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Adoption of drug metabolizing enzyme genetic testing by clinicians

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ABSTRACT

Before starting a medication, PGx looks at how different people's drug metabolizing enzymes are from one another. As a result, adverse events caused by toxicity and the metabolism of the patient can be avoided. This paper looks at two different uses: a genetic test of the CYP 2C9 enzyme and the Thiopurine methyltransferase gene before beginning mercaptopurine drug therapy and before administering the anticoagulant warfarin. According to the biomedical literature, barriers to PGx have limited clinician experience. A lack of prospective clinical trials, legacy business models between the pharmaceutical industry and physicians, inadequate regulatory oversight, payer reimbursement practices, and physician habits are among these. PGx is unlikely to see widespread use until these issues are addressed. The most significant obstacles to clinician adoption are unproven utility and ingrained business models.

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INTRODUCTION

A 2008 article published by the Society for Experimental Biology and Medicine listed "improved patient outcomes, lower drug development cost, faster drug development timelines, and lower drug spending" as likely consequences of personalized medicine [1]. In this paper I examine the factors that may be preventing PGx from realizing its potential. Patient safety is used as a frame of reference when examining the possible barriers. Though the pharmaceutical industry is a very large and at times an extremely profitable industry, drug therapy is ineffective in from of therapeutic areas. For example, at the high end of the range, psychiatric drugs may be effective in up to only 62% of patients [2]. Much more dismal is the low end of the range where cancer and Alzheimer patients are treated with drug therapy that is beneficial in only 25–30% of cases. Drug therapy's lack of efficacy may be partially due to inter-individual variability of drug response. Unfortunately, due to this variability, patients all too common experience adverse drug reactions, sometimes resulting in life-threatening situations [3]. For the purposes of this paper, I use a short form for personalized medicine, PGx, as the terms pharmacogenomics and pharmacogenetics are commonly used in the same context. Within the biomedical literature, the definitions tend to zero in on the common issue of genetic variability to drug response and related topics such as metabolism and patient safety [4]. In their 2004 paper from pharmacogenetics to personalized medicine, Frueh and Gurwitz define pharmacogenetics as "the study of inter-individual differences in drug response due to genetic variations. They define pharmacogenomics as "the genome-wide analysis of genetic determinants of drug efficacy and toxicity, including the identification of drug targets as a result of such studies". Pharmacogenetics has two forms, safety and efficacy. Efficacy pharmacogenetics predicts drug response.4 Here we are concerned with pharmacogenetics for preventing adverse drug reactions (ADRs), that is to say, safety pharmacogenetics [5]. Research in the field has increased greatly. PubMed citations for the term pharmacogenomics were 191 in 2000, in 2004 were 598 and increased to 8,638 at the time of writing this paper. In March 2007, a Medline search for publications containing the term pharmacogenetics or pharmacogenetics* yielded 4,985 hits. The same search at the time of writing yielded 7,438 hits. When a drug does not provide the patient with the normal drug effect, but rather the patient experiences an unwanted effect, that is an adverse drug reaction (ADR) [6].Taking some drugs, with efficacy that is suboptimal to begin with, can frequently result in unintended

consequences. These consequences have implications for the patient, for the health care system, for provider hospitals and clinicians, and for the pharmaceutical industry. ADRs cost the U.S. health system billions of dollars annually and are believed be one of the leading causes of death in the United States each year [7].1,3 In 2001, 2.2 million people were affected by ADRs resulting in an annual cost in excess of $177 billion. Studies have suggested that ADRs account for approximately 7% of hospital admissions and 100,000 deaths annually. Drug pharmacokinetics is concerned with metabolism, the means by which a drug is broken down within the body. As pharmacogenetics focuses on genes that drive drug metabolism, pharmacokinetics is the core of drug response [8]. An enzyme is made by a gene or a combination of genes. Diagnostic tests can identify the various forms of these enzymes.2 Many ADRs are due to the effect of cytochrome P450 enzymes on metabolism.9 The cytochrome P450 enzyme, CYP2D6, for example, metabolizes over 60 commonly used drugs such antiarrhythmic, antihypertensive and analgesics. For many drugs, there exist patients that are poor metabolizers (PM), intermediate metabolizers (IM), and ultra-rapid metabolizers (UM). The risk of toxicity may increase for poor and intermediate metabolizers whereas for ultrapid metabolizers, these patients may require higher than normal doses for a therapeutic effect [9]. It is not just PM patients that face potential danger. UM patients, in particular for certain cancer drugs, must be identified so as to ensure that therapeutic drug levels are maintained. Nearly 60% of the most frequently cited drugs in ADR studies were metabolized by at least one enzyme with a variant, or allele, causing poor metabolism. Some important ADR examples stemming from gene-drug combinations include codeine and the cytochrome P450 2D6 gene (CYP2D6), mercaptopurine drugs and the TPMT gene, fluorouracil and the DPD gene, irinotecan and the UGT1A1 gene, and phenytoin, warfarin and the CYP2C9 gene [10].

