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Measuring the value of pharmacogenomics evidence

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Abstract

In recent years, there is a growing need to measure the value of pharmacogenomics testing so that policymakers are well-informed to decide about adopting and reimbursing pharmacogenomics testing, prioritizing pharmacogenomics research and development and encouraging the application of companion diagnostics. Presently, there are limited economic evaluation studies of genome-guided treatment modalities that would allow decision makers to comparatively assess the value and clinical utility of such interventions.

Pharmacogenomics (PGx) aims to correlate the role of genomic variants on drug efficacy and/or toxicity (1). PGx can play an important role towards a more efficient healthcare system with more beneficial treatment modalities and less therapies that either pose substantial risk or are unlikely to improve outcomes to the patients. In recent years, there is a growing need to provide evidence and precisely measure the value of PGx testing so that policymakers are well-informed not only for decision making related to adoption and reimbursement, but also to prioritize PGx research and development. Research efforts to increase the evidence levels of genome-guided treatments should be coupled with pharmacoeconomics studies (the economics of drugs). As such, it is absolutely necessary to undertake more pharmacoeconomics studies of genome-guided treatment modalities that would offer stakeholders and policymakers comparative assessments of the value of such interventions. Lack of such studies would not provide the available options for drug treatment rationalization and the consequences for adopting them for the population's

health and the country's healthcare budget, which constitutes a hurdle to the implementation of PGx in the clinic. Presently, very few such studies have been performed (2,3).

The effects of the human variome on individual drug responses are well established for a number of medications, particularly in oncology, cardiology, psychiatry and organ transplantation (1). As a result, more than 120 medications currently bear PGx information on their labels, approved by major regulatory bodies worldwide, allowing treating physicians to select drugs and doses more precisely to customize health care. However, the last decade, despite the rapid advances in the field of PGx and the enthusiasm of many clinicians and researchers, regarding the potential of this new discipline in improving provision of healthcare, there has also been some skepticism as to how feasible this new discipline is and how quickly PGx testing can be implemented in the clinic.

Successful translation of PGx findings into the clinic relies, among other barriers, on demonstrating that genome-guided treatment modalities are cost-effective, so that they can be ideally reimbursed by national healthcare systems. Despite the growing scientific evidence and hype regarding the potential applications of PGx, many stakeholders, particularly payers and decision-makers (e.g. Ministries of Health), often request additional evidence about the expected economic impact of PGx testing. In other words, and based on the existing evidence, policy makers must clearly decide to either include PGx testing in clinical practice, taking into consideration the associated opportunity costs, or to invest in additional clinical trials to generate stronger evidence for genome-guided dosing strategies, which will decrease decision uncertainty. This can be particularly important in case of healthcare systems that often face budget constrains (4).

In this issue of *Clinical Pharmacology and Therapeutics,* Dhanda and coworkers attempted to quantify evidence requirements for the implementation of PGx to individualize warfarin treatment (5). The authors used an approach in health economics, known as Value of Information (VOI), previously employed to prioritize research funding policies, to quantify and compare evidence levels for pharmacogenomics-based versus clinical (drug-drug interaction)-based warfarin dosing, generated from 9 randomized controlled trials that have been currently performed. The authors concluded that the decision uncertainly was higher for dose adjustments based on clinical dose individualization compared to genome-guided warfarin dosing (5), while the decreasing costs for the companion PGx testing for warfarin further suggests that evidence sufficiency is increased. Also, these authors concluded that the expected value of perfect information – the price that one would be willing to pay in order to gain access to perfect information – was lower for the genome-based compared to the clinical-based warfarin drug dose individualization.

The minimum requirement to adopt a PGx test lies in the strong association of PGx biomarker(s) and primary outcomes, mainly drug toxicity, or often, lack of efficacy, accompanied by a clear recommendation as far as the drug dose adjustment is concerned. Once such an association is available, economic evaluation, which constitutes a systematic analysis of the relationship between clinical outcomes and the respective costs, comes into the picture to model results, based on clinical and economic data (6). The value of a PGx test is calculated mostly considering the additional benefit to the patient and the extra costs incurred (6) and as such, if there is no clear evidence of the clinical utility of a PGx test, it makes no sense to implement or reimburse it.

