups of MEAs: one group links reimbursement to health outcomes (e.g. payment for performance, coverage with evidence development); the second facilitates access to new medicines through the use of financial instruments (e.g. price-volume agreements, rebates). The former group can help to address uncertainties that may exist in some cases about the performance of technologies (using for instance coverage with evidence development, payment for performance or dose-capping schemes) or to manage the adoption of technologies in order to maximise their effective use (using for example patient registries). The development of these MEAs reflects the reality that certain information can only be obtained when a drug is used in daily practice. Collection of this information allows tailoring HTA recommendations on the basis of real-life effectiveness and outcomes data in different patient subgroups rather than solely randomised controlled clinical trials (RCCT)-derived efficacy.

The current legislative framework, which requires the generation and communication of these data, would benefit from increased coordination. Currently, post-marketing data on effectiveness

of medicines is required by regulators in the framework of post-approval surveillance studies,[30] and by payers and their associated HTA agencies at the national level. While it is essential to recognise the different roles and responsibilities of regulatory and reimbursement decision makers, there is also a need to address their disconnection. This should go hand in hand with horizon scanning projects [31], which are valuable instruments to generate pre-licensing information on the drug effectiveness, and should allow drug-reimbursement authorities to make faster decisions once a drug is licensed or receives conditional marketing authorisation. Increased dialogue early in development and along the life-cycle of products, involving all decision-makers and the manufacturer, could help identify the right level of requirements and reduce duplication between different bodies. It would also help the acceptance of different types of data by different decision-makers. For example there have been cases where regulatory conditional authorisation in some countries is not accepted as sufficient evidence to grant access to patients through reimbursement. The need to address the disconnection between regulators and HTA bodies has been recognised in the recommendations of the 2005-2008 High Level Pharmaceutical Forum[32] and in the EMA Road map plan to 2015 which envisages two main initiatives to increase collaboration and reduce duplications in data requirements by the EMA and national drug reimbursement agencies[33]. First, it aims to increase transparency regarding its decision-making process by providing more information in the European public assessment reports which can be useful to reimbursement authorities. Second, it aims to engage with drug reimbursement authorities from early stages in the drug development process until post-launch. The need for more coordination between regulatory and reimbursement activities to enable faster access to innovative therapies has led the US Food and Drug Administration and the Centres for Medicare and Medicaid to launch a parallel pilot review programme for medical devices in 2011[34].

Member States should strengthen their infrastructure and use of electronic patient records and mobile health solutions to collect and analyse both clinical and patient-reported outcomes. Member States' efforts should feed into existing initiatives at EU-level like for example EU-initiatives on rare diseases[35]. This will require standardisation of data collection methods and use of common definitions as some of these initiatives have started to do, as well as discussions about the potential of uses real-life data and methodologies for analysis[36]. Collection of evidence post-marketing also requires a thorough discussion about the involvement of health

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30   The 2010 pharmacovigilance legislation opens the possibility for regulators to request post-approval efficacy studies (PAES).

31   Examples: Horizon scanning centre UK, http://www.hsc.nihr.ac.uk/

Italy: Joppi R, Demattè L, Menti AM, Pase D, Poggiani C, Mezzalira L; Italian Horizon Scanning Project Group.The Italian Horizon Scanning Project. Eur J Clin Pharmacol. 2009 Aug;65(8):775-81.

32   High Level Pharmaceutical Forum 2005-2008 http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/pharmaforum_final_conclusions_en.pdf

33   http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/01/WC500101373.pdf

34   http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm274833.htm

35   These include the European platform for rare diseases registries (EPIRARE), the patient registry initiative (PARENT), the European Union Committee on rare diseases (EUCERD) joint action and the International Rare Disease Research Consortium (IRDiRC).

36   More insights into the use of ICT for clinical research is included in chapter 4

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professionals and patient, since the collection of qualitative data depends on their dedication and commitment, and the right legislative framework of access to data. The current Directive on Data Protection, addressed in chapter 2, is a crucial framework to ensure that the right data and clinical research can be conducted in Europe.

