Opinion Paper

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Personalized medicine into health national services: barriers and potentialities

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Abstract: Research and innovation in personalized medicine (PM) are extensive and expanding, with several pharmacogenetic/pharmacogenomic (PGx) testing options currently available for a wide range of health problems. However, PGx-guided therapy faces many barriers to full integration into clinical practice and acceptance by practitioner/patient: utilization and uptake by payers in real-world practice are being discussed, and the criteria to guide clinicians and policy makers in PGx test selection are not fully incorporated. This review focuses on the advances of pharmacogenomics to individualize treatments, the relationship between pharmacogenetics and pharmacometabolomics, the new paradigm of the Big Data, the needs and barriers facing PGx clinical application and the situation of PGx testing in health national services. It is based on lectures presented by speakers of the European Society of Pharmacogenomics and Personalised Therapy (ESPT) Fourth Conference, held in Catania, October 4th, 2017.

Keywords: barriers; personalized medicine; pharmacogenetic; potentialities.

Introduction

Research and innovation in personalized medicine (PM) are extensive and expanding, as measured by the number of scientific publications, biomarker discovery and targeted therapies. However, despite the steady increase in the number of clinically useful molecular diagnostic and targeted therapies, the healthcare system is slow to integrate PM into clinical practice [1]. This review focuses on identifying barriers and potentialities related to pharmacogenetics and pharmacometabolomics, Big Data, as well as the needs and barriers facing pharmacogenetic/pharmacogenomic (PGx) clinical application in actual health national services.

Personalized medicine and pharmacometabolomics potentialities

Initiatives in PM were launched in many parts of the world. PM and precision medicine are not exactly the same: the term PM first appeared in published works in 1999 and means selection of treatment best suited for an individual [2]; meanwhile, precision medicine was coined in 2008 to describe how molecular diagnostics allows physicians to unambiguously diagnose the cause of a disease without having to rely on intuition [3]. Thus, these two terms should not be used interchangeably. The best known is the precision medicine initiative initiated by US President Obama in his State of the Union address on January 2015. In Europe, the implementation of PM is a major objective, too. A substantial amount of research has led to many innovative findings. However, we are still at an early stage, and evidence for real benefits in the national health systems remains insufficient. Results must now be consolidated, and pilot

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studies conducted, so that PM can be implemented into everyday healthcare. This is an ongoing process in Europe as well as in each member state, demonstrated, e.g. by the 2018 European Commission call for demonstration pilots for the implementation of PM in healthcare (H2020-SC1-BHC-2018-2020). A significant paradigm shift will need to take place in medical research and healthcare for this innovative approach to be fully exploited.

A PM strategy will require all diagnostic services to be "state of the art" with the ability to integrate and analyze data in real time and to produce comprehensive individual patient diagnostic profiles. This will require the transformation of healthcare systems to make them more proficient at generating, storing and processing health-related information, in order to recommend appropriate actions. Genomics has transformed our understanding of disease and our ability to deliver care in a way that is specific and personal to each individual patient. Genomics opens up the shift toward personalized precision treatment, allowing us to examine the underlying causes of disease, rather than just identifying and managing patients once disease has taken hold [4].

In this context, pharmacogenomics, included nowadays in the omic sciences field, is the study of how genetic variations modulate drug responses between individuals, and so far, around 2000 genes are involved in drug response. Nevertheless, variability in patient responses to drugs is also dependent upon many environmental factors, which can condition the individual´s phenotype. In this situation, metabolomics emerges as an omic science capable of determining the end products of any molecular or cellular process. Specifically, metabolomics studies low-molecular weight metabolites present in biological samples, as blood or urine. The concentration of specific groups of metabolites may be sensitive to pathogenically relevant factors such as genetic variation, diet, age, immune system status or gut microbiota, and therefore, their study may be a powerful tool for the characterization of complex phenotypes affected by both genetic and environmental factors. In this sense, we are currently able to study the individual´s phenotype through the metabolic profile, which will provide a quantifiable readout of the biochemical state. This represents a picture ranging from normal physiology to diverse pathologies, as well as of the mechanisms underlying the interindividual differences in drug responses, in a manner that is often not obvious from gene expression analyses [5].