Warfarin is perhaps one of the few medications in cardiology for which there is substantial evidence for genome-guided dose individualization and several algorithms to

calculate the dose requirements, based on the *CYP2C9*/*VKORC1* genotype. Also, apart from the 9 randomized controlled trials, based on which the Dharma et al study (5) was performed, there are several other nonrandomized controlled trials (**Table 1**), suggesting that genome-guided warfarin dosing can improve drug safety and effectiveness. Warfarin though is a rather cheap medication and as such, the PGx test costs, which are moderately high, somehow balance the overall cost savings resulting from dose individualization and hence minimization of adverse drug reactions, mainly bleedings; as such, several decision makers are often reluctant to reimburse warfarin PGx test costs, even though the costs required to treat adverse drug reactions due to warfarin can also be significantly high. There are however, different examples of genome-guided drug dosing, where not only are the medications significantly more expensive but also the cost of care increase, due to the PGx test, is justified by a significant improvement in the treatment outcomes. Such examples are the *KRAS* gene test to predict response to cetuximab in metastatic colorectal cancer patients (7), or the HLA-B*57:01 genotyping, linked to the anti-retroviral medication abacavir (8). Although both medications are very expensive, the overall improvement in patient outcomes would well justify the increased cost of care.

Another parameter to consider is the fact that clinical utility of a genome-guided intervention can not only be judged based on financial costs but also based on the effectiveness of treatment individualization. Both of these elements are needed to assess the value of healthcare resources used. In other words, one should not only look at the overall costs of a specific treatment but also at the quality of life and life-year gained as a result of a new treatment or technology. An easily conceivable analogy is to compare the better road safety offered by driving a more expensive car compared to driving a cheaper car. In the case of warfarin, even if the drug is relatively cheap and with the present PGx test costs, the PGx-guided dose adjustment was shown to be cost-effective in a variety of

settings, ranging from developed (9) and developing countries (4). As such, one can assume that lower prices for PGx testing could represent a more acceptable financial risk for health care payers.

From the above, it becomes evident that there is an urgent need to evaluate additional PGx studies, based on different types of economic evaluation. These efforts will aim to demonstrate that PGx testing is ready for clinical implementation, based on the continuously increased evidence for their clinical utility and, at the same time, that PGx testing costs can be reimbursed by healthcare systems, as PGx testing costs continue to decline.

Lastly, pre-emptive PGx testing may constitute an even better and a more cost-effective approach than the classical PGx approach. With pre-emptive PGx testing, genotyping is simultaneously and prospectively performed for multiple actionable PGx biomarkers for each patient such that they are readily available at the time of decision making for a wide variety of common drug treatment modalities. In this case, the immediate knowledge of a patient's PGx variation, along with the corresponding interpretation and accompanying recommendations, does not disrupt routine clinical care, standing as a clear advantage and perhaps a cost-effective option compared to the classical PGx approach when PGx biomarker genotyping occurs each time prior to the prescription of a certain medication, respectively. This approach, which is already implemented as 8 separate collaborative projects in the United States and currently in 7 clinical centers in Europe, as part of the Ubiquitous PGx project (UPGx; www.upgx.eu), may be potentially cost-saving, compared to the conventional genotyping approach, since PGx biomarker genotyping is performed simultaneously for a large number of pharmacovariants. Also, this approach is time-efficient, as the patient's PGx information and corresponding recommendations are available at the time physicians need to decide on the optimal drug

dose, hence increasing the chances of reaching the optimal drug dose faster. In this case both quantitative and qualitative evidence still needs to be provided, which will be instrumental for policy makers to adopt this new technology in healthcare systems in Europe. To this end, the UPGx project stands as a unique opportunity to explore whether pre-emptive PGx intervention for a number of treatment modalities is indeed cost-effective, by assessing the cost effectiveness of pre-emptive PGx testing in various clinical settings and from a variety of healthcare systems in countries with both strong and weaker economies in Europe.

Dhanda and coworkers conclude in their study that the evidence level for genome-based warfarin drug dose individualization was stronger than the evidence level for clinical drug dose individualization and that the expected value of perfect information was lower for the genome-based compared to the clinical-based warfarin drug dose individualization (5). It is, therefore, imperative to provide evidence to regulatory authorities and healthcare payers that PGx testing is ready for clinical implementation and that can genuinely improve the quality of life and increase life expectancy of patients in a cost-effective manner, so that PGx testing costs are reimbursed by healthcare systems (10) and PGx gets broadly implemented.

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