Barriers

Payers are unlikely to pay for PGx tests, regardless of how expensive they are. The need for payers to ensure that plan members reap the benefits of their contributions is a recurring theme. Quarterly pressure to report higher sales and profits motivates insurers, particularly publicly traded ones. When a subscriber may not be submitting claims related to the PGx test to the same insurer, whether due to job-related attrition or otherwise, it may be difficult for an insurer to subsidize the cost of the test. Up to this point, payers have not been persuaded that PGx offers great worth. Due to a perceived lack of efficacy, both clinicians and payers are reluctant to adopt PGx. The prospective randomized clinical trial is the gold standard for evidence-based medicine for forward-thinking clinicians who want to practice personalized medicine. Sadly for advocates of PGx, the majority of the evidence has come from retrospective, non-randomized studies or case reports with inherent bias. The PharmGKB Knowledge Base initiative has curated a number of relevant genotype-phenotype associations that have been documented, despite the fact that clinical trials are lacking. The majority of clinically relevant associations, on the other hand, are complex and polygenic, whereas almost all associations to this point have been monogenic.3 Payers have suggested that PGx studies should include control groups that receive standard or usual care rather than the PGx diagnostic. In doing as such, the payers would be more sure concerning whether the new expenses with PGx would be pretty much than what they have been paying. A significant obstacle to clinician adoption of PGx is physician behavior, whether based on genetic knowledge, practice guidelines, or alternatives to personalized medicine. It is challenging for clinicians to keep up with the rapid expansion of genetic knowledge. How clinicians can use genetics in practice to improve patient care might be a more reasonable challenge. Most of the time, doctors don't know enough about PGx to give the right advice to patients. When treating patients based on their disease susceptibility and genetics-driven drug response, PGx-based decision support might be used in the future. PGx diagnostics will need to be added to practice guidelines. In the Unified Realm, despite the fact that PGx has been taken on to a little degree inside specific claims to fame, there is irregularity of training rules for TPMT testing, for instance. Although this important PGx test could be beneficial to dermatologists, gastroenterologists, and rheumatologists, only the British Association of Dermatologists, the association of dermatologists, has recommended measuring TPMT prior to treatment for all dermatological conditions before prescribing azathioprine in the United Kingdom. Practice guidelines are unlikely to change significantly without evidence, whether in the form of prospective randomized clinical trials or otherwise, just like payer reimbursement. Because they have already successfully implemented alternatives to personalized medicine, clinicians may be biased. Although not ideal, phenotypic testing for TPMT activity levels is a proxy for genotype, as previously mentioned.

CONCLUSION

Therefore, patient safety is not the easy win that many had hoped personalized medicine would be. However, things are not over. Pharmaceutical companies and payers may be motivated to assist in removing these obstacles by the early successes of PGx test manufacturers. Databases that link ADRs to DNA samples, such as those maintained by the International Serious Adverse Events Consortium, may serve as the foundation for overcoming some of the primary financial obstacles outlined earlier. Clinician review investigations of perspectives towards and familiarity with customized medication might give helpful data to help with defeating doctor propensities.

REFERENCES

1. **Aspinall MG, Hamermesh RG.** Realizing the promise of personalized medicine. *Harv Bus Rev*. 2007; 85(10):108–17. 165.
2. **De Leon J.** Pharmacogenomics the promise of personalized medicine for CNS disorders. *Neuropsychopharmacology*. 2009; 34(1):159–172.
3. **Manolopoulos VG**. Pharmacogenomics and adverse drug reactions in diagnostic and clinical practice. *Clin Chem Lab Med*. 2007; 45(7):801–814.
4. **Bakker JA, Drent M, Bierau J**. Relevance of pharmacogenetic aspects of mercaptopurine metabolism in the treatment of interstitial lung disease. *Curr Opin Pulm Med*. 2007; 13(5):458–463.
5. **Madadi P, Ross CJ, Hayden MR, et al**. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther*. 2009; 85(1):31–35.
6. **Hill CE, Duncan A.** Overview of pharmacogenetics in anticoagulation therapy. *Clin Lab Med*. 2008; 28(4):513–524.
7. **Flockhart DA, O'Kane D, Williams MS, et al.** Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med*. 2008;10(2):139–150.
8. **Seidman EG, Furst DE.** Pharmacogenetics for the individualization of treatment of rheumatic disorders using azathioprine. *J Rheumatol*. 2002; 29(12):2484–2487.
9. **Deverka PA, McLeod HL.** Harnessing economic drivers for successful clinical implementation of pharmacogenetic testing. *Clin Pharmacol Ther*. 2008; 84(2):191–193.
10. **Owen RP, Klein TE, Altman RB.** The education potential of the pharmacogenetics and pharmacogenomics knowledge base (PharmGKB). *Clin Pharmacol Ther*. 2007; 82(4):472–475.