Integrating Pharmacogenomics into Clinical Practice

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ABSTRACT

Pharmacogenomics has the potential to improve patient-centered care and lead to an overall decrease in healthcare costs. This would be achieved through fewer hospitalizations due to adverse drug reactions, individualized and effective therapies, and decreased drug development costs with single nucleotide polymorphism pre-screening. Although challenges do exist in encouraging the use of pharmacogenomics—specifically in regards to resources, regulation, and impacts on the pharmaceutical industry—the benefits may outweigh the costs in terms of patient health and safety. In implementing pharmacogenomics, various clinical, ethical, legal, social and economical factors must be considered.

RÉSUMÉ

La pharmacogénomique aurait le potentiel de diminuer le coût des soins de santé et d'optimiser les soins primaires aux patients. Il serait possible d'y parvenir en réduisant les hospitalisations suite aux effets secondaires associés aux médicaments, en utilisant des thérapies individualisées plus efficaces et en diminuant le coût associé au développement de médicaments grâce au test de dépistage de polymorphisme d'un seul nucléotide. Malgré les défis associés à l'utilisation de la pharmacogénomique surtout sur le plan des ressources, de la régulation et de l'impact dans l'industrie pharmaceutique, les avantages en terme de santé et de sécurité sont à considérer. Plusieurs facteurs cliniques, éthiques, légaux, sociaux, et économiques doivent être pris en considération pour l'utilisation de la pharmacogénomique.

INTRODUCTION

Personalized medicine is an emerging practice that uses an individual's genetic profile to direct disease diagnosis, prognosis, and therapy [1]. In 2013, the Government of Canada granted $165 million to Genome Canada, the majority of which was applied to large-scale projects in the division of applied human health to develop personalized medicine [2]. Within the realm of personalized medicine are the fields of pharmacogenomics and pharmacogenetics.

Pharmacogenomics is an examination of common genetic variants within a population to determine associations with specific traits. In this field, genome-wide association studies are used to identify common single nucleotide polymorphisms (SNPs) in the human genome, which in turn may be used to identify genetic risk variants that could impact disease susceptibility and responses to certain therapies [3]. For instance, the pharmacogenomic association between the *apolipoprotein E4* allele and Alzheimer's disease has allowed clinicians to better identify patients at increased risk for developing this form of dementia [3]. Thus, physicians can educate high-risk patients and their families regarding ongoing monitoring and care. With increasing knowledge of genetic risk factors in relation to disease, researchers can continue to apply genome-wide association studies to obtain clinical risk assessments for various disorders [3].

Pharmacogenetics, on the other hand, studies both individual genetic profiles and possible responses to specific drug therapies in order to optimize treatments by maximizing drug efficacy and minimizing drug toxicity. The CPIC (Clinical Pharmacogenetics Implementation Consortium) has developed clinical guidelines for the dosing of multiple drugs based on pharmacogenetic studies of genetic variations among individual patients [4]. Most research done in the field of pharmacogenetics relates to the Cytochrome P450 (CYP450) family of enzymes, who together are capable of metabolizing over 30 classes of drugs [5–7]. Importantly, genetic variability (i.e., SNPs) within these enzymes may influence a patient's response to commonly prescribed drug classes [7]. A number of other successful applications have been recorded in recent years. In 2007, the U.S. Food and Drug Administration (FDA) used pharmacogenetics to recommend a change in warfa-

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rin usage [8,9]. Warfarin, a commonly prescribed anticoagulant, is difficult to dose due to its narrow therapeutic index and variability in dose-response [8,9]. These studies resulted in a new label for warfarin dosing, advising patients with genetic variations in either of the Vitamin K Epoxide Reductase Complex subunit 1 (VKORC1) or Cytochrome P450 2C9 (CYP2C9) genes to consume altered doses of warfarin to account for this unpredictability [8]. Recently, a prospective study carried out by Medco and the Mayo Clinic demonstrated that dose modifications based on genetic testing for CYP2C9 and VKORC1 variants decreased hospitalization rates by approximately one third [10]. Pharmacogenetics is also used to screen patients for thiopurine methyltransferase (TPMT) deficiency when prescribing 6-mercaptopurine (Purinethol) or azathiopurine (Imuran) [11–13]. This screening test is done to ensure that TPMT is active and able to metabolize thiopurines to prevent the formation of toxic metabolites, prior to initiating therapy [12,13,15]. Approximately 11% of the population has reduced TPMT activity and 0.3% of the population has a true TPMT deficiency [14]. In these patients, active 6-mercaptopurine accumulates and a larger proportion is converted to the cytotoxic 6-thioguanine nucleotide analogues, which can lead to bone marrow toxicity and myelosuppression [15].

Given the broad scope of personalized medicine, we have decided to focus our discussion on the role of pharmacogenomics in therapy, and more specifically to illustrate and evaluate the potential use of pharmacogenomics in personalized patient care. We aim to explore possible benefits to the community at large, and stimulate thought with respect to future considerations and challenges of implementing pharmacogenomics into clinical practice.

