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Personalised Medicine: European academies' discussion of issues

What is personalised medicine?

Clinicians have often sought to personalise patient care according to individual circumstances. However, recent advances in the biosciences have led to much greater understanding of some of the causes of disease and its progression, underpinning new opportunities to tailor individual prevention and treatment measures for greater efficacy and fewer side-effects.

Personalised medicine can be described in various ways (and alternative terms are used, including individualised, stratified and precision medicine), but in essence the aim is to improve the appropriateness and quality of customised healthcare by classifying and characterising disease based on information (genetic and other determinants) obtained for individuals and for well-specified groups of individuals.

These principles apply to every branch of clinical practice but personalised medicine has progressed further in the oncology area, e.g. Herceptin (trastuzumab) for breast cancer and crizotinib for non-small cell lung cancer. Abacavir is used for HIV and ivacaftor has recently been used to target an underlying cause of cystic fibrosis.

Work by academies in Europe

In June 2015, the Biosciences Steering Panel of EASAC organised a meeting in Brussels to discuss issues for personalised medicine, with involvement of experts from FEAM, the European Commission and other interested parties. Discussion was initiated by presentation of recent work from the German National Academy of Sciences Leopoldina[1] and the UK Academy of Medical Sciences[2]. The purpose of the present EASAC paper is to summarise the main conclusions from this work by individual academies in order (i) to bring key points to the attention of those other national academies in Europe who may be developing interests in this area[3] and (ii) to examine issues to address collectively at the European level.

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[1] http://www.leopoldina.org/en/publications/detailview/?publication%5Bpublication%5D=628&cHash=4d15af0067a2846aa69bf4527a0dfeb7.

[2] http://www.acmedsci.ac.uk/policy/policy-projects/Stratified-medicine.

[3] Several other EASAC members, for example, have already contributed to other discussions, including in the UK , by the Royal Society ("Personalised medicine: hopes and realities", 2005 http://www.royalsociety.org); Switzerland, by the Swiss Centre of Technology Assessment which includes the Swiss Academies of Arts and Sciences (https://www.ta-swiss.ch/en/project/biotechnology-medicine/personalised-medicine); Austria, by the Austrian Academy of Sciences (http://www.oeaw.ac.at/aa).

Increased implementation of personalised medicine depends on progress across a broad front of science and innovation. The principal recommendations from the German and UK academies[1,2] presented in this EASAC-organised meeting cover the following areas:

1. Research and development

Among the main priorities are:

(i) To increase understanding of the complex molecular and environmental causes of disease, and interaction between the various determinants, perhaps particularly for metabolic, neurodegenerative and mental health disorders, as well as the therapeutic areas already being addressed, such as oncology.

(ii) Using extensive sample collections and information from Omics research to identify suitable biomarkers and characterise their sensitivity and specificity for diagnosis and therapy. This requires interdisciplinary collaboration between academia, health services and industry.

(iii) To increase research in relevant areas for health technology assessment and in economics, ethics and law, e.g. relating to issues for distributive justice if access to therapies were to be restricted and for the potential reclassification of certain subtypes of common diseases into the category of orphan diseases, as well as to issues for informed consent and privacy.

2. Harmonisation and standardisation

There is increasing need for large-scale data sets and for their potential to be maximised, e.g. in selecting biomarkers. Specific biomarkers are needed for a wide range of purposes, e.g. disease prediction, diagnosis, prognosis, prediction and estimation of therapeutic response. Biobanks are an important tool for identifying and validating biomarkers, requiring standardisation of protocols and practices, particularly in terms of quality-assured tissue sampling, assay and documentation. There will also be increasing challenges to be faced in storing, handling and linking very large data sets.

Significant progress has been made in genomics standardisation but there is further need to improve methodological consistency and, in order to elucidate how genomics and other molecular factors influence health and disease, there is often a concomitant problem in assessing and recording specific and accurate clinical characteristics. There is significant scope for national and international standardisation for consistency in recording medical history and phenotypes.