A new pricing and reimbursment model – coordinating assessments

Across Europe, HTA is increasingly used to support P&R decisions of medicines[37]. One concrete practical difficulty that arises today concerns the different ways medicines and diagnostic tools are assessed and reimbursed[38]. With personalised medicines, the success of the treatment depends to a large extent on a diagnostic test which measure validated 'biomarkers, i.e. biological factors that serve as indicators of disease status or of drug response, e.g. proteins or DNA in body fluids and tissues or images, such as MRI or CT scans'[39]. However, different institutions come into play, working on the basis of different methods, and at different levels (national, regional or local). This might lead to differences in time of reimbursement, and therefore the difficulty for the patient to appropriately access personalised medicines. To overcome these issues both the drug and its companion diagnostic test should be included in a common HTA which will determine the added value of a treatment as a whole rather than the medicine only [40]

In line with the need for more efficient generation of data across decision-makers, there is also a need for continuous assessment of added value (for payers) and benefit-risk (for regulators), which should ultimately lead to adapting prescribing, dosing and reimbursement conditions as new evidence emerges. This need has been recognised in recent proposals by the European Medicine Agency around adaptive licensing[41]. Today there is sometimes still a time lag between marketing authorisation and reimbursement. A recent example of conditional marketing authorisation[42] illustrates this well. Crizotinib (Xalkori®), a drug for the treatment of non-small lung cancer for patients with a mutation in the anaplastic lymphoma kinase gene, has received conditional marketing authorisation by the EMA in October 2012[43], meaning that it has been recognised as addressing an important area of unmet medical need. In many countries the medicines is still being reviewed by HTA agencies: for example it is currently under review by

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37   See chapter 8

38   more extensive discussion on the challenges facing diagnostics is provided in chapter 4

39   Patient Network for Medical Research and Health (EGAN), Personalised healthcare FAQs , updated 2012

40   See chapter 4

41   EMA. 2010. Road map to 2015. In the European Medicines Agency's contribution to science, medicines and health: European Medicines Agency, p. 21 and p. 22. HG Eichler, F Pignatti, B Flamion, H Leufkens, A Breckenridge. 2008. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nature Reviews Drug Discovery 7:818-826.

42   To obtain conditional marketing authorisation a medicine needs to fulfil the following conditions: the risk-benefit balance of the medicinal product must be positive, the manufacturer is likely to be in a position to provide the comprehensive clinical data requested, the medicine will fulfil unmet medical need, and the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

43   http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002489/human_med_001592.jsp&mid=WC0b01ac058001d124

IN ASSOCIATION WITH   eu2013.ie

the National Institute of Health and Clinical Excellence (NICE) in England and a decision is not expected before July 2013[44]. After a recommendation has been issued by NICE, the National Health Service has generally up to three months to provide the necessary funding and resources to implement NICE guidance[45]. This means that there is at least a one year time-delay between the date crizotinib has received conditional marketing authorisation by the EMA and the day patients will be able to access the medicine as part of NHS funded services, provided the NICE recommendation is positive.

The European Commission recognized in its October 2012 Communication on industrial policy that "the lack of coordination between Member States on methodologies and criteria for taking decisions on pricing/reimbursement of medicinal products causes incoherencies and delays in access to innovative medicines". To support the efficiency of HTA across Europe, the EU is strongly supporting European collaboration on HTA[46]. European collaboration on HTA has the potential to streamline HTA methodologies and requirements across European countries. Joint relative effectiveness assessment of pharmaceuticals has the potential to establish a sound European basis for P&R discussions at the national level. For this to happen any joint assessment should be limited to the clinical part of HTA, and conclusions on the clinical added value of medicines should be translated in appropriate P&R levels at the national level.

A new pricing and reimbursment model: rewarding innovation

Personalised medicines have the potential to revolutionise healthcare and patient experiences. However for this to happen; patients need to access these medicines, and therefore healthcare systems need to be able to appropriately assess them and reimburse them. Today there is substantial inequality in access to medicines in Europe, be it between countries; between regions in countries; and between genders and socioeconomic groups[47]. This growing inequity is not compatible with European social values and policies for cohesion.

