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Policies to aid the adoption of personalized medicine

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Abstract

Recent policy developments in the European Union and elsewhere aim to tackle some of the key issues responsible for the limited adoption of personalized medicine approaches so far.

The sequencing of the human genome raised expectations for a new era in which ‘omics’ information would allow the widespread implementation of personalized medicine, harnessing biomarkers to improve the probability of achieving desired treatment outcomes and/or reduce the risk of adverse effects. However, the development and application of personalized medicines has been more limited than hoped. Given this, a range of recent policy initiatives in the European Union (EU), the United States and elsewhere aim to more effectively address some of the issues that have hampered progress in the field^{1,2}. Here, we focus in particular on the new EU regulatory framework¹, which revises and augments legislation to tackle issues including biomarker validation, biobanking, clinical trials, protection of personal health information, funding and the value of personalized medicines.

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Competing interests

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SUPPLEMENTARY INFORMATION

See online article: S1 (box)

Biomarkers: clinical and analytical validity

Omics technologies have contributed substantially to the development of biomarkers that could prospectively identify patient populations that are more likely to benefit from a drug or experience an adverse reaction. Two key issues for the successful use of a biomarker to achieve such goals are its clinical and analytical validity.

Clinical validity can be considered as how useful the biomarker is in identifying the relevant patient populations. Related to this, recent guidance from the European Medicines Agency (EMA) integrates ‘genetic’ end points at the earliest stages of drug development³. That is, if *in vitro* or *in vivo* data indicate that >50% or >25%, respectively, of a drug is ‘cleared’ by a single functionally polymorphic protein, the relevant gene is to be genotyped in the first-in-human study population, as well as in all consecutive phases, to avoid safety issues related to genetic differences in active substance exposure. Potential clinically relevant pharmacogenetic influences on drug pharmacokinetic properties from Phase I studies must be considered in consecutive phases, either by investigating genotype/phenotype-based dosing, or by exploring therapeutic drug monitoring or biomarker-guided dosing.

Analytical validity assesses the method used to measure the biomarker. Related to this, the European Commission (EC) has proposed a regulation for *in vitro* diagnostics (IVDs) that provides a new legislative framework for biomarker assays — strengthening oversight through dedicated centres throughout Europe, post-market safety, transparency, traceability and overall regulatory management¹. If implemented, the proposals would limit the exemption for lower-risk ‘in-house’ IVDs by requiring that their manufacture and use occurs under the quality management system of a single health institution that is compliant with recognized standards. High-risk ‘in-house’ tests (when failure predisposes to serious health risk) and ‘companion diagnostics’ would be subject to requirements of the new regulation.

Biobanks: harmonization of sample handling

Defining the molecular mechanisms that underlie personalized medicine approaches requires high-quality, standardized collection of biospecimens. Moreover, data reproducibility from emerging technology platforms is determined by consistency in the handling of biospecimens and the associated data. The development, dissemination and harmonization of best practices for sample procurement and processing is therefore important and ideally would be consistent across different regulatory agencies. Recent EU regulatory policies seek to address these issues¹ (Supplementary information S1 (box)). EMA guidelines highlight the importance of prospective DNA banking for genotyping in all phases of drug development, even when no obvious indications of a relevant genetic influence on pharmacokinetic properties or drug response exist, thus ensuring that unknown genetic variants or biochemical pathways of importance can be retrospectively identified and their clinical effects tested with adequate statistical power³. Similar efforts to address such issues are in progress at the US Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and further global harmonization might soon be a realistic goal.

Clinical trials: pharmacovigilance and harmonization of guidelines

The clinical validity of biomarkers is established through clinical trials. To boost clinical research in Europe in general, the EC has proposed a new EU regulation in place of the current directive for clinical trials, which is being discussed in the European Parliament and Council¹. Its adoption is important for personalized medicine, as it includes drugs targeted to a narrowly defined patient population, for which the involvement of several (or even all) member states in trials may be important in reaching recruitment targets.

Enrichment strategies for clinical trials, which have been addressed by the FDA² and considered by the EMA (Supplementary information S1 (box)), could help to optimize biomarker validation and reduce the number of patients needed for enrolment in clinical trials to demonstrate drug effectiveness. However, markedly reduced pre-market exposure increases the importance of post-marketing pharmacovigilance, which is also covered by EMA and FDA guidelines^{1,2} (Supplementary information S1 (box)). Ultimately, the harmonization of such regulatory guidelines would be desirable.

Personal data protection

The protection of personal health information continues to be a high priority in the EU framework, and needs to be carefully managed in consultation with all stakeholders so that it does not become a barrier to harnessing the benefits from integrating clinical, personal and demographic data with biomarker profiles. Generally, anonymization is impractical because traceability is required to link biomarker profiles with the disease phenotype and treatment outcomes of individual patients. So, sufficient harmonization of data protection statutes is needed to allow safe cross-border data transfer in multinational collaborations. The EC is 'modernizing' the current General Data Protection Regulation to meet the digital challenges of new technologies and harmonizing data protection requirements across the EU. Once adopted, the new Directive will still prohibit the processing of sensitive medical data without consent of the patient¹. This constraint can, however, have specific exceptions: when the data are relevant for public health protection or for historical, statistical and scientific purposes. Unification of data protection requirements in the EU, under a robust control system, would increase the trust and confidence of patients and consumers, and not only improve the ability of industry to conduct biomedical research but also allow better monitoring of benefit–risk profiles of drugs and data mining on treatment outcomes.

Research funding

A key barrier to the development of personalized medicine has been the lack of resources to generate a critical mass of the necessary scientific data and enabling tools. In Europe, the new EU Framework Programme for Research and Development (known as Horizon 2020) will invest ~€70 billion in collaborative health research, which could enable personalized medicine approaches¹. Within Horizon 2020, funding through the Framework Programmes for Research and Technological Development, the Competitiveness and Innovation Framework Programme and the European Institute of Innovation and Technology will be unified, and proposals in the area of personalized medicine are one research priority. Moreover, there are plans to extend the existing Innovative Medicines Initiative (IMI)

framework into IMI-2, which could provide further funding for public–private partnerships in this area.

Establishing the value of personalized medicine

Another concern is that the new wave of expensive personalized medicines could overwhelm health-care systems. So far, however, there is no unified approach on how to value a personalized medicine at individual and public-health levels. The French Cancer Institute has shown that molecular testing can produce significant savings, as the costs of testing are more than offset by reduced non-effective prescribing and its consequences, but such examples are scarce. Health technology assessment (HTA) could be used to evaluate therapeutic benefits and economic impacts of the use of personalized medicines for individual patients and society overall. In this respect, the EC recently established the Joint Action EUnetHTA, a permanent HTA network between EU member states, including regional organizations and stakeholders' representatives, which is intended to facilitate information exchange and develop common methodological approaches to HTA¹. In addition, the EMA is running a collaboration with HTAs, providing parallel advice on evidence needed to determine both a medicines' benefit–risk balance and value.

Outlook

There are substantial opportunities to adapt current regulatory frameworks to aid the development of personalized medicines. As discussed here, the new regulatory framework in the EU, as well as efforts underway elsewhere, are important steps forward. In addition to the aspects described above, general initiatives that could facilitate the adoption of personalized medicine are steadily progressing in Europe, including the EMA Innovation Task Force network, the qualification of novel methods for medicines development, the provision of scientific advice through EMA working parties involving experts from academia, and the participation of HTA specialists, health-care professionals and patients' representatives^{1,3}. The EC plans to continue to evaluate developments in personalized medicine to define additional opportunities to accelerate its national and international application¹.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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