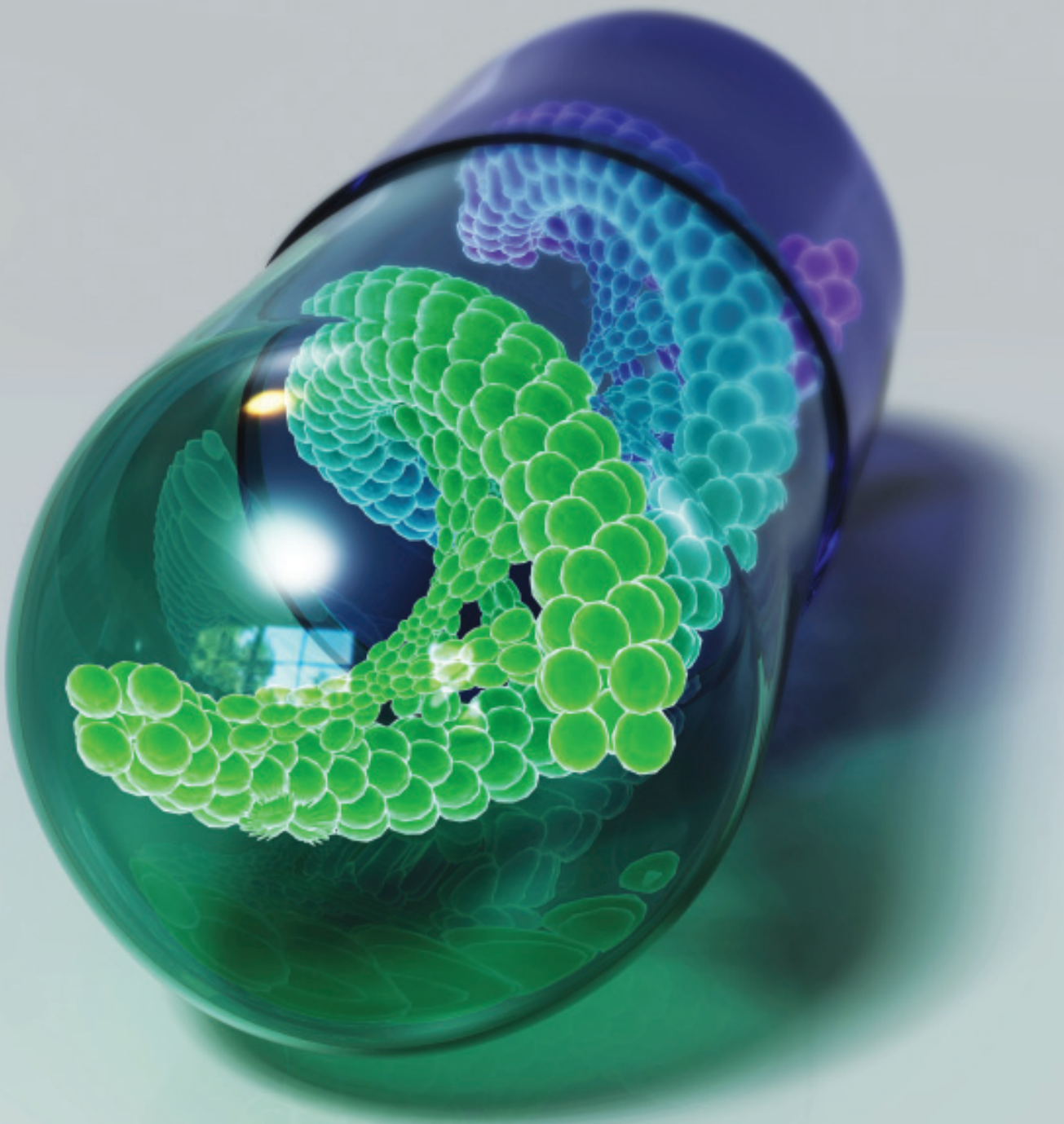


The
Pharmacogenomics
Phenomenon



Pharmacists should be on the leading edge of 'personalized medicine'

By Thomas Kupiec, PhD, and Craig Shimasaki, PhD, MBA

Wow! I really enjoyed that show! You might have liked it, but I really didn't care for it! Wasn't that game exciting? No, I don't like baseball! An event that evokes an enthusiastic response in one individual may seem unremarkable to another. We each possess unique tastes and varied affinities for movies, sports, and recreation, but is there a genetic basis for our differing responses?

