



Researchers Draft Guidelines for Clinical Use of Pharmacogenomics

Tracy Hampton, PhD

WHILE MOST INDIVIDUALS MAY not notice any personal benefit resulting from the well-celebrated completion of the sequencing of the human genome in 2003, researchers and physicians say that the information gleaned *has* changed care for many patients with various conditions and will increasingly do so in the years ahead. And one area the human genome information is expected to revolutionize is pharmacogenomics, the science of how genes affect the way individuals respond to drugs.

As pharmacogenomics is a relatively new field and no evidence-based guidelines have been set, the National Academy of Clinical Biochemistry, the professional academy for scientists in the field of clinical biochemistry, has assembled a committee of about a dozen experts from academia, industry, and the government to establish laboratory management practice guidelines for the application of pharmacogenetics testing in health care (<http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/DraftGuidelines/Pharmacogenetics/>). The proposed guidelines, which are currently open for comment, are slated to be finalized by the end of 2006 for use by scientists, pharmacists, clinical practitioners, regulatory agencies, and others.

PHARMACOGENOMICS MODELS

Pharmacogenomics includes the role genes play in how drugs are processed by the body (pharmacokinetics) and how drugs interact with receptors on cells to cause a response (pharmacodynamics). Several examples are presented in the proposed laboratory management practice guidelines that illustrate the importance of the clinical implementation of pharmacogenomics: the administration of warfarin for

anticoagulation, atomoxetine for psychiatric conditions, and irinotecan for cancer. "We decided that it would be better to focus the guidelines not on a wide variety of drugs but on specific ones that could be used as models we could then apply to other drugs that are being developed," said Roland Valdes, Jr, PhD, of the University of Louisville School of Medicine, in Kentucky, and the chair of the guidelines committee.

Warfarin is often prescribed for the treatment and prevention of thromboembolic complications, but individuals have varying responses to the drug, and interactions with other common drugs can make warfarin more active. Therefore, it has a narrow therapeutic index, and complications can range from occult bleeding to hemorrhage.

"There is a broad range of warfarin maintenance-dose requirements within the population," said guidelines committee vice chair Mark Linder, PhD, of the University of Louisville. Some individuals benefit from a weekly 5 mg dose; others require as high as 80 mg/wk to obtain the same benefit. "What is the basis for this variability and are there tools available to identify this a priori and limit the trial-and-error process of dose optimization?" asked Linder.

This trial-and-error process of warfarin dosing leads to a number of complications linked to individuals' underlying genetics. Warfarin is metabolized by a particular enzyme called CYP2C9 (Linder MW et al. *J Thromb Thrombolysis*. 2002;14:227-232; Sconce EA et al. *Blood*. 2005;106:2329-2333), and approximately 25% to 35% of the population have CYP2C9 genetic variants, or alleles, that lead to deficient enzyme activity. These alleles, which are detectable by DNA analysis, can cause alterations in initial warfarin dose sensitivities, delays in achieving a stable maintenance dose, and increased bleeding complications.

Variants in the gene that encodes a blood clotting protein, the vitamin K epoxide reductase complex protein 1 (VKORC1), are also believed to account for an approximate 25% of the differences in responses to warfarin (Rieder MJ et al. *N Engl J Med*. 2005;352:2285-2293). Therefore, the draft guidelines recommend that CYP2C9 and VKORC1 genotyping be done as an adjunct to individually adjusted dosages of warfarin therapy. Clinicians are advised to begin therapy with standard warfarin dosing, establish CYP2C9 and VKORC1 genotyping before first dose adjust-



Researchers anticipate that by studying how genes affect the way individuals respond to drugs, the field of pharmacogenomics will transform and personalize medicine.



ment (usually 3 to 5 days), and combine pharmacogenomics results with patient physical attributes (weight, age, etc) to adjust warfarin dosing recommendations for particular genotypes (provided in the guidelines).