Payers need to recognize the key role they play in incentivising and providing access to innovation by developing a new model for P&R which rewards innovation and value and is transparent. This new model should address the limitations of current P&R models which often fail to include appropriate measures of quality of life and patient relevant health outcomes as well as setting budgets which reflect the value of personalised medicines to society. Such a model should include flexibilities to ensure that innovation is incentivised across all disease areas where unmet medical need exist and not only in the areas where innovation and added value are most easily achieved and demonstrated. By rewarding innovation and value, this new

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44   http://guidance.nice.org.uk/TA/Wave28/3

45   http://www.nice.org.uk/media/8BD/2B/Legal_context_nice_guidance.pdf

46   The EUnetHTA project, see chapter 8 and www.eunethta.eu

47   Source: Innovation and solidarity in Pharmaceuticals, 23-24 September 2010 EU Belgian Presidency Ministerial Conference

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reimbursement model should ultimately foster the development of targeted medicines which have the potential to increase effectiveness of treatment, reduce side-effects, and therefore lower costs to the healthcare system.

Rewarding innovation means that:

- P&R conditions should reflect value assessments, building on aligned and complementary regulatory assessments and HTAs, followed by price discussions at a national level; international reference pricing cannot overrule value assessments of medicines and differential pricing should be made possible by agreeing on an appropriate framework for use of international reference pricing amongst EU Member States.

- P&R conditions should be regularly updated, in order to learn from new data produced post-authorisation; managed entry agreements are a first step in a longer-term evolution of progressive patient access, i.e. progressive authorisation and progressive reimbursement mechanisms.

- A medicine could have a different price for different indications according to its effectiveness and the health benefits it brings to different patient groups

Furthermore, to overcome some of the financial barriers which lead to unequal access to medicines in Europe, prices in a given country should be commensurate to the affordability of that country to pay, and therefore prices could differ between European countries. This, together with the other measures discussed above, will ensure that all patients across Europe can have access to personalised medicines in a timely and equal manner.

Action/ changes needed

Working towards reducing time to access for patients by:
- Collaborating with regulatory authorities and leveraging on evidence generated during the process of marketing authorisation Recognition by payers of the need to reward innovation
- Ensuring that marketing authorisation findings are used as the basis of HTA, and that HTA findings are translated in P&R conditions
- Aligning post-approval requirements across decision-makers
- Coordinating assessment and reimbursement mechanisms for drugs and diagnostics
- Using evidence generated on drug use in real-life to update coverage

decisions
- Identifying, by means of research and testing, new methods include patient relevant outcomes and reflect the value of new medicines to society
- Exploring the practical feasibility and acceptability by different stakeholders to introduce differential pricing for different indications of the same medicine and whether introducing such reimbursement system would provide a concrete incentive to develop new medicines for conditions with unmet medical need
- Engaging reimbursement authorities in testing, by means of pilots, the feasibility of using MEAs such as coverage with evidence development, linked or not with performance based reimbursement, to study off-label and compassionate use of medicines with particular emphasis on rare conditions

Appropriate mechanisms

- The Transparency Directive review should acknowledge the role of HTA in supporting P&R decisions and call for shorter timelines for P&R decisions for innovative medicines building on efficiencies created at the European level
- Better integration between ongoing data collection efforts on payers, manufacturers and provider side.
- Efficient data collection infrastructure to monitor use and effectiveness of medicines in real life at national level which can be linked at EU-level.
- Alternative methods to randomised clinical trials which allow assessment of the value of new drugs by using routinely collected data.
- Transparent assessment procedures which reward value-creation across all areas of unmet medical need.
- Managed entry agreements.
- Appropriate use of international reference pricing, recognising impacts on health inequalities and access to treatment.

