PHARMACOGENOMICS: The Practice of Medication Prescribing Advances toward Personalized Therapy

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Since the dawn of modern medicine, it has been recognized that what could be a potential cure for one patient may cause harm or worse for another. Pharmacogenomics (PGx) is the study of how one’s individual genetic variation affects their ability to metabolize different medications. This rapidly emergent science is becoming a key phase of new drug development; examples of which can be seen in medications used in pain management, chemotherapeutics, hypertension and various metabolic disorders. The purpose of this article is to discuss how pharmacogenomics is being used in modern practice and how, with a simple test, the use of PGx can help guide practitioners to prescribe the correct medication at the correct dose for a patient’s ailment.
Previously, medications were chosen based on prescriber preference; it was known what drugs had been shown to work for that prescriber’s patients in the past for a disease. However, not much existed in the way of comparison of therapies; i.e. each prescriber developed his/her own list of “favorite” drugs to prescribe.

Today, the idea of evidence-based medicine guides the decision making of most enlightened prescribers. Using knowledge gleaned through scientific studies and randomized control trials, prescribers assign medications that have proven to work best within the general population into which their patient belongs. Even with this approach, however, prescribing still contains an element of “trial and error” due to the varied individual response within a population. The final step in the evolution of medication prescribing is to base such decisions not only on population data, but also on the individual patient’s drug metabolizing characteristics. Pharmacogenomics is the method which can move us towards this goal of “personalized prescribing.”

Pharmacogenomics identifies how individual variations in the human genome affect disposition, transport (through the bloodstream) and response to medications. While humans each have about three billion DNA base pairs (which are segmented into approximately 30,000 genes), pharmacogenomics only focuses on the 225 genes responsible for the approximately 1,900 drug metabolizing enzymes, and receptors. Drug metabolizing enzymes may either activate a “pro-drug” by converting an inactive drug into an active molecule that produces an effect or, conversely, deactivate a drug so that it may be more easily excreted from the body.

There are four possible variants of each gene which lead to differing rates of metabolism based on a person’s genetics: “normal” (or “extensive”) metabolizer, “partial” (or “intermediate”) metabolizer, “non” (or “poor”) metabolizer, and “ultra rapid” (or “accelerated”) metabolizer. Based on a person’s rate of metabolism, it is easy to see how there can be differences in response to medications. Among patients considered to be in the same treatment population, differences may be observed, regardless of whether the enzyme is responsible for deactivation or activation of the drug.

Determination of an individual’s genetic variation is accomplished by analysis of metabolizing DNA gathered via a non-invasive collection of saliva or cells via cheek swab. Most commercial insurers and Medicare are reimbursing for pharmacogenomic testing in relevant diagnostic situations. Because one’s genetic profile does not change over one’s lifetime, once typed for a specific gene, a patient need not be tested for that gene again.

**Adverse Reactions to Common Drug Therapies**

The Cytochrome P450 (CYP450) family of enzymes, located predominately in the liver, is the most well studied and understood group of drug metabolizing enzymes. The CYP2D6 enzyme constitutes only 1 percent of all CYP450 enzymes, however is responsible for the metabolism of approximately 25 percent of medications. The influence of genetic variation in CYP2D6 on medication response can be seen in the case of the commonly used pain medication, codeine. Codeine is a pro-drug that requires CYP2D6 for conversion into its active form, morphine. A patient who is a “partial” or “non” metabolizer will get little or no analgesic effect from the medication, yet may experience side-effects attributed to the inactive “parent” formulation. Conversely, if a person is an “ultra rapid” metabolizer, it can lead to increased and possibly toxic levels of morphine in the patient.

While incidents of these extreme responses to codeine therapy are rare, they are real as seen in an example from the New England Journal of Medicine in 2009. A two year-old boy underwent elective adenotonsillectomy (surgical removal of tonsils and adenoids) and was prescribed acetaminophen with codeine liquid for post-operative pain. While the dosage prescribed was within the recommended pediatric dosage range for post-operative pain, the prescriber did not know the child was an “ultra rapid” (“accelerated”) metabolizer of CYP2D6. As a result, the boy incurred a higher conversion of codeine to morphine which resulted in respiratory failure and death after a single dose of the medication. Had the child’s CYP2D6 status been known prior to prescribing, a safer alternative may have been prescribed.

The effect of genetic variation on patient response to medications can also be demonstrated with metabolism of clopidogrel (Plavix®) by CYP2C19. Clopidogrel is an antiplatelet drug used to ensure blood flow in patients with vascular disease. CYP2C19 is responsible for converting clopidogrel into its active form responsible for making the blood’s platelets less “sticky” (decreases platelet aggregation). Poor CYP2C19 metabolizer status is linked to a decreased antiplatelet response to...
clopidogrel; if the drug is not activated or activation is decreased, the patient may not receive full protection from myocardial infarction, thrombotic stroke (caused by clot or blockage in the brain), and cardiovascular death. Accelerated metabolism of 2C19 may result in a patient having problems with spontaneous bleeding episodes and increased risk of hemorrhagic stroke (caused by bleeding in the brain). If the prescriber were aware that a patient’s genetics prevented the drug from attaining a desired response, another medication could be prescribed to avoid complications due to unexpected therapeutic response of clopidogrel.

With approximately 1,900 enzymes being involved in drug metabolism, these are just two of numerous examples of how genetic variation of these enzymes can not only lead to suboptimal treatment, but also serious adverse drug reactions or even death. Medication-related problems, if thought of as a disease, would be the fifth leading cause of death in the U.S.4

Drug related problems are not only dangerous, but also costly. In one study of Utah Medicaid participants, the average pharmacy cost per month for patients with at least one drug related problem was $1,081 versus the average pharmacy cost of $91 per month for all other patients receiving at least one prescription. 5Although individual diversity in drug metabolizing enzymes is not the only cause of adverse drug reactions, utilization of pharmacogenomics and “personalized medicine” can help decrease these numbers. According to Dr. Edward Abrahams, executive director of the Personalized Medicine Coalition, “The point of personalized medicine is to develop better efficacy, better outcomes, fewer adverse events and lower systemic costs.” The science of pharmacogenomics provides the foundation for personalized medicine.

Throughout history, medicine and prescribing have evolved with advances in science and technology. With the application of personalized prescribing, there can be a shift from “trial and error” prescribing to precision prescribing. When the individual characteristics of the patient are considered, adverse medication outcomes can be decreased and the therapeutic outcomes can be optimized for the patient. A key tool in personalized medicine is the use of pharmacogenetic testing to understand the extent to which the patient will metabolize, and in turn respond to a medication. Although genetics are not the only cause of drug-related problems, it is one that can be predicted and avoided with the use of pharmacogenomics. Thus, with a simple test a patient’s medication regimen can be tailored specifically for that patient.

References
3 Plavix is a registered trademark of Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership
5 Lafleur et al. “Prevalence of drug related problems and cost-savings opportunities in Medicaid high utilizers identified by a pharmacist run drug regimen review center”. JMCOP 2006; 12:8: 677-685