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Is Pharmacogenomics Ready for Prime Time?

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Abstract

Although there is a large body of data available on clinical and translational pharmacogenomics, the clinical use is still very limited. This editorial will address why the clinical application of pharmacogenomics is not widely adopted and how to promote the use of pharmacogenomic knowledge in clinical practice. Pharmacogenomics has the potential of changing the pipeline model of drug discovery, clinical development, and mass customization marketing. Although there are established techniques for molecular genotyping and phenotyping in major research institutes, the facilities for genetic testing and measurement of drug and its metabolite concentrations are not always accessible in the diagnostic laboratory. What's more, mutational screening using the current state-of-the-art technology is still laborious and time-consuming. Furthermore, the lack of adequate education provided to physicians in clinical practice as well as medical students and trainee physicians and it is yet to be incorporated into the curriculum of medical courses worldwide.

Introduction

Two general approaches are typically employed in pharmacological interventions of various diseases. The first is a "trial and error" approach, employed for drug treatment of diseases such as hypertension, diabetes, depression, schizophrenia, arrhythmias, and esophageal acid reflux. For these diseases, there are several drugs that are reasonable first-line therapy. Finding the most effective drugs for a given patient is often done through, trial and error and can often take months to accomplish. The other approach to drug management of disease is a "per protocol" approach, where the treatment for a given disease is essentially the same for everyone with that diagnosis. Examples of diseases treated in this way include most cancers, heart failure, myocardial infarction and organ transplantation. In both scenarios, a certain percentage of patients will obtain no benefit from a given drug, or will experience serious adverse reactions [1]. For drugs with a narrow therapeutic index (e.g. cytotoxic anticancer drugs, anticoagulants, & immune modulators), both approaches may increase their risk-benefit ratio for individual patients.

It is a well-recognised fact that individuals respond differently to drug therapy and that no single drug is 100% effective in all treated patients [1]. While some individuals obtain the desired effects, others can have little or no therapeutic response. Additionally, certain patients might experience adverse effects that vary from mild and tolerable to life-threatening events. The remarkable inter-individual variability in drug response is thought to be a consequence of multiple factors such as disease determinants, genetic and environmental factors, variability in drug target response or idiosyncratic response and other factors including age, gender, disease status, concomitant therapies and lifestyle factors such as smoking and alcohol consumption [2].

Pharmacogenomics is the study on how genetic factors influence individual responses to different drugs, which may affect drug efficacy, clearance, and adverse events related to the therapy. The clinical goals of pharmacogenomics are to minimize adverse drug events and maximize drug efficacy. By incorporating genetic information, health professionals can identify the patient's polymorphisms and disease subtypes to determine most advantageous management. This can include the immediate administration of the most efficacious and least toxic drugs at correct doses. Understanding and identifying an individual's genetic variations has the potential to decrease both the time expended in achieving effective therapy and the number of visits required for proper dose adjustment [3]. Thus, there are two general goals for the clinical application of pharmacogenomics; the ability to predict those patients at high risk of toxicity (and in whom a lower dose or a different drug would be administered), and the ability to predict those patients who are most likely to obtain the desired therapeutic effect from the drug [3].

Clinical Application of Pharmacogenomic Testing

Unlike other genetic testing, pharmacogenomics does not aim to specifically determine or predict the risk of disease, but rather characterises an individual based on disease susceptibility, risk of severe adverse effects, or even efficacy of certain drugs [3]. Pharmacogenomic testing has the ability to give an estimate of the likely effectiveness, thereby removing much of the uncertainty surrounding current pharmacotherapy. The ultimate goal of pharmacogenetic testing is to aid physicians in the prescription of the appropriate medication at the correct dose prior to the initiation of the therapy in an attempt to minimize adverse events and toxicity and maximize efficacy by excluding those who are unlikely to benefit (non-responders) or who may be harmed (adverse responders) [2,3]. The promise of pharmacogenomics lies in its potential to identify the right drug at the right dose for the right individual patient. The application of pharmacogenomics also aims to discover better drugs and improve the efficacy and safety of both prospective as well as licensed drugs [4]. Minimal pharmacogenomic testing is required for all new drug applications to the FDA, including a requirement for germline DNA to be prospectively collected from

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all subjects participating in pre-approval clinical trials and genotyping studies for drugs that are metabolized by enzymes whose genes contain polymorphisms with significant functional impacts.

For many drugs, the rare occurrence of serious adverse reactions may require that genetic studies focus on surrogate markers of toxicity [1]. For example, much work has been done to identify gene variants influencing serum creatine kinase level as a measure of statin intolerance and hepatic transaminases for drug-induced hepatotoxicity [2,5]. However, the extent to which genetic determinants of intermediate toxicity will predict the more extreme phenotypes is yet to be determined. Although genetic and clinical studies of drug-induced QT interval prolongation have provided some insight into predictors of life-threatening ventricular arrhythmias, the findings have primarily highlighted the clinical importance of extremely rare variants of a small number of genes such as *hERG*, *KCNE5*, *KCNQ1*, and *NOS1AP* [2,6,7].