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Mission: promoting a shift among clinicians and other healthcare professionals away from traditional reactive medicine towards proactive healthcare management, employing screening, early treatment, and prevention - Education and training of healthcare professionals in the personalised medicine era

Implementing personalised treatment and care is likely to significantly impact patients, healthcare professionals (HCPs) and health services. It will require a shift in the mentality and day-to-day practice of clinicians and other HCPs as they move away from traditional reactive medicine (treating an already established disease) towards proactive healthcare management, employing screening, early treatment, and prevention. Information and expertise will have to be aggregated from the laboratory and diagnostic tests, from imaging technologies and drug utilisation. And as the role of HCPs changes, adaptation will be needed in the traditional models of education - for future professionals and for in-service training.

The public legitimately expects HCPs to demonstrate professional competence that reflects the latest advances and discoveries in medical research. But developing, maintaining and updating this competence will require concerted efforts - not just in terms of personally commitment from HCPs themselves, but also from employers, professional organisations, certification entities, regulatory agencies, and others.

Behind personalised medicine: key areas

New technologies and professional competences
Biologists will need new competences in technologies such as patient profiling, sequencing, and the "'omics". Data will need analysing with new software, and the biostatistician will acquire a prominent position between biologists and clinicians. 'Omics data will be carried out by relevant professionals supported by advanced software, but all HCPs will need an

understanding of basic principles to competently review the information presented to them and make the appropriate decisions. Bio-imaging technologies have advanced too, and diagnostics is no longer morphological, with metabolic imaging technologies permitting recognition of disease biomarkers through their biological rather than morphological information. It is now possible to see not only how big a tumour is, but how aggressive it is or could become.

Communication
Effective communication will be more important, both amongst HCPs and between HCPs and patients. HCPs, scientists and biotechnologists must be able to communicate effectively with each other in a two-way dialogue. That way new technologies can be understood and applied correctly and efficiently in clinical practice, and advances in technologies can be based on direct information about what clinicians need.

The treatment continuum for increasingly informed and empowered patients will require that HCPs translate complex information into messages that the patient can understand, with the correct balance between saying too much and saying too little. HCPs will also need to be alert to the ethical and data protection debate over personal data for research.

Current Problems

Graduate HCPs are not considered to be adequately prepared for this changing clinical reality and the changing needs of their patients[48][49][50]. But a further challenge faces HCPs in the future, for which they are not fully prepared: continual interaction with other professional figures in a streamlined, multidisciplinary, translational continuum bridging the gap between the bench and the bedside that often prevents the translation of findings from research into clinical practice.

A recent analysis of cancer research education programmes in some of Europe's top comprehensive cancer centres and research institutes carried out within the Education & Training Work Package of the FP7 project EurocanPlatform revealed that multidisciplinarity is currently woefully under-represented. Just five out of the 185 events surveyed specifically stated that basic and clinical researchers would engage in discussion during the event. This finding, in a field as large as oncology, clearly shows that change is needed.

Many educators have developed programmes in personalised medicine/targeted therapy, but an overall structure is needed to achieve shared understanding among healthcare professionals, patients and the public. Education and training that is high quality, transparent and transferable

48   Carlberg C. The need for education in personalized medicine. In Personalized Medicine (2012) 9 (2) 147-150
49   Salari K (2009) The Dawning Era of Personalized Medicine Exposes a Gap in Medical Education. PLoS Med 6(8): e1000138. doi:10.1371/journal.pmed.1000138
50   Medical Research Education in Europe; European Science Foundation Science Policy Briefing paper, September 2012

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will be needed for the cross-disciplinary approach vital to translating personalised medicine into widespread clinical practice.

Multidisciplinarity and interprofessional collaborative practice

Only collaboration among all professionals can successfully transfer knowledge from laboratory and clinical research into mainstream practice. HCPs will have to classify and treat disease in a new way, interpreting information from across sources that blur the traditional boundaries of individual specialties. Under- and post-graduate education curricula must prepare a generation with a true interdisciplinary approach and related skills.

For established professionals, continued training should move away from the traditional, linear approach where different professions learn in isolation, and towards a multidisciplinary learning environment where all professions can meet and discuss, with the ensuing knowledge sharing and overlap.

