

Pharmacogenomics and its Role In Drug Safety

"Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease . . ."
— Sir William Osler (1849-1919)

Pharmacogenomics is the science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effect.¹ With increasing knowledge of the molecular basis for a drug's action has come the recognition of the importance of an individual's genetic makeup in influencing how he or she may respond to a drug.

This understanding of the genetic variations in drug response opens the door to "personalized medicine" by (1) identifying patients who are more prone to experience adverse events from a drug and (2) identifying patients who are more likely to benefit from a particular therapy. This information has the potential to guide the selection of a drug for a particular patient and to tailor the drug dose to achieve the optimal therapeutic effect. In addition, knowledge of the genetic makeup of infectious agents is being used to guide treatment. For example, the identification of the specific drug resistance mutations in a patient's human immunodeficiency virus (HIV) is used to select the therapy most suitable or best "targeted" for that patient. In these ways, pharmacogenomics has the potential to assist physicians in adapting drug treatments to the characteristics of individual patients, ultimately leading to safer and more effective prescribing and dosing.

IMPROVING DOSING AND DECREASING ADVERSE EVENTS

Genetic variants in drug metabolizing en-

zymes can have a significant effect on the way a person responds to a drug. They can speed up or slow down enzymatic activity, or even inactivate an enzyme. In some patients, known as rapid metabolizers, drugs are metabolized too quickly. As a result, the average dose of the drug may be broken down too quickly to be effective, and a higher dose may be needed. Conversely, where the metabolite of the drug is active, as in the case of codeine (see below), rapid metabolism may lead to excessive accumulation of the active metabolite, which may result in toxic levels. In slow metabolizers,

a drug administered at the recommended dose can accumulate due to such slow metabolism, potentially reaching toxic levels in the patient's system and leading to adverse reactions. Such patients may require a smaller dose. In conjunction with other factors, pharmacogenomics offers the potential to enable doctors to identify the patients who are rapid or slow metabolizers of certain drugs and to adjust dosing accordingly to achieve both effective and safe treatment.

PHARMACOGENOMICS DETERMINES HOW GENETIC VARIABILITY INFLUENCES RESPONSE TO A DRUG.

Potential applications in the clinic:

- Tailor dosing to decrease risk of adverse events.
- Identify patients for targeted therapy.
- Detect viral drug resistance.

To view a table of drugs with pharmacogenomics information provided in product labeling go to:

WWW.FDA.GOV/CDER/GENOMICS/GENOMIC_BIOMARKERS_TABLE.HTM

CLINICAL APPLICATIONS OF PHARMACOGENOMICS

Warfarin (Coumadin and generics), an

anticoagulant, is a recent example of the clinical use of pharmacogenomics to improve dosing. Warfarin has a narrow therapeutic window and a wide range of inter-individual variability in response, requiring careful clinical dose adjustment for each patient. Genetic variants in the warfarin target, the vitamin K epoxide reductase (VKORC1), as well as the warfarin metabolizing enzyme, cytochrome P450 2C9 (CYP2C9), influence the variation in patient response. Patients with certain variants of these genes eliminate warfarin more slowly and typically require lower warfarin doses. In those individuals, a traditional warfarin dose would more likely lead to an elevated International Normalized Ratio (INR), a longer time to achieve a stable warfarin dose, and a higher risk of serious bleeding events during the induction or dosetitration period of warfarin therapy.³ (FDA News: WWW.FDA.GOV/BBS/TOPICS/NEWS/2007/NEW01684.HTML)

Another recent example involves ultra-rapid metabolizers of codeine, who have multiple copies of the gene for cytochrome P450 2D6 (CYP2D6), the enzyme that converts codeine into morphine, its active metabolite. Nursing mothers who are taking codeine and are ultra-rapid metabolizers could have high levels of morphine in their breast milk, increasing the risk of morphine overdose in their nursing infant.⁴ Although most nursing mothers can take codeine safely after childbirth, health care practitioners should

prescribe the lowest dose for the shortest period of time to relieve pain and nursing infants should be carefully monitored when breastfeeding women receive this drug. (FDA Information to Healthcare Professionals: WWW.FDA.GOV/CDER/DRUG/INFOSHEETS/HCP/CODEINEHCP.HTM)

Pharmacogenomic studies have recently identified a genetic marker in patients, the human leukocyte antigen (HLA) allele HLA-B*1502, which is associated with dangerous, sometimes fatal, skin reactions (Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)) following treatment with the antiepileptic drug carbamazepine (Carbatrol: WWW.FDA.GOV/CDER/FOI/LABEL/2007/020712S029LBL).

PDF, Equetro: WWW.FDA.GOV/CDER/FOI/LABEL/2006/021710S003LBL.PDF, Tegretol: WWW.FDA.GOV/CDER/FOI/LABEL/2007/016608S098LBL.PDF, and generics).⁵ Since the HLA-B*1502 allele is found almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians, health care practitioners should screen patients with ancestry in at-risk populations for the HLA-B*1502 allele prior to initiating treatment with carbamazepine.^{6,7,8,9} Patients who test positive for HLA-B*1502 should not be treated with carbamazepine unless the expected benefit clearly outweighs the increased risk of SJS/TEN. In weighing these risks and benefits, it is important to recognize that other antiepileptic drugs are associated with these serious skin reactions as well. (FDA Information for Healthcare Professionals Sheet: WWW.FDA.GOV/CDER/DRUG/INFOSHEETS/HCP/CARBAMAZEPINEHCP.HTM)

Tests to identify the three genetic polymorphisms for warfarin, codeine, and carbamazepine described above are commercially available.