3. Designs for clinical studies

New research approaches, e.g. stratification of well-characterised groups[4], have implications for study design and logistics and, if simplifying clinical trials, may also help to shorten development times and regulatory authorisation steps.

The opportunity to accelerate the pre-approval phase of clinical development brings with it additional responsibilities for post-marketing evaluation of side-effects in routine practice and for the publication of complete study data, including negative results.

4. Hospital infrastructure

Advances in genomic sequencing, large-scale protein analysis and other Omics technologies provide new opportunities for high throughput bioanalytical procedures locally, e.g. in university hospitals, at reasonable cost. However, the necessary analytical infrastructure needs to be established and accompanied by extended IT infrastructure and improved bioinformatics capabilities, including data curation.

Progress in personalised medicine depends on the implementation of translational medicine – the transfer of research results into innovative and integrative clinical practice – and this depends on interdisciplinary research as well as on the close interaction between many medical professionals. There are significant opportunities and challenges for increasing interdisciplinary research in many medical centres and for networking between centres.

5. Data protection

Procedures for the protection of personal data and for the legal protection of non-medical scientists vary between Member States. One issue that is of vital importance to all Member States is to support the appropriate use of patient data for health research purposes while retaining adequate safeguards to protect citizens' privacy within a proportionate governance framework. Personalised medicine probably does not raise new issues for the protection of personal data (although advances in the mental health therapeutic area may be particularly sensitive) but the European Parliament's amendments to the proposed Data Protection Regulation would create significant problems for health research more broadly. At a time when the Data Protection Regulation is moving to the trialogue stage, it remains essential for academies to inform about the value of health research so that crucial progress in personalised medicine is not put at risk[5].

[4] Biomarkers are increasingly being used for stratification in clinical trials, e.g. in oncology where 49% of trials (up to April 2015) are now designed in this way (Scrip 2015 May 22nd p 6).

[5] Issues for the Data Protection Regulation have been addressed in detail by FEAM and its partners in the health research community, see http://www.feam-site.eu/cms/index.php/policy-priorities.

6. Joint development of therapeutics and diagnostics

Individualised therapy requires high quality diagnosis. Historically in the EU the regulatory procedures and timescales for commercial development of therapeutics and diagnostics have been different and this has created challenges for co-development of therapeutics with companion diagnostics. There is a need to create novel and flexible approaches for regulatory assessment, including the provision of scientific advice, to cope with evolving business models, encourage collaborations and promote a range of co-development strategies. The current European Commission initiative on the In Vitro Diagnostic Medical Devices Regulation provides an opportunity to create a supportive regulatory framework[6].

7. Reimbursement and pricing

Payment systems in healthcare often lack the capability to reflect specific benefits arising from personalised medicine. Furthermore, there are twin disincentives to industry to engage in personalised medicine: the likely smaller market size of more precisely targeted, group-specific therapies and the cost of development of an associated diagnostic. A case can be made for constructing a more flexible reimbursement system that enables prices to be adjusted as new information is collected to document clinical utility. Flexibility in pricing mechanisms should incentivise and encourage innovation.

8. Education and training

There will be increasing opportunities for doctors and patients to make decisions jointly about care – and, thereby, also to manage patient expectations. The challenges for this information sharing are compounded by the increasing complexity and interdisciplinarity of the information available. These challenges bring new needs for education and professional development (and clinical guideline provision) for healthcare practitioners and for access to quality-assured sources of information for citizens.

9. Raising awareness of policy makers and stimulating broader partnerships

There are major implications for clinical practice in taking account of research advances, including those for rare diseases, and in implementing personalised medicine. Additional public funding for health services is needed to underpin structural adaptations and ensure that societies can capitalise on the scientific advances. If this funding is not forthcoming, it is likely that social and health inequities will be exacerbated.