In the clinic, multidisciplinarity and effective interprofessional collaboration present a particular challenge. Not all HCPs will be enthusiastic adopters, and this approach will need to be taught like any other skill. Medical education researchers and practitioners have begun to explore Interprofessional Education - defined by the World Health Organization (WHO) as "when students from two or more professions learn about, from and with each other to enable effective collaboration and improve health outcomes[51]" - and Interprofessional Collaborative Practice.

"Core Competencies for Interprofessional Collaborative Practice", the 2011 publication by the Interprofessional Education Collaborative expert panel, which comprised six national associations of schools of the health professions in the USA[52], identified four competencies essential if HCPs are to work "effectively within and between all professions, with patients, families, and communities, and in the arena of public policy."[53] These competencies are summarised in the following table [54]:

51   Framework for Action on Interprofessional Education & Collaborative Practice (WHO/HRH/HPN/10.3) World Health Organization 2010. http://www.who.int/hrh/resources/framework_action/en/index.html. Accessed 3 October 2012.

52   Interprofessional Education Collaborative Expert Panel. (2011). Core competencies for interprofessional collaborative practice: Report of an expert panel. Washington, D.C.: Interprofessional Education Collaborative.

53   Madeline Schmitt, Amy Blue, Carol A. Aschenbrener, and Thomas R. Viggiano. Core Competencies for Interprofessional Collaborative Practice: Reforming Health Care by Transforming Health Professionals' Education. Academic Medicine, Vol. 86, No. 11 / November 2011

54   Adapted from 6

Competency Domain	Description of Core Competence
1. Values/Ethics for Interprofessional Practice	Work with individuals of other professions to maintain a climate of mutual respect and shared values.
2. Roles/Responsibilities	Use the knowledge of one's own role and of other professions' roles to appropriately assess and address the health care needs of the patients and populations served.
3. Interprofessional Communication	Communicate with patients, families, communities, and other health professionals in a responsive and responsible manner that supports a team approach to the maintenance of health and the treatment of disease.
4. Teams and Teamwork	Apply relationship-building values and the principles of team dynamics to perform effectively in different team roles to plan and deliver patient/population-centred care that is safe, timely, efficient, effective, and equitable.

Teaching Modalities

Research into effective formats[55] suggests that traditional approaches such as presentations, face-to-face or online, are less effective (20% retention rate) than discussion-based formats (50%), and that active involvement is more valuable than passive participation. Accordingly, the classic current meeting format at events should give way to workshops, round-table discussions and small group seminars. A case study of a patient, from the genetic basis of their disease through outcomes of treatment, can form a useful basis, with interaction among professionals from a range of specialisms ensuring that all the available knowledge is brought to the discussion. The opinions of patients, their families and care givers and the knowledge they have should not be underestimated, and patient participation in education events should always be considered.

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[55]   NTL Institute, Bethel, Maine, USA. http://www.ntl.org

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Action/ changes needed

- education is needed at all levels: undergraduate, post-graduate specialist training and continuing professional development, to produce competent interdisciplinary professionals.

Appropriate mechanisms

- education and training activities based on the curricula of diverse professions (medical school, nursing school etc);
- integration of elements of core competencies highlighted by research into interprofessional collaborative practice, ;
- promotion of shared understanding and collaborative development of the tools for personalised medicine;
- transparent education, transferable between countries, professions and public, using E-learning and blended learning, and overcoming language barriers;
- provision of evidence-based practice for the benefit of patients and public and the use of results from research so that they provide documented results of patient treatment and care.

Mission: promoting a new, open, more collaborative environment for drug research and development in Europe to help drive personalised medicine to deliver more of its potential benefits - Public-private partnerships – pioneering personalised medicine research with the Innovative Medicines Initiative

Public-private partnerships and personalised medicines research

Biomedical research is already delivering personalised medicines and benefiting patients in areas such as cancer, and it is becoming increasingly clear that a personalised approach to treatment is needed in many other disease areas. However, identifying the different and distinct diseases that are currently considered to be one disease and developing the appropriate tests to diagnose them and the treatments to tackle them requires a large scale research and innovation effort involving all key players in the drug development process.