Although the answer to that question is uncertain, we do know for certain that genetic variation is a key reason for differing responses to medication.

What Is Pharmacogenomics?

While one medication may work effectively in one patient, the same medication may have little to no effect in another. The study of individualized responses to medications is pharmacogenomics. Pharmacogenomics is really the melding of classical pharmacology with the science of human genetics. More specifically, it is the utilization of a patient's genotype to optimize the efficacy of drug therapy while minimizing drug toxicity. Pharmacogenomics is often broadly referred to as "personalized medicine." The promise of foreknowing what dosages of which medications will work most effectively for every individual is what drives the future of pharmacogenomics; it is the promise of better outcomes, greater safety, and improved health care.

Rapid Advances in Genetic Sequencing

Pharmacogenomics has come about because of a greater understanding of individual variations within the DNA (deoxyribonucleic acid) code. It has been 10 years since the complete elucidation of the 3 billion base pairs in the human genome. The sequencing of a single human genome required 13 years to complete, at a cost of approximately \$2.7 billion. Since then, great strides have been made in sequencing technology; within the next few years, the cost of sequencing an entire human

genome will be less than \$1,000 and will be completed in one day. As a result of these technological advances, it will be commonplace for every individual to know their complete genetic makeup and have instant access to their personal genetic information for health care and medical purposes.

Importance of Understanding Pharmacogenomics

Pharmacists have always played a vital role in the education of and consultation with patients about prescribed drugs. They have also been advisors to physicians in matters of medication, dosage, and adverse drug reactions. Because of this key role, the pharmacist's knowledge base will likely be required to expand to include pharmacogenomics. There is a growing void in the understanding of pharmacogenomics in clinical practice, drug prescribing, and drug dosing. This will create an opportunity for pharmacists to participate in the interpretation of pharmacogenomic testing results, in the selection of medication, and in dosing decisions.

Pharmacist subspecialties could also evolve so that pharmacists might be trained in interpretation of genetic testing results and in counseling patients on behalf of the physician. There is an early movement to designate a professional suitable for the interpretation of pharmacogenomic testing. Some consideration is being given to genetic counselors to fill this role because of their experience in patient counseling for hereditary genetic testing results. However, genetic counselors are not trained in pharmacodynamics, pharmacokinetics, and drug metabolism. Therefore, this group is not ideally suited for advising patients and physicians on medication decisions.

As pharmacogenomic applications expand, there will no doubt be significant business and career opportunities for pharmacists who understand pharmacogenomics and can interpret genetic testing results. A key

determining factor for any future role is the knowledge and practical understanding pharmacists have about pharmacogenomics. It is therefore incumbent upon pharmacists to expand their knowledge and understanding of genetics, genetic testing, and the implications of pharmacogenomics on the administration of new and existing medications.

Basics of Genetics

Within the 3 billion base pairs of our DNA, 99.9 percent are identical to every other individual living on this planet. The 0.1 percent of differences, or 3 million base pairs, are what constitute our individual characteristics (phenotype), our susceptibility to disease, and our differing responses to medications. For instance, a particular DNA sequence may contain the bases ATGGA, and a variant could be ATTGA. This single DNA base pair change from one individual to another is called a polymorphism. The acronym used to refer to these changes is SNP, for “single nucleotide polymorphism.” It is likely that other genetic modifications such as epigenetics, copy-number variation, genomic imprinting, and RNA (ribonucleic acid) interference may play a role in the alteration of an individual’s response to medication; however, the present focus of all pharmacogenomic testing is on SNPs.

Genetics and Drug-Metabolizing Enzymes

The vast majority of drugs are metabolized by enzymes in the liver into more water-soluble forms, which are then excreted from the body. There are more than 30 families of drug-metabolizing enzymes, and virtually all of these enzymes contain genetic variants that can impact the functionality of these enzymes. The cytochrome P450 (CYP450) group of liver enzymes is the most important group of drug-metabolizing enzymes, which act by modifying certain functional groups on drugs.