Success also depends on collaboration, bringing together patient organisations, policy makers, regulatory authorities, healthcare systems, health technology assessment, research

[6] However, see concerns raised by EASAC and FEAM and others regarding proposed European Parliamentary amendments to the draft Regulation, http://www.easac.eu/home/easac-news/detail-view/article/joint-statem.html.

funders, academia, and industry. The example of the UK Stratified Medicine Innovation Platform, together with the very recently announced Precision Medicine Catapult[7] illustrates what is achievable at the national level. Similar initiatives might be found useful in other Member States. In addition, however, there are opportunities for EU collaboration, harmonisation and added value in generating and using the research tools and data[8]. There is continuing need to create critical mass for personalised medicine research across Europe, both in pursuing fundamental research priorities and in exploring the practical implications for healthcare delivery.

10. General discussion

Additional key points emerged in discussion:

- Cost-effectiveness: how to demonstrate and how to reward? Member States have various mechanisms to analyse new health approaches but these assessment procedures may not yet be adapted to the issues arising from combining therapeutic and diagnostic. Many healthcare funders have yet to commit to paying for new approaches that may be subject to pressure of higher costs in the short term, albeit more cost-effective for both health services and society in the longer term.
- Supporting collaboration between academia and industry Public-private sector partnership is essential to capitalise on the scientific opportunities now coming within range and find new ways to capture innovation. For example, using biomarkers to re-analyse previous data from clinical trials to re-evaluate compounds in terms of efficacy for new patient sub-groups. However, perspectives on industry-academia partnership are becoming increasingly polarised and there is need to establish new models to encourage collaboration in clinical research. There is also a general, strategic challenge that must involve healthcare services and academia as well as industry in ensuring proportionate resource for disease priorities.

[7] https://www.catapult.org/precision-medicine-catapult.

[8] The 2013 European Commission Staff working document (http://ec.europa.eu/health/files/latest_news/2013-10_personalised_medicine_en.pdf covers a wide range of challenges to be addressed by new research: basic knowledge and cross-disciplinarity; tool development, including for patient stratification; standards and bioinformatics for clinical testing; diagnostics and regulatory issues; translation to medical applications and clinical practice; and understanding value and economics including pricing and health technology assessment. The ESF Forward Look in 2012 ("Personalised medicine for the European citizen") also analysed a broad range of enabling factors in the development and implementation of the technologies. The Framework Programme 7 project PerMed (http://www.permed2020.eu), whose main partners are Member State research and health ministries, together with others in the scientific community, is developing a Strategic Research and Innovation agenda for Europe in personalised medicine. The European Alliance for Personalised Medicine, linking patients' groups, industry and academia has an initiative "Specialised Treatment for Europe's Patients" (STEPS, http://euapm.eu/what-is-it-about), providing successive briefings to EU Council Presidencies. The new ERA-Net ERACoSysMed ("Collaboration on systems medicine funding to promote the implementation of systems biology approaches in clinical research and medical practice", https://www.eracosysmed.eu) aims to help make personalised medicine a reality. This ERA-Net brings together 14 national funding bodies including the Slovak Academy of Sciences

- EU initiatives and opportunities in clinical data and collaboration One very encouraging example of collaboration is the Innovative Medicines Initiative (www.imi.europa.eu), a pre-competitive research collaboration across pharmaceutical industry and academia to establish procedures for clinical data collection and standardisation. The European Bioinformatics Institute linked to EMBO (www.ebi.ac.uk) is an example of a strong European collaboration in large scale data storage and bioinformatics analysis, with both multinational company and European Commission funding. ECRIN, the European Clinical Research Infrastructure Network (http://www.ecrin.org) has also been useful in providing synergy between national research capacities and there is also significant potential in the Biobanking and Biomolecular resources Research Infrastructure initiative (http://bbmri-eric.eu). Nonetheless, it is acknowledged that there is more to be done to build and link new repositories of clinical data (including imaging data) and in developing clinical standards. A role can be envisaged for the EU to lead international efforts to establish coherence. However, this depends in turn on activity in the Member States to attain consistent standards at the national level – a case can be made for a centralised system in each country rather than leaving the responsibility to individual institutions. One example of what has been achieved at the EU level is the data base of standardised adverse drug reaction data that has resulted from national convergence.
- Role of SMEs Smaller companies have been productive in identifying biomarkers but they often cannot afford the validation step. Significant resource has been made available in the first year of the SME instrument of Horizon 2020 for the clinical validation of biomarkers and the EMA also provides advice to support SMEs in product development. Nonetheless, it remains the case that the fate of most successful health research SMEs in Europe is to be bought by larger companies rather than themselves maturing into a larger company.
- Biobanks With genomics as the driver, the assumption is often made that only a single sample is required from each individual (or with an additional one from the tumour in the field of oncology) but for proteomics (and metabolomics) consecutive samples from an individual are often required to support the identification and validation of biomarkers. This is necessary both for individuals to serve as their own controls and in order to increase the likelihood that samples will be available to identify markers for early diagnosis in individuals who later manifest clinical symptoms. This has implications for the design of biobanks, curation of data sets and application in routine clinical practice as well as for the research priorities to improve techniques to accumulate Omics information[9].