If we focus on that biochemical-metabolic "signature" related to drugs, pharmacometabolomics appears as a new omic discipline that, when integrated with others, will improve our knowledge about drug response and even about disease heterogeneity. It can be particularly useful when the studied phenotypes are complex, not well defined or arise from a variety of different pathophysiologic processes. The application of a research strategy that allows the metabolomic data to "guide" genomics, e.g. pharmacometabolomics-informed pharmacogenomics, might be particularly useful in selected situations. In fact, there are several studies already published about this topic. Jit et al. [6] studied 880 patients with major depressive disorder treated with citalopram or escitalopram. They showed the involvement of a new pathway related with the nitrogen metabolism and also identified new genetic variants associated with serotonin concentrations in these patients. In order to study the relationship between depression and stress pathologies, we started a stress study in our hospital [7]. A metabolomic analysis was performed with a noninvasive and precise technique as direct infusion mass spectrometry, to find and characterize metabolic differences between two different biological situations of an individual: relaxed and stressed states. The comparison of the metabolomic composition profiles showed that the cortisol and its related metabolites, among others, are predominant in the stress state, while serotonine, melatonine and tryptophan were found to be the most predominant in the relaxed state. Another study [8] investigated the molecular basis for variation in aspirin response at both genomic and metabolomic levels. It also provided integration of these two omic data sets. The results showed the association of new gene variants with concentrations of a series of purine metabolites both before and after aspirin intervention, and, consequently, allowed the identification of a novel genetic locus that may play a role in individual variation in response to aspirin. These studies, along with several others, exemplify how metabolomics data can complement and inform genetic data in defining ethnic, sex and gender basis for variation in responses to treatment, which illustrates how pharmacometabolomics and pharmacogenomics are complementary and powerful tools as a strategy to reach PM. This approach sets a more complex scenario where the therapy should be guided by clinical, genetic, genomic and environmental information, which are all different for each individual patient.

Regional genetic laboratories that have been the focal point for adoption of genomic technologies into healthcare in the last years are expected to play a central role in this evolution, supporting the future PM requirements, including molecular and genetic diagnostics. The key elements in the implementation of PM are the ultimate healthcare delivery professionals who would require a significantly different approach in the delivery of their training [9].

Clinicians do not use PGx info

However, what happens if, after all the efforts for translating the knowledge to the patients, clinicians just do not use PGx info?

During the Fourth Conference of European Society of Pharmacogenomics and Personalised Therapy, this idea was floating in the air, but it was not nearly until the end of the meeting when it was clearly stated and discussed. Nowadays, we have achieved cost-effective ways to test the PGx variants in a reliable and efficient manner. In addition, we have the clear consensus that there is a concrete group of tests for selected drug-variant pairs that should be implemented in the clinic, and last but not the least, we have the support to this consensus of the drug authorities, namely, the FDA (www.fda.org) and EMA (www.ema.eu). This last point means the legal backing and also the legal duty for clinicians to implement PGx results in their prescription decisions. However, this is hardly ever a reality.

During the meeting, several decision-support tools were presented and discussed, most of them under the concept of pre-emptive testing and many others trying to include in a single tool, not only PGx but also other relevant data such as interactions between concomitantly administered drugs, interactions between drugs and food and even lifestyle data influencing drug effects. Integrating all this information would be our final goal in order to understand and *interpret* every patient as a whole. However, is it realistic trying to implement this kind of tools now?

From the point of view of countries like Spain, the answer is definitely "no", first of all, because the feasibility of having all that kind of information is just impossible due to legal issues and technical problems in many European countries, apart from the lack of the habit of collecting in the electronic medical records this kind of data. Second, which is even more practical, and in the heart of the problem, clinicians usually do not have much more than a few minutes for assisting each of their patients. They literally do not have the time to take a look at all the results from a pre-emptive PGx panel, with much more information of that what they really need for their patients at that very moment. They just need a very simple tool, with easy-to-understand results and instructions for actionability, only for the drugs that the clinician intends to use for that specific patient, in that specific scenario.

If today we could make a poll among clinicians, after showing them just two-paged colorful PGx pre-emptive test results, we are pretty sure that 95%, or even more, would say "this report is very well prepared, very interesting, very attractive for research purpose… but please tell me what I have to do with my patients regarding these two drugs here. I can not pay attention to see anything else". Therefore, we should not intend to make our clinicians real experts in PGx in just 1 day. The best approach could be just trying to give them the small pieces of the puzzle that they really need for their daily routine, only with the highest level of significance, and in agreement with the recommendations of the drug agencies and/or the big international consortia (www.pharmgkb.org). Once they realize the usefulness and benefits for their patients, they will never give up asking for more pieces of that helpful and comprehensive puzzle.