For this reason, public-private partnerships (PPPs) represent a suitable model for driving forward personalised medicines research, as they bring together experts from academia, research centres, the pharmaceutical industry, small and medium sized enterprises (SMEs), hospitals, regulators, and patient groups.
In practice, this means that new research findings benefit from the expertise and input of, and can be rapidly exploited by, all key groups. In addition, PPPs very often involve all partners pooling data (including companies' historical or legacy data) to create immense databases that offer new opportunities for research.

Introducing IMI

The Innovative Medicines Initiative (IMI) was established in 2008. With a €2 billion budget, it is by far the world's largest PPP in life sciences research - €1 billion comes from the European Commission's Seventh Framework Programme (FP7), while pharmaceutical companies that

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are members of the European Federation of Pharmaceutical Industries and Associations (EFPIA) contribute a further €1 billion in in kind contributions (e.g. researchers' time, access to equipment and facilities, etc.).

Today, IMI supports 40 projects. Some focus on specific health issues such as neurological conditions (Alzheimer's disease, schizophrenia, depression, chronic pain, autism), diabetes, lung disease, oncology, inflammation & infection, tuberculosis, and obesity. Others focus on broader challenges in drug development like drug and vaccine safety, knowledge management, the sustainability of chemical drug production, the use of stem cells for drug discovery, drug behaviour in the body, the creation of a European platform to discover novel medicines, and tackling antimicrobial resistance. In addition to its research projects, IMI supports a number of education and training projects. Many projects have a focus on personalised medicine, and a selection of these will be presented in this chapter.

The projects are delivering excellent results that have an impact on all aspects of the drug development procedure, from adding to our understanding of the underlying biology of diseases, through the identification of potential drugs and testing for safety and efficacy, to the design of clinical trials.

Most significantly, IMI is pioneering a new, open, more collaborative environment for drug research and development in Europe.

IMI and personalised medicine

Disease areas where IMI is working on patient stratification and the tools needed to develop targeted therapies include rheumatoid arthritis (RA) and related immunoinflammatory conditions, diabetes, severe asthma, and brain disorders such as autism, Alzheimer's disease, chronic pain, depression, and schizophrenia.

Furthermore, other IMI projects contribute to this work, especially in the area of knowledge management (as combining data from different sources is not a simple task).

A breath of fresh air for severe asthma patients — the U-BIOPRED project

Most people with asthma are able to control their symptoms with medication. However, for the patients with severe asthma, this is not always the case, even though they take large amounts of medication every day. Severe symptoms include chest tightness and breathlessness and affect around six million people in Europe. A severe attack can require hospitalisation and be life threatening; asthma kills 12 000 Europeans annually. On a day-to-day basis, severe asthma

profoundly impacts patients' lives, hampering their ability to work, go to school, engage in physical activity, and spend time in areas with high levels of traffic congestion or where smoking is allowed.

There is therefore a clear and urgent need for new treatments for severe asthma. However, it is not always easy to identify the patients who will benefit from a particular drug and find enough patients to participate in clinical trials.

The U-BIOPRED ('Unbiased biomarkers in prediction of respiratory disease outcomes') project was launched in 2009 with the goal of enhancing our understanding of the different types of severe asthma and determining which drugs will prove most effective at treating them. The project has a budget of €20.7 million and brings together researchers in universities, industry, small companies, and several patient groups.

The project has recruited more than 1 000 people, including severe asthma patients and healthy volunteers, into a major clinical study. Drawing on data from blood and tissue samples, lung function tests, exhaled air samples and examinations of the airways, plus reports of people's own experiences, the project is building up a detailed picture (or 'handprint') of each individual's condition. By comparing data from hundreds of people, the team hopes to identify groups of patients with similar handprints. These groups will allow researchers to define different kinds of severe asthma, paving the way towards personalised treatments for patients.

Concretely, the projects will refine the 'handprints' and use them to develop tools for predicting which drugs will be effective for different groups of severe asthma patients. The handprints will also be used to update the criteria for defining and diagnosing severe asthma.