*The nomenclature for the cytochrome P450 genes and enzymes are identified with the abbreviation CYP, followed by a number indicating the gene family, a letter indicating the subfamily, and another numeral for the individual gene (eg. CYP3A4). Additional variants of these genes are described as “star” (asterisk) with a number designation such as CYP2C19*2 and CYP2C19*3*

So how can a single DNA base pair change have such an impact? A single nucleotide base change can result in an amino acid substitution in an enzyme, which in turn can affect the conformational structure of the enzyme, which in turn can modify the activity of the drug-metabolizing enzyme. Some polymorphism patterns of inheritance are also known to be more common in certain ethnicities. In addition to genetic variation, some individuals may completely lack a particular gene. For instance, 7–10 percent of Caucasians are deficient in the CYP2D6 gene, which controls the metabolism of codeine and more than 30 other drugs.

Various polymorphisms can create four metabolizer types:

1. Poors
2. Intermediate
3. Extensive (normal)
4. Ultrarapid

Examples of Pharmacogenomics

Plavix (Clopidogrel)

In patients with coronary artery disease, aspirin and clopidogrel are part of standard therapy to prevent life-threatening cardiovascular events. Clopidogrel is a “pro-drug” that requires transformation in the liver into an active drug metabolite that is mediated by CYP2C19. The mutations CYP2C19*2 and CYP2C19*3 have been associated with a decreased antiplatelet response to clopidogrel and an increased risk of major adverse cardiovascular events. Non-functional forms (alleles) of CYP2C19 have been found at higher frequencies in Asians than in Caucasians. In May 2009, the Food and Drug Administration first required the Plavix manufacturer (Bristol-Myers Squibb/Sanofi-aventis) to add pharmacogenomic information to the drug’s label and include the frequencies of non-functional alleles of CYP2C19 among different ethnicities. The FDA also required the manufacturer to describe the impact of non-functional alleles of CYP2C19 on the activation and clinical response to clopidogrel. In March 2010, the FDA required further labeling changes in the form of a black box warning describing the reduced effectiveness of clopidogrel in poor metabolizers, and recommending that health care providers consider alternative dosages or other antiplatelet medications.

Warfarin

Warfarin is an antiplatelet drug prescribed for the prevention of stroke and thrombotic disease. It is the most widely prescribed oral anticoagulant in North America and Europe, with more than 20–30 million prescriptions per year. Warfarin therapy can be difficult to manage because of the drug's narrow therapeutic index, and it is among the top 10 drug-related causes of serious adverse effects, including death. The active component of warfarin is metabolized by CYP2C9 and VKORC1, and slow metabolism causes a higher than expected concentration of the active drug in patients. CYP2C9*1 metabolizes warfarin normally, CYP2C9*2 reduces warfarin metabolism by 30 percent, and CYP2C9*3 reduces warfarin metabolism by 90 percent. Depending on the genotype, conventional dosetitration with warfarin could lead to either an increased risk for bleeding events or an increase in time required to achieve therapeutic anticoagulation. In August 2007, the FDA required a warning label on warfarin to include the relationship between genotype and warfarin clearance.

Irinotecan

Irinotecan is a leading treatment for colorectal cancer, despite occasional adverse effects such as diabetes and neutropenia. Irinotecan is converted into the active metabolite, which is later inactivated by the enzyme UGT1A1. This UGT enzyme exhibits genetic variability, which can lead to irinotecan toxicity. During chemotherapy, these patients effectively receive a larger than expected dose because their bodies are not able to clear irinotecan as fast as those with normal UGT1A1. The genotypes UGT1A1*28 and UGT1A1*6 are risk factors for severe toxicity, as evidenced by case reports of severe neutropenia associated with these polymorphisms. In July 2005, the FDA required changes to the labeling of irinotecan to add pharmacogenomic recommendations that patients with polymorphisms in UGT1A1 gene, specifically the *28 variant, should receive reduced drug doses. Irinotecan was one of the first widely-used chemotherapy agents dosed for each patient according to their genotype. Irinotecan labeling has been recently updated to suggest a one-level reduction in the initial high-intensity dose for patients with two copies of the UGT1A1*28 gene. Subsequent dose titrations however, are considered based on individual patient response to treatment.

Tamoxifen

Tamoxifen is indicated for prevention of recurrence in estrogen receptor-positive (ER-positive) breast cancer and to prevent disease in high-risk women with ductal carcinoma in situ (DCIS). Tamoxifen is metabolized to the active forms 4-hydroxytamoxifen and endoxifen by CYP2D6. Both metabolites have an approximately 100-fold greater affinity for the estrogen receptor and ability to inhibit cell proliferation than the parent drug. The poor metabolizers and the severely impaired or intermediate metabolizers of the CYP2D6 gene are associated with higher cancer recurrence rates. In October 2006, the Pharmaceutical Science Clinical Pharmacology Subcommittee of the FDA recommended including information on CYP2D6 genotypes and their potential effect on patient outcomes in the label for Nolvadex (tamoxifen). Subsequent to that recommendation, branded tamoxifen (Nolvadex) was discontinued and no further guidance was given by FDA on whether to amend the label for generic tamoxifen.

