Systems-Based Approach to Drug Response

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Abstract Pharmacogenomics (PGx) involves investigation into the genetic basis of interindividual differences in drug responses, such as efficacy, dose requirements, and adverse events. PGx can be used as a tool for personalizing health care on the basis of individual genetic variations. It may decrease the amount of time needed to identify the most beneficial drug and dosage for a patient, minimize exposure to ineffective treatments, reduce the rates of adverse drug reactions, and improve the economic efficiency of the health care system. However, there are a number of obstacles blocking the achievement of personalized therapy through the full implementation of PGx. In this review, we focus on the barriers to the implementation of a system for PGx in the pretest, the PGx test, and posttest phases, and the solution for these barriers.

Keywords Pharmacogenomics · Drug responses · Dose requirements · Personalized therapy · Genetic variations · Genome-wide association studies

Introduction

Personalized medicine is an essential component of modern medical practice. In recent years, there have been

reports of a number of great pharmacogenomics (PGx) successes [1•, 2•]. PGx is one of the cornerstones of personalized medicine, and can be used as a tool for personalizing health care on the basis of individual genetic variations. It may decrease the amount of time needed to identify the most beneficial drug and dosage for a patient prior to the prescription, minimize exposure to ineffective treatments, reduce the rates of adverse drug reactions, and improve the economic efficiency of the health care system. There are routine PGx tests for target genes for some specific drugs: thiopurine methyltransferase (*TPMT*) for 6-mercaptopurine and azathioprine; *UGT1A1* for irinotecan; *CYP2C9* and *VKORC1* for warfarin; and *CYP2C19* for clopidogrel. Research in PGx has grown over the past decade, evolving from a candidate-gene approach to genome-wide association studies. PGx researchers aim to investigate the genetic basis of interindividual differences in drug responses, such as efficacy, dose requirements, safety issues, and adverse events [3]. Although there is promising evidence that PGx is becoming more widely adopted in clinical settings, there are a number of obstacles blocking the achievement of personalized treatment through full implementation of PGx [4]. In this review, we focus on the barriers to the implementation of a system of PGx in each of the three phases of the process (pretest, PGx test, and posttest; Fig. 1), and the solution for these barriers.

Pretest Phase

Evidence

Lack of reproducible evidence for the advantages of PGx over standard medical practice is one of the reasons why

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Fig. 1 Steps for a pharmacogenomics (PGx) test and the barriers (*italic*)

PGx testing has not become more commonplace in clinical settings. This evidence was categorized on the basis of the type of study, the magnitude of the benefit, the existence of clinically useful data, and the existence of professional society guidelines. The studies were classified in view of the evidence; evidence from randomized controlled trials as the strongest form of evidence, evidence from large epidemiologic studies as moderate evidence, and evidence from small epidemiologic studies and in vitro studies as weak evidence [5]. The slow rate at which PGx tests are being adopted in clinical practice is partly due to the lack of specific guidelines on how to adjust medications on the basis of the genetic test results [6]. The Clinical Pharmacogenetics Implementation Consortium of the National Institutes of Health's Pharmacogenomics Research Network and the Pharmacogenomics Knowledge Base is providing peer-reviewed, updated, evidence-based, freely accessible guidelines for gene/drug pairs [6]. The development of therapies targeted at selected patient populations may require the development of diagnostic tests that are sold in combination with such drug therapies. This type of diagnostic test is commonly known as a “companion diagnostic.” To advance new drug development and regulatory science, regulatory agencies globally have promulgated guidelines on PGx for nearly a decade in Europe, the USA, and Japan [7].

Drug Labels

Drug labels are the most fundamental document to provide the necessary information on drugs to health care professionals. According to the Food and Drug Administration (FDA), 77 approved drugs contain PGx information in their labeling [8], but in many cases, the labels do not provide action-oriented information for physicians and patients. The information provided is probably of limited use to most physicians and patients. However, the most recent

label for warfarin in the USA includes a table showing the appropriate starting dose to be given based on the patient's *CYP2C9* and *VKORC1* genotype combination. This type of information should be more useful to physicians than the information commonly provided in labels. The inclusion of clear and comprehensive drug labeling that provides information about genetic tests that are relevant to the safety or efficacy of use is critical to enhancing patient care [8]. The information of drug label differs among countries [9]. For *UGT1A1*, the adjustment decision making (how best to use the genetic information for prescribing a drug) dosage was not included in the label for irinotecan in Japan.

Cost-Effectiveness

Cost-effectiveness remains an important concern in implementing new genetic PGx tests. Cost-effectiveness analysis is a widely used tool to assess the value of health care interventions, but only a few studies have addressed the cost-effectiveness of PGx interventions in health care. To demonstrate its economic benefits, a PGx test needs to show evidence of clinical effectiveness, with increasing need for greater participation by experts in comparative effectiveness research [10]. If a PGx test were covered by health insurance, the number of patients tested might increase. Although some countries, such as the UK, explicitly consider cost-effectiveness in coverage decisions, in the USA, this is dependent on the particular payer. In Japan, national health care insurance covers the *UGT1A1* genotype test for irinotecan therapy [11], but it does not cover any other PGx test.