A table describing the valid genomic biomarkers that are currently part of FDA-approved drug labels can be found at WWW.FDA.GOV/CDER/GENOMICS/GENOMIC_BIOMARKERS_TABLE.HTM.² The table provides a list of these markers, links to pharmacogenomic data that support their validity, and recommendations for the clinical use of some of these biomarkers.

RAPID METABOLIZERS may break down a drug too quickly and require higher doses.

SLOW METABOLIZERS may build up toxic levels of the drug and require smaller doses.

PHARMACOGENOMICS LEADS TO MORE EFFECTIVE TARGETED THERAPIES

The incorporation of genomics in the pre-clinical and clinical research of anticancer drugs has resulted in significant progress in the development of new drugs. Discovering targeted therapies that are specifically directed at tumor cells with particular protein characteristics that differ from those of normal cells has been a primary focus of innovation in cancer treatment. Targeting drugs specifically to tumor cells can decrease the toxic effects of anticancer drugs on normal cells. For some targeted

therapies, diagnostic genetic tests that can help identify the tumors that are likely to respond to those particular treatments have been co-developed with the drug. Examples of these drugs and their targets include:

- Imatinib (Gleevec) for bcr-abl tyrosine kinase in several tumor types
- Cetuximab (Erbitux) for epidermal growth factor receptor (EGFR) in head and neck cancer and colorectal cancer
- Trastuzumab (Herceptin) for variants in the Her2 receptor in breast cancer

PHARMACOGENOMICS CAN DETECT RESISTANCE IN VIRUSES

HIV genomes are constantly and rapidly evolving. Changes in targeted viral proteins may cause the HIV virus to become resistant to anti-viral drugs or vaccines. HIV patients often have to try different drug combinations when the virus becomes resistant to drugs they are taking.

An FDA-approved kit, the TRUGENE HIV-1 (WWW.FDA.GOV/CBER/510KSUMM/K000038S.PDF) Genotyping Kit, is now commercially available to detect several drug-resistance gene variants in the protease and reverse-transcriptase regions of the HIV virus. These two regions are targets of anti-retroviral treatments.

If drug resistance is found to be present, the physician can alter the treatment regimen accordingly.

FDA'S ROLE IN PHARMACOGENOMICS AND PERSONALIZED MEDICINE

Pharmacogenomics holds the promise to individualize our health care and to improve drug safety and effectiveness for the population as a whole. FDA is in a unique position to promote pharmacogenomics and personalized medicine. It encourages the incorporation of pharmacogenomics in the drug development process (Genomics at FDA: WWW.FDA.GOV/CDER/GENOMICS/). In 2004, FDA launched the Critical Path

Initiative (WWW.FDA.GOV/OC/INITIATIVES/CRITICALPATH/), a national effort to stimulate and facilitate the modernization of the sciences through which regulated products are developed, evaluated, and manufactured. The Critical Path Initiative is aimed

at facilitating development of innovative tools, such as predictive genetic tests, valid biomarkers, assays, and information technology, to enable the efficient

development and evaluation of safer and more effective drugs and promote the safe use of FDA-regulated products.

As part of the Critical Path Initiative, FDA is working to develop guidance for the pharmaceutical industry on co-development of drugs and diagnostic tests. FDA is also collaborating with the National Institutes of Health (NIH) and other research institutions in applied research efforts to study the genetic basis of drug-related toxicities. These research networks are working to improve the safety profiles of drugs in preclinical and clinical development as well as those, like warfarin and carbamazepine, that are already in the marketplace. Much work remains in understanding the role that genetics plays in achieving the goal of tailoring therapeutics to the individual patient. ●

Reprinted from the *FDA Drug Safety Newsletter*, Winter 2008.

REFERENCES

1. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. *Nat Rev Drug Discov* 2004;3:763-9.
2. Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels, available at: www.fda.gov/cder/genomics/genomic_biomarkers_table.htm
3. Gage BF, Lesko LJ. Pharmacogenetics of warfarin: regulatory, scientific, and clinical issues. *J Thromb Thrombolysis* 2007;25:45-51.
4. Koren G, Cairns J, Chitayat D, et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeinoprescribed mother. *Lancet* 2007;368:704.
5. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. *Nature* 2004;428:486.
6. Alfirevic A, Jorgensen AL, Williamson PR, et al. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics* 2006;7:813-818.
7. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. *Pharmacogenomics* 2006;16:297-306.
8. Lonjou C, Thomas L, Borot N, et al., RegiSCAR Group. A marker for Stevens-Johnson syndrome ... : ethnicity matters. *Pharmacogenomics* 2006;6:265-268.
9. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. *Epilepsia* 2007;48:1015-1018.