Abacavir

Abacavir is a nucleoside analog reverse transcriptase inhibitor used to treat HIV and AIDS. This drug has decreased long-term toxicity (for example, liver or metabolic toxicity) compared to many other antiretroviral drugs. However, abacavir hypersensitivity reaction (HSR), which is a reversible immune-mediated systemic reaction, can occur within the first six weeks of use and is potentially a treatment-limiting factor. Once HSR is identified, the symptoms usually resolve during the course of a few days if abacavir is discontinued. Several polymorphisms within the Human Leukocyte Antigen gene-B (HLA-B) region were found to occur more frequently in individuals exhibiting abacavir hypersensitivity. Screening for the HLA-B*5701 gene prior to abacavir therapy has resulted in a decrease in abacavir HSR. In July 2008, the FDA required labeling changes stating the association with the variant HLA-B*5701 and HSR. In the United Kingdom, France, and Canada, results of genetic screening for this genetic variant has led to a decrease in the incidence of HSR from as high as 12 percent to less than 0.5 percent. One model reflecting the overall savings in health care costs with genetic screening reported a savings of approximately \$32,000 per HSR avoided.

Pharmacogenomic Testing

Currently, the performance of tests of individual SNP genetic variants is a highly complex procedure that requires trained and experienced laboratory personnel. Most pharmacogenomic testing is performed in CLIA-certified laboratories using in-house-developed procedures rather than off-the-shelf kits. In the future, more genotyping kits will become readily available, and it is conceivable that tests will become available for point-of-care and eventually be performed in a physician's office or pharmacy. Because SNP tests examine germline genetic information, testing needs to be performed only one time on any individual for any particular set of SNPs.

Changes in FDA Regulatory Climate

Widespread clinical adoption of pharmacogenomics will be driven in part by the FDA's position and any new regulations related to genetic testing and drug development. Since 2003, the FDA has had a Voluntary Genomic Submission Program, whereby drug makers submit genetic information about the patient population used for clinical trials of their drugs. Since that time, the FDA has taken a position that it intends to use pharmacogenomics in all ways possible to promote the development of medicines. As a result of this, more drug labeling changes are being made to reflect the relationship of genotype to, and its impact on, the clinical effectiveness of these drugs. It is expected that the FDA will accelerate their use of pharmacogenomic information in more drug and diagnostic applications in the foreseeable future.

How Can Pharmacists Prepare for Pharmacogenomics?

Although there are many clinical applications of pharmacogenomics, widespread utilization of pharmacogenomic testing may take many years to materialize. However, there is a real need for experienced pharmacists who understand pharmacogenomics and can advise physicians and patients appropriately. To become better educated, pharmacists can take a number of avenues, from self-help reading to formal courses and continuing education seminars. There will no doubt be more options in the near future as more pharmacy schools are retooling their programs to include the study of pharmacogenomics. For the interested reader, there are a couple

of good websites to explore: <http://pharmacogenomics.ucsd.edu> and www.ipit.unc.edu.

It has taken longer than anticipated to see the impact of genomics in the development of pharmacogenomic diagnostics and therapeutics. The delay is because drug development and the translation of research into new products encompass a 10–15 year cycle. New FDA regulations are also pivotal for the adoption of innovative products into clinical practice. However, over the next 10 years, a large gap of knowledge will emerge about the genetic-based selection of medications, dosing, and interpretation of pharmacogenomic testing results. Complex issues will surround the selection of appropriate genetic testing laboratories and how to evaluate the reliability and clinical utility of new genetic tests.

Pharmacists are ideally positioned to serve the role of educator, gatekeeper, and interpreter for pharmacogenomic testing. They are already the trusted interface between the patient and physician, and they are the trusted advisors on prescribing decisions. Pharmacogenomics will no doubt provide an emerging opportunity to strengthen and expand the key role of the pharmacist in the practice of 21st century medicine. **ap**

Editor's Note: In the September 2010 America's Pharmacist, Tina Schlecht will cover the practical applications of pharmacogenomics for independent community pharmacists.

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