Patient's Background

Responses to virtually all drugs can differ between individuals because of intrinsic factors, such as genotype and also age and health. Furthermore, responses can also differ because of extrinsic factors, such as diet, use of concomitant drugs, and adherence that may affect drug pharmacokinetics and/or pharmacodynamics parameters [12]. In vitro model systems such as cell lines from large numbers of individuals are an attractive and cost-effective approach that has been used to help identify genes associated with variation in drug response by the application of genome-wide techniques [13]. Ethnic variation should be considered when interpreting genomic data and should be carefully addressed. For example, recent data showing a higher prevalence of a warfarin-sensitive genotype of *VKORC1* in Asians than in Caucasians is consistent with past FDA labeling of warfarin and practices in some Asian countries that are based on evidence that Asians require a lower starting dose than Caucasians do [14].

PGx Test: Techniques for the PGx Test

The PGx test is usually based on genetic variation in one or more biomarkers as evidenced by single-nucleotide polymorphism in the germline, by gene expression level, or by a specific change in the target pathogenic tissue (e.g., tumors). The criteria for evaluating PGx genetic tests can be summarized by the ACCE analytic framework: analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications. In the USA, test results can be reported only by laboratories that are certified according to the provisions of the Clinical Laboratory Improvement Amendments (CLIA). CLIA oversees clinical laboratories, and by extension, the performance of laboratory-developed tests. Although the FDA has the legal authority to regulate laboratory-developed tests, including genetic tests, it has opted to regulate only test kits and some components of laboratory-developed tests. The PGx test is generally outsourced by hospitals to private companies, which is a time-consuming and costly process. Many commercial companies have been developing genotyping platforms that offer rapid sample-to-result assays that will be highly beneficial for integrating PGx at the point of care [15]. A PGx test targeted for somatic mutations or gene expression must be optimized and standardized with regard to the type of samples (tumor) in the preanalytical steps compared with a targeted test for germline mutations.

Posttest Phase

Treatment Decisions Based on Genotype Results

After the PGx test results have been obtained, translation of the genotype information into a treatment decision is very important. The final treatment decision requires cooperation between physicians and patients. By guiding the initial warfarin dose, PGx algorithms incorporating genetic and clinical factors may improve the safety of initiation of warfarin therapy [16, 17]. Patients should be provided with appropriate and sufficient explanations by scientists and physicians as to why they should, or should not, select a specific drug. Whenever possible, alternative therapies should also be presented to patients.

Handling of Genetic Information

To protect human rights, rules regarding the treatment of individual genetic information as well as genomic DNA in samples should be established. Genomic data have specific properties of magnitude, stability, implications to kin, and ease of dissemination that render their management a challenge at is qualitatively different from that of the

management of traditional, self-limited, and often temporally transient medical information [18•]. In particular, an important element of concern is raised by the storage of a large amount of information in databases, with the potential for loss of confidentiality or privacy because such databases link an enormous amount of individual genotypic, phenotypic, and demographic data [18•]. However, fears regarding genetic diseases and the implications of access to information about such diseases for life and health insurance appear to have been overstated. The risk that PGx information will negatively impact life and health insurance is likely to be even lower than that associated with genetic disorders. Patients, pharmacists, and physicians are all critical players in the pharmacotherapy process. Patients should be supportive of sharing information with physicians and pharmacists and of personally maintaining their test results.

Electronic Medical Records

The use of electronic medical records is becoming well established in some health care systems. A primary challenge for genomics measurements is their integration with more traditional sources of health care information. The most important of these information sources is the electronic health record, or electronic medical record. PGx tests must be up-to-date and evidence-based, and guidelines for gene/drug pairs must be freely accessible [19]. Such guidelines can facilitate the translation of PGx knowledge from the bench to the bedside.

Education: How To Overcome Barriers

Physicians make decisions regarding the prescription of drugs and their understanding of the PGx test also strongly influences its successful integration into clinical practice. PGx is a rapidly developing field; therefore, there is a lack of education about what PGx is and how it can improve clinical outcomes. Molecular diagnostics has only recently been introduced into some undergraduate and medical curricula, where the major focus is currently on detection of infectious and genetic diseases. Physicians envision a major role for themselves in the delivery of PGx testing, but recognize that they lack adequate knowledge of and experience with these tests [20]. Development of effective tools for guiding physicians in the use of PGx tests should be a high priority. The research process includes genomic and PGx education of physicians prior to patient recruitment and education of study participants regarding informed consent. Informed consent education includes discussion of the potential for incidental findings. Patients are randomized to receive either in-person genomic

counseling or no counseling so that the impact of genomic counseling on multiple outcomes can be measured. Providing genetic counseling to all patients prior to a PGx test is important and is crucial for broadening the field of PGx.

Conclusion

Although understanding of the molecular basis of responses to medications is increasing, there remain a number of barriers to the integration of PGx tests for the design of personalized prescriptions into clinical practice. The desired result of the PGx test is the maximization of safety and effectiveness by matching the best available drug or dose with the genomic profile of an individual. However, many countries will not have access to PGx resources to individualize patient therapy for decades to come. The level and guidelines for PGx differ among countries. There are some efforts to make PGx applicable on a global level, for example, the Pharmacogenetics for Every Nation Initiative [21]. The WHO embraces evidence-based medicine to formulate an essential medicines list considering disease prevalence, drug efficacy, drug safety, and cost-effectiveness [22]. The essential medicines list is used by developing countries to build a national formulary. Even though there are many unanswered questions, systematically incorporating PGx tests at the national formulary level promises to improve global drug use. The future holds the promise of giving countries, physicians, and patients the opportunity to select more effective therapies and manage fewer untoward effects.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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