Easing the pain of rheumatoid arthritis – the BT-Cure project

Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease that is characterised by stiff, painful and swollen joints. Although treatments exist to relieve the symptoms, there is as yet no cure for RA and many RA patients report a poor quality of life. The underlying causes of RA remain unknown, although a number of genes are thought to be involved. The BT-Cure ('Be the cure') project, which was launched in 2011 and has a total budget of €38.1 million, aims to tackle these challenges and pave the way for the development of new therapies to treat and even cure RA before it has caused irreparable damage to patients' joints.

Research suggests that different genetic, environmental and molecular events could be involved in triggering different varieties of the disease. Where the underlying molecular cause of the disease is different, an alternative treatment may be needed.

The BT-Cure team is working to add to our understanding of disease-causing factors and

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disease progression in RA. It will apply this knowledge to the identification of improved or targeted therapies. It will also work on the generation of new diagnostic tools to identify early forms of RA and distinguish them from one another.

Patients play an active role in the project – with their personal experience of the disease, they are well placed to advise the researchers on what patients need.

Diabetes research gets personal – the DIRECT project

Some 285 million people worldwide have type 2 diabetes, and that figure is set to rise to 439 million by 2030. It arises when the body cannot make enough insulin (the hormone responsible for managing blood sugar levels), or when the body fails to respond to insulin. Although type 2 diabetes is a chronic, lifelong condition, it can be managed through a combination of medicines and lifestyle changes. If left unmanaged, patients' blood sugar levels become too high, triggering damage to the cardiovascular system, kidneys, eyes, and nerve endings.

Type 2 diabetes is a highly heterogeneous condition largely because the phenotype of people who develop diabetes is highly variable, as evidenced by the rate at which their subsequent diabetes progresses, how they respond to diabetes therapy, and who develops micro- and macrovascular complications. Although there are a number of risk factors for type 2 diabetes (such as obesity), it is not always clear why some people develop the condition while others do not. Furthermore, the development, progression and treatment response of diabetes vary from one patient to another; this is likely to reflect subtypes of diabetes with different pathophysiology. In other words, there are a number of different kinds of type 2 diabetes, and that is where the DIRECT project comes in.

The focus of the €43.1 million DIRECT ('Diabetes research on patient stratification') project, which started in 2012, is identifying different subgroups of type 2 diabetes patients.

The overarching aims of DIRECT are to develop a stratified medicines approach for the treatment of type 2 diabetes with either existing or novel therapies. Thus, there is a need to

1. identify biomarkers that can be used for stratification of patient populations by risk of disease progression to allow targeted intervention

2. identify biomarkers for response to treatment intervention leading to new therapies or to a better use of existing therapies

3. carry out stratified clinical trials of existing and newly-developed therapies which will be more powered in high risk groups.

The consortium will identify biomarkers predictive for type 2 diabetes subtypes with rapid diabetes development and progression as well as altered response to diabetes treatments,

and surrogate response biomarkers that reflect the underlying disease progression. These biomarkers will be developed and used in clinical trials. Therefore, this 7-year project is divided into two phases – a discovery phase and a validation and clinical trial phase.

To maximise the likelihood of finding biomarkers suitable for patient stratification, the consortium will concentrate the phenotyping and multi-level genomic analysis on the extreme phenotypes of rapid and slow glycaemic deterioration and extreme response to therapeutic intervention. A robust and secure data repository will be developed to enable computational multi-level integration across phenotypes and data types. To facilitate rapid deployment of biomarkers into drug development and clinical trials, DIRECT will develop and validate high throughput assays for biomarkers that arise from the discovery phase. As the ultimate aim of DIRECT is patient stratification, biomarkers arising from the discovery phase will be used to design one or more prospective clinical trials. These will aim to further validate the biomarker(s) of interest, and establish utility in clinical practice and/or clinical trial design and drug development.

DIRECT will gather large amounts of data as well as samples from patient cohorts at risk of type 2 diabetes, people with diabetes, and people undergoing diabetes treatment. This will enable the project team to identify novel biomarkers (biological markers such as the level of a certain molecule in the blood) that are predictive for disease progression. These biomarkers will then be tested in prospective clinical trials, to determine which drugs are effective in the treatment of different varieties of type 2 diabetes, thereby paving the way for their use as new diagnostic tests as well as in the creation of personalised therapies.