Paradigm of the Big Data

Most genes are found only weakly associated with disease and, thus, unlikely to lead to great improvement in diagnostic and therapeutic precision. What barriers and potentialities does the Big Data offer?

The Big Data boasts of the possibility of possessing data from the total population and claims that correlation can displace causation. In fact, the term has been used to refer to the massive amounts of data collected over time that are difficult to analyze and handle when using common database management tools. This new paradigm raises many expectations, particularly in the field of health [10].

The Big Data collected for research purposes (Big research Data) and the Big Data used for research, although collected for other primary purposes (Big secondary Data), are discussed in the light of the fundamental common requirement of data validity, prevailing over "bigness" because there are serious misleading concepts. In medicine, a large sample size is required only when the anticipated effect is small and clinically slightly meaningful, and emphasis on correlation over causation could lead to futile interventions. Furthermore, in proving the effectiveness of intervention, analyses of real-world Big Data cannot displace the role of randomized controlled trials.

Curiously, even though medical biology laboratories generate a large amount of data, the opportunities offered by this new field are poorly documented. The contribution of Big Data analytics seems very promising for better understanding the clinical context of chronic disease follow-up and setting strategies of preventive PM [11]. In fact, the number of tests increases, and millions of PGx tests are done in Europe, with a market expectation of 11% annual growth rate between the years 2017 and 2026,

based on early diagnosis, increased number of adverse drug reactions cases, high prevalence of chronic diseases and advancements in genetic science, among others.

We need to generate working groups to methodologically assess prospective studies integrated in the assistance, to define the applicability of the PGx tests and the proper use of the Big Data.

Barriers for incorporation of genomic research findings in medical practice

Numerous barriers were found in the implementation of PGx projects, such as the lack of appreciation of the potential of PGx to improve patient care by some physicians, health institutions and payers, limited evidence of clinical validity (the precision of a test to identify or predict a given phenotype) and usefulness (the net balance of risks and benefits associated with the use of a routine practice test), difficulty to interpret the results of genetic tests, limited access to PGx testing and inability to integrate genetic tests into clinical decision support [12].

Many common solutions could be proposed for each barrier. Ideally, clinical validity and usefulness should be derived from well-conducted randomized clinical trials. However, observational studies can also provide valuable information. For example, a retrospective analysis in the post-authorization phase could identify the signals or replicate the association of different data sets and, in this way, add significant value. The agencies should promote the development of this kind of PGx studies. One way would be to encourage the incorporation of genetic biomarkers in the earliest phases of drug development process, which could be used in future clinical trials or in guidelines for clinical practice, or financing PGx translational research projects and organizing consortia to conduct multicenter trials. Scientific societies should also help to develop clinical evidence through launching platforms that allow advising the execution of these types of studies and/or the recognition of this type of studies in scientific meetings [13].

The lack of evidence is far from being the only barrier. Institutional inertia typically demands convincing arguments and robust data before clinical practice is changed. Frequently, healthcare providers and physicians look for professional society recommendations to assist them in the best available evidence of PGx tests, to elaborate recommendations and to monitor their clinical implementation. They could focus to identify specific educational needs about the utility of PGx tests and provide education and support on when to order a test and how to interpret it. This education should include information on the identification of at-risk populations, clinical scenarios, variant alleles and drug-dose recommendations based on genotypes in a consistent and clear manner, according to the strength of the available evidence and the efficacy and safety expected consequences [14].

It should be better pointed out that the validation methods of biomarkers that can be used in evidence-based medicine are not compatible with the strategy of precision medicine. Fortunately, there are areas, such as psychiatry, in which clinicians already ask for metabolomic and genomic studies, in an attempt to reach a better understanding of their patients' response to treatment [15]. Finally, in some nations, the scientific societies propose the use of the precautionary principle of new knowledge and resources of the PM.

Thus, it is necessary to build an infrastructure to underpin PM in health systems, including informatics and data systems, commissioning, procurement and financial frameworks. National health systems have to embrace technology and innovation. In summary, the overall benefit-risk balance, cost effectiveness of the tests, magnitude of the genomic effect and the strength and conclusiveness of the evidence should guide the inclusion and positioning of PM information in medical practice.

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