BENEFITS

The benefits of implementing pharmacogenomics may be substantial. Presently, pharmacogenomics has proven successful in identifying genetic variants associated with disease risk in many genome-wide association studies [16], and may one day replace "trial-and-error" prescriptions with therapy based on individualized genetic information [17]. Furthermore, increasingly rapid turnaround times are becoming realistic. Previously, most genetic testing for SNP analysis or copy number variant (CNV) testing would typically take days before results were received. Roberts et al. (2012), however, have described a point-of-care CYP2C19 genetic test for personalizing anti-platelet treatment with a three-hour turnaround time [18].

Pharmacogenomic testing may also be used to decrease adverse drug events [17]. A Canadian adverse events study reviewed 3,745 patient charts in 20 hospitals across Canada [19,20]. Of the 255 serious adverse events, 59 were related to medical management caused by drug therapy [19,20]. With 2.5 million hospital admissions annually, this suggests that approximately 40,000 serious, drug-related adverse events occur in Canadian acute care hospitals annually [19]. By decreasing adverse events through the application of pharmacogenomic technologies, trust in patient-physician relationships may be strengthened and stress on our healthcare system could be reduced. For example, a severe hypersensitivity reaction to the anti-HIV drug abacavir is characterized by a skin rash, as well as gastrointestinal and respiratory symptoms [21]. Mallal et al. (2002) initially demonstrated an association between abacavir hypersensitivity and haplotype *HLA-B*57:01* using a candidate gene approach [22]. This association was then replicated in other cohort studies [23,24]. Ultimately, these findings were confirmed in a large randomized controlled trial, which showed that cases of abacavir hypersensitivity could be reduced from 7.8% to 3.4% by excluding *HLA-B*5701*-positive patients from abacavir treatment [25]. This has since led to widespread adoption of genetic testing for *B*57:01* prior to the initiation of abacavir treatment.

Finally, SNP screening may allow pharmaceutical companies to exclude participants with variant forms of a gene from clinical trials who would react unsafely or ineffectively to the drug [17, 26]. Excluding these participants may eliminate the confounding of results due to genetic variation. This select participant exclusion could also decrease healthcare visits for patients who would have otherwise needed assistance for adverse events. As a result, drug efficacy will become easier to demonstrate within a specific population group, which in turn could help to expedite market availability [6,17]. Furthermore, improvements in efficiency will likely increase treatment options for illness, decrease drug development costs for pharmaceutical companies, and ultimately reduce purchasing costs for patients [6].

CONSIDERATIONS

Various challenges exist in incorporating pharmacogenomics into clinical practice. Primarily, we have a limited understanding of the complexities of the human genome. Studies are difficult to evaluate due to limited clinical phenotypes and multifactorial drug responses that may mask small genetic effects [16]. Millions of SNPs will therefore need to be assessed for their involvement with the pharmacokinetics and pharmacodynamics of common medications, a process which may be very time-consuming, complicated, and expensive [26]. Further research will be required, both to alleviate these uncertainties and to determine the most cost-effective approach for the integration of pharmacogenomics into clinical practice.

Secondly, pharmacogenomics may have an impact on the pharmaceutical industry. Pharmaceutical companies are driven by the prospect that the drugs they produce could serve more people than existing first-line therapies. As a result of competition and

restricted knowledge regarding which product will work best for the majority of the population, multiple drug alternatives may be created for a given condition. If pharmaceutical companies determine that their drug will only serve a small proportion of the population, they may not invest in further development [26]. Fewer drug alternatives will come to market for medical conditions, and more patients may go untreated if they do not respond to the limited number of available therapies [26].

Thirdly, private insurance companies may use the likelihood of response to certain drug therapies as criteria for insurance eligibility or premium rates. Safeguarding an individual's genetic profile, in terms of storage, control, access and information sharing, must therefore be considered [17,26–28]. Additionally, the consent, privacy and confidentiality concerning the genetic information would need to be reviewed with the patient before sequencing [17,26–28].

Finally, given the complexities of pharmacogenomics and its application to patient care, continuing education for healthcare providers will be of utmost importance. An inter-professional, team-based approach will likely be necessary in maximizing the potential benefits for patient care.

CONCLUSION

As pharmacogenomics becomes further entrenched in healthcare, a number of considerations must be taken into account. Although the clinical utility of pharmacogenomics has been discussed and demonstrated in certain contexts, the primary barrier for wider implementation is our limited knowledge within the field. Further research is needed to alleviate uncertainties and to determine the most cost-effective approach for implementation and integration of pharmacogenomics into clinical practice. A cautionary approach will need to be taken with respect to regulating access to genetic information and protecting patient confidentiality. Furthermore, depending on the technology used, genomic screening may take a significant amount of time. Finally, healthcare professionals will need appropriate training and education in using such information to make competent decisions. Despite these challenges, it is our opinion that the scope of medical management and patient care will be advanced by pharmacogenomics and personalized medicine. Further research will be required, however, before pharmacogenomics can be effectively integrated into our current healthcare system.

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