[9] It should also be noted that Omics studies are progressing rapidly in profiling gut microbiota in order to understand certain human disorders, e.g. inflammatory disease, and there will also need to be increasing facility to link human microbiota data with other clinical data sets, e.g. see Anon “Big data meets mechanism” Nature Medicine 2015 21, 673.

- Self-diagnosis The technology for testing outside of the health services settings is developing rapidly[10]. However, some of the developments, e.g. in consumer genomics with Direct-to-Consumer Genetic Testing, are hard to regulate effectively and risk un-managed and un-validated use[11].
- Collection of personal data Public concerns about the use of personal data for research encompass twin issues: confidentiality and the commercial use of data generated in the publicly-funded health services. The scientific community still has much to do to explain that confidentiality can be protected[5] but also that the use of patient data in support of public-private partnership in healthcare innovation is a public good.
- EU Cross Border Health Directive One other legislative development that has potential for promoting personalised medicine in improving healthcare throughout the EU is the Cross Border Health Directive[12], which may help to share and disseminate good practice in using biomarker-based diagnosis and targeted therapy.

Conclusions

Personalised medicine is relevant to several public policy sectors in addition to health, e.g. for industry, finance and education. There is significant European potential for personalised medicine to transform healthcare and deliver economic value, both in increasing global competitiveness in innovation and by improving cost-effectiveness of health services. It is important to enlarge the debate about the issues for personalised/precision medicine for other areas of clinical medicine. But it is also important to avoid hyperbole in claims about the pace of innovation, and to be realistic about the time and effort required, e.g. to validate biomarkers. It is also necessary still to address key issues for research, standardisation, networking, infrastructure and the policy environment to enable the endeavour in the longer term. Many actions can be taken at the Member State level and there are also opportunities for increased EU level coherence and support. There are valuable European Commission initiatives underway in support of personalised medicine but there is room to do more. For example, the JRC might consider building on previous expertise in clinical chemistry and in oncology databases to extend their public health efforts in the validation of biomarkers and the construction of linked large-scale data sets. It is also essential to explore the opportunities for networking and collective work between

[10] E. Elenko, A. Speier and D. Zobar "A regulatory framework emerges for digital medicine" Nature Biotechnology 2015 33, 607-702.
[11] These issues for consumer genomics and implications for established health services are discussed in detail in the EASAC-FEAM report on Direct-to-consumer Genetic Testing, http://www.easac.eu/home/reports-and-statements/detail-view/article/direct-to-co.html.
[12] Directive 2011/24/EU, see http://ec.europa.eu/health/cross_border_care/policy/index_en.htm.

the EU and other international partners. The US initiative in Precision Medicine[13] is likely to be particularly noteworthy in driving research and its reduction to practice[14].

Academies of science and of medicine have a continuing responsibility to help inform, initiate, steer and monitor national efforts by their scientific and policy communities. There may also be potential for collective work by academies in Europe to share good practice in optimising approaches for personalised medicine and to inform policy development by the EU institutions, adding value to what has already been achieved by other bodies.

[13] F.S. Collins and H. Varmus "A new initiative on precision medicine" New England J Medicine 2015 372, 793-795

[14] One recent commentary on the strategic priorities for the USA is I.S. Kohane "Ten things we have to do to achieve precision medicine" Science 2015 349, 37-38.