There is though, increasing evidence that applied pharmacogenomics is beginning to take on a role in health care with the emergence of commercially provided services, such as AmpliChip from Roche (http://www.amplichip.us), which claims to provide personalized, fact-based pharmacogenomics information to assist physicians in optimizing individual patient's drug therapy. AmpliChip is the first FDA-cleared test for genotype analysis of *CYP2D6* and *CYP2C19* using a microarray hybridization method. The AmpliChip tests the DNA from patients white blood cells collected in a standard anticoagulated blood sample for 29 polymorphisms and mutations from the *CYP2D6* gene and two polymorphisms from the *CYP2C19* gene.

The FDA has approved four warfarin pharmacogenetic test kits, but most third-party payers are reluctant to reimburse for such testing because it is not currently considered a standard of care [6]. These tests typically cost a few hundred dollars, but it should become less expensive as it becomes more commonplace. The current FDA-approved product label for warfarin does not recommend routine pharmacogenomic testing for determining initial or maintenance doses, but it does acknowledge that dose requirements are significantly affected by *CYP2C9* and *VKORC1* and states that genotype information can assist in selecting the proper starting dose. A well-developed warfarin-dosing algorithm incorporating conventional clinical factors and genetic status is available at the website www.warfarindosing.org.

In the case of TPMT, there is a Clinical Laboratory Improvement Act-certified test available and clinical use of this test is increasing as physicians become more aware of the benefits of genotyping before treating patients with thiopurine drugs. Additionally, the FDA-approved product labelling for azathioprine indicates that prospective *TPMT* genotyping might help identify those patients at risk of hematological toxicities. It is interesting to contrast the test used to determine the TPMT phenotype with that used originally to classify subjects as having either poor or extensive metabolism of CYP2D6. In the case of TPMT, a blood sample is obtained and the enzymatic activity measured directly, whereas for CYP2D6, a probe drug is administered and a urine sample collected. The fact that TPMT is expressed in easily accessible cells (red blood cells) facilitated the introduction of this pharmacogenomic test into clinical use. The availability of DNA-based tests means that the clinical application of pharmacogenomics could be greatly accelerated for a large number of genes that encode proteins important in drug response.

Genetics-Guided Prescribing System and Drug Labelling

Allelic variations in the genes encoding drug targets, drug transporters, and drug metabolizing enzymes as a result of polymorphism has the potential to have a substantial effect on drug clearance and response [3]. It is expected that personalized treatments will be offered in the near future based on the genotypes of individuals therefore optimize the dosage and decreasing the frequency of adverse drug reactions. Personalized medicine is the use of detailed information about a patient's genotype or level of gene expression and a patient's clinical data in order to select a medication, therapy or preventative measure that is particularly suited to that patient at the time of administration [8]. The benefits of this approach include accuracy, efficacy, safety and speed.

Pharmacogenomic profiling may consequently affect drug labelling to limit prescriptions only to those individuals with the appropriate genetic profile. To date, about 10% of labels for FDA-approved drugs (>110 drugs, see http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm) contain pharmacogenomic information — a substantial increase since the 1990s. The label information involves at least 32 important genes that encode drug metabolzing enzymes, important proteins or drug targets. This means for drugs already approved by the regulatory agencies, succeeding discoveries that individuals with certain genetic profiles might experience adverse drug effects would require addition of this information to the label and as well as a warning that genetic screening is necessary. For example, the first label update for warfarin was issued in August 2007, and was in reference to its sensitivity in CYP2C9 poor metabolizers. The second warfarin label update was issued in January, 2010, and this label included the effect of a second gene, *VKORC1*, as well as a table with pharmacogenomics-guided dosing ranges for the drug. One could then take the view that pharmacogenomics is not about individualized drug therapy but rather about re-classifying risk factors. For example, instead of hypertension being a coexisting risk factor that should be considered before starting a new therapy, the risk factor will be patients with *CYP2D6/2C9* allelic variants who may have a reduced ability to eliminate the administered drugs.

Tamoxifen lacks efficacy in those female patients who are poor CYP2D6 metabolizers (i.e, 7% in the white population) [9,10], but the FDA has not made firm recommendations about *CYP2D6* testing before prescribing tamoxifen since the evidence of benefit has been considered insufficient. Importantly, clinicians should be aware that the clinical efficacy of tamoxifen is greatly decreased by concomitant drugs that are potent CYP2D6 inhibitors [11,12].