In its organisation as a PPP, the DIRECT preojct brings together key expertise of academic and pharma partners in diabetes, which will lead to novel therapeutic approaches to personalised medicines for the disease. This cannot be achieved by each participant alone. The close collaboration in different aspects of diabetes research and development is required to achieve the ambitious goals of the holistic consortium approach.

The tests developed by DIRECT will ultimately usher in a new era of personalised medicine for diabetes patients. In practice, this means doctors will be able to diagnose their patients more accurately and tailor treatments to suit their own particular subtype of type 2 diabetes. In this way, patients will be able to manage their condition more effectively and hopefully avoid the complications associated with diabetes. Furthermore, patients who are at risk of diabetes could be identified and monitored.

The work carried out under the DIRECT project will substantially boost industry's understanding of the underlying causes of type 2 diabetes, helping it to develop tailored treatments that can be targeted to the right patients. The work carried out in DIRECT complements the efforts of IMI's other diabetes projects. IMIDIA ('Improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in diabetes') is studying the beta cells of the pancreas, which are responsible for producing insulin, with a view to developing a cure

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for diabetes. Meanwhile SUMMIT ('Surrogate markers for micro- and macro-vascular hard endpoints for innovative diabetes tools') is developing tools to identify the patients at greatest risk of developing complications relating to diabetes.

Knowledge management

IMI's projects typically work with vast amounts of data; some of this is pre-existing or 'legacy' date brought into the project by the partners, and some is generated during the project itself. Integrating and analysing diverse types of biological and medical data from a range of sources is extremely challenging, and for that reason IMI has launched a number of knowledge management projects.

An example is eTRIKS ('Delivering European Translational Information & Knowledge Management Services'), which is working on creating an open, sustainable translational research informatics / knowledge management platform based on agreed standards. The starting point of the project is an open source platform called tranSMART that is already being applied successfully in IMI's severe asthma project U-BIOPRED. The eTRIKS team will provide a suite of support services covering the whole translational research project life cycle, including business analysis, platform development, curation and hosting support, standards development, and ethics consultation. By creating a single, open source platform that meets industry needs while remaining affordable for public partners, eTRIKS will deliver considerable cost savings for public private partnerships that use it. Furthermore, by ensuring the consistent implementation of format and content standards, eTRIKS will facilitate the reuse of data (with appropriate governance) to study new issues and speed up the development of new drugs for patients.

Towards a new classification of diseases

Looking to the future, IMI recently launched a Call for proposals which included topics on the classification of diseases (also known as disease taxonomy). There is now broad recognition that the way diseases are classified needs to change, and the immense scale of the challenge means that only a large public-private partnership could take this on.

The two topics launched under the 8th Call will embark on a new approach to disease classification, focusing initially on two disease areas where the problems of patient classification are well known: immunoinflammatory disorders (e.g. systemic lupus erythematosus (SLE) and rheumatoid arthritis) and neurodegenerative diseases (particularly Alzheimer's disease and Parkinson's disease). The projects will deliver data, tools and recommendations that can be used by the biomedical community to develop new treatments and diagnostic tests.

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Action/ changes needed

- Filling the need for a strong understanding of the underlying causes of diseases to enable development of personalised medicines
- winning recognition for PPPs as a strong tool for facilitating collaboration and promoting the development of personalised medicines in diverse fields.

Appropriate mechanisms

- support for multidisciplinary research engaging a wide range of stakeholders
- promoting open collaboration among all stakeholders in health research and drug development.

Useful links and further reading [56]

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56   IMI

IMI website: www.imi.europa.eu

IMI 8th Call for proposals: www.imi.europa.eu/content/8th-call-2012

Relevant IMI projects

BT-Cure: www.btcure.eu

eTRIKS: www.etriks.org

DIRECT: www.direct-diabetes.org

U-BIOPRED: www.ubiopred.european-lung-foundation.org

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