Clopidogrel, taken by about 40 million patients worldwide, is widely used to prevent atherothrombotic events and cardiac stent thrombosis when given along with aspirin. It is a prodrug and CYP2C19 is responsible for its metabolic activation. *CYP2C19* loss-of-function alleles appear to be associated with higher rates of recurrent cardiovascular events in patients receiving clopidogrel [6]. A current FDA boxed warning states that poor CYP2C19 metabolizers may not benefit from clopidogrel treatment and recommends that prescribers consider alternative treatment for patients in this category (e.g. prasugrel that is not metabolized by CYP2C19). However, routine *CYP2C19* testing is not recommended, and no firm recommendations

have been established regarding dose adjustments with regard to CYP2C19 status.

Main Obstacles that Limit the Use of Pharmacogenomic Testing

Regrettably, the pharmacogenomic approach to clinical medicine is currently very limited despite its discovery dating back to the early 1960's and presence of a large amount of pharmacogenetic information. At present, prescription genetic screening is largely confined to teaching hospitals and specialized laboratories and is not yet a part of routine practice. The strategy of prescription genotyping is seldom practiced in the clinic, even for substrates of extensively characterized SNPs such as *CYP2D6* and codeine or tamoxifen; *CYP2C19* and phenytoin; and *CYP2C9* and warfarin. Its limited use may be due to the fact that the *CYP2C9* genotype contributes to <10% of the total variability in an individual [6].

Although there are well established techniques for molecular genotyping and phenotyping in major research institutes, the facilities for genetic testing and measurement of parent drug and pharmacologically active metabolite concentrations are not always accessible in the diagnostic laboratory. What's more, mutational screening using the current state-of-the-art technology is still laborious and time-consuming. Furthermore, the lack of adequate education provided to physicians in clinical practice as well as medical students and trainee physicians and it is yet to be incorporated into the curriculum of medical courses worldwide. Thus, the bridging between medicine and basic science requires the collaborative efforts of both clinicians and researchers.

Another obstacle impeding the advancement of pharmacogenomic approaches to therapeutics is the precision of the genotyping results and the confidence in associating genotypes/SNPs with altered drug response. The ambiguity that can potentially arise in classifying an individual's genotype based on the laboratory data is a contributing factor. It is still unclear what the exact association between SNPs of the drug target genes with therapeutic outcome is. For the large number of SNPs in human genome, only a small number of these mutations have been characterized to establish their potential functional impact. As such, the functionality of most SNPs and their causative role remain largely unknown.

Can Pharmacogenomics Reduce Idiosyncratic Drug Toxicities?

Although through pharmacogenomics it is possible to reduce pharmacokinetic-related toxicities in some situations, decreasing the occurrence of toxicities that are not predictably associated to drug concentration may be more difficult. These so-called idiosyncratic toxicities are rare, unpredictable but often serious. Examples include drug-induced agranulocytosis, hepatotoxicity, *Torsades de Pointes* and rhabdomyolysis. Efforts are presently in progress to identify the genetic basis of numerous types of these toxicities, yet this may eventually prove to be the most challenging field in which to apply pharmacogenomic information. This is due to the fact that the drugs causing these types of toxicities with any frequency are not approved for use (or are withdrawn from the market). Additionally, as these toxicities are very uncommon, it is a daunting task to accrue adequate numbers of patients who have experienced the toxicity.

Conclusions and Future Perspectives: Is Pharmacogenomics Ready for Prime Time?

What have we learned from pharmacogenomics? The most important lesson is the fact that all drug effects vary between individuals, and all drug effects are influenced by genes. The majority of drug effects are multifactorial, i.e. they are affected by numerous genes, typically with some influence by environmental factors. However, some single mutations can alter a drug response considerably.

However, a number of challenges remain for clinical based pharmacogenomics to become a reality. Overtime, improvements in multi-genic testing promise to increase the role of personalized medicine. However, the pharmacogenomic complexities and particularly time-dependent changes of gene expression, will never allow personalized medicine to become an error-free entity. One challenge for the future lies in documenting enough of the drug response variability to make the genetic information clinically predictive. In some cases this might only require information on a few polymorphisms of genes; in others it might require very complex studies that involve relatively large numbers of genes or a genomic-based approach.

In the future, genetic testing to identify slow and fast metabolizers of a wide range of drugs may be conducted early in life, on a one-time basis, with the information placed on file in an individual's medical record. Such testing could have many benefits, both for individuals and drug companies. It could identify people who are susceptible to adverse drug reactions, and could also identify those who are unlikely to benefit from a particular dug. It would also make possible the resurrection of some older drugs that are safe and effective for most people but have been taken off the market because a few people had serous reactions. Companies would be able to reduce the size of clinical trials, creating greater efficacy. Therefore, pharmacogenomics has the potential of changing the pipeline model of drug discovery, clinical development, and mass customization marketing.

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