Another related enzyme, named CYP2D6, appears to be important for metabolizing atomoxetine, the first non-stimulant medication approved by the US Food and Drug Administration (FDA) for the treatment of attention-deficit/hyperactivity disorder in children, adolescents, and young adults (Ring et al. *Drug Metab Dispos.* 2002; 30:319-323; Kratochvil CJ et al. *Expert Opin Pharmacother.* 2003;4:1165-1174). Accurate prescribing of other similar drugs will also likely benefit from pharmacogenomics, and as more than half of children with attention-deficit/hyperactivity disorder are prescribed medication, this will be an important area of study. "If [as a child], you get a diagnosis of attention-deficit/hyperactivity disorder, chances are you're going to land on some kind of pharmacotherapy. And it's moving beyond pediatrics into the adult population," said committee member Gualberto Ruaño, MD, PhD, of Hartford Hospital and Genomas Inc, in Hartford, Conn.

The proposed guidelines recommend genotyping for CYP2D6 as part of the regimen for prescribing atomoxetine and they present it as another model for drug-related dosing applications. There is already significant CYP2D6-related information listed in the product insert label for atomoxetine, including a warning that "poor metabolizers" have plasma concentrations of atomoxetine that are 5 times greater than those of "extensive metabolizers" when given the same dosage and that the drug has an increased half-life in the poor metabolizers. There are 15 different alleles within the CYP2D6 gene, with effects that vary from minor deficiencies in the enzyme to no production of the enzyme whatsoever. Because excessive dosage of atomoxetine can result in hyperactivity, appetite loss, and suicidal ideation, the dosage should be reduced in

patients who are carriers of CYP2D-deficient alleles and contraindicated in those who are double carriers of null (nonfunctional) alleles, said Ruaño.

The anticancer drug irinotecan, also presented in the guidelines as a model, can cause intolerable and potentially fatal toxic effects in some patients, and genetic variations likely play a role in these effects. Specifically, the gene that produces UDP-glucuronosyltransferase 1A1 (UGT1A1), an enzyme that alters the active metabolite of irinotecan, appears to be important (Ando Y et al. *Ann Oncol.* 1998;9:845-847), and therefore genotyping of UGT1A1 is recommended as part of the regimen for prescribing this drug for patients. UGT1A1 activity is reduced in individuals with a particular genetic polymorphism that is homozygous in approximately 10% of the North American population and is associated with a 5-fold increase in the risk of drug-related toxicity.

"We are talking about toxicity of drugs that might be associated with the inability of the patient to inactivate the agent through metabolism," said guidelines committee member Felix Frueh, PhD, of the Office of Clinical Pharmacology at the FDA. "Clearly, this is a situation where information about the genotype might help to guide treatment or help to make a decision about whether an alternative treatment should be chosen," he added.

The genes that play a role in metabolism of these "model" drugs are also important for the metabolism of other drugs, and future studies should help decipher which alleles affect patient responses to various medications. There are a number of other examples that illustrate how genetic testing can be used to reduce drug-related adverse events (Hosford DA et al. *Toxicol Pathol.* 2004;32[suppl 1]:9-12), and more research will likely uncover additional ones. The FDA plans to provide information on their Web site that will summarize the pharmacogenomic information printed on drug labels and recommendations for genetic testing (<http://www.fda.gov/cder/genomics>).

DNA typing services are now provided at Hartford Hospital and the University of Louisville, as disclosed by Ruaño and Linder, and commercial kits are produced by Roche Diagnostics Corporation (Indianapolis, Ind) and TM Bioscience Corporation (Toronto, Ontario).

CHALLENGES AHEAD

Using pharmacogenomics to predict patients' responses to the drugs that line pharmacy shelves is in its infancy, and much more research is needed to understand how various factors work together to determine how a drug will affect individual patients. "We really need to make sure before we come up with a recommendation that we know what we're talking about," said Frueh. Some genetic variables will have more of an impact than others, and the interplay of different genes may also be important. In addition, nongenetic confounders (such as drug interactions and diet) can influence how an individual will respond to a particular medication (Evans WE and Relling MV. *Nature.* 2004;429:464-468).

Additional challenges arise when considering issues of informed consent and potential discrimination. Although no specific federal genetic non-discrimination legislation has been enacted, parts of existing laws (including the Americans with Disabilities Act and the Health Insurance Portability and Accountability Act) may be interpreted to include genetic discrimination. The National Human Genome Research Institute provides links to policy and legislative information on this topic at <http://www.genome.gov/10002077>.

While many hurdles exist, scientists are optimistic that they will one day be able to decipher, at least to some extent, which patients will respond well to a particular drug and which patients will experience adverse effects. "For people who have been suffering adverse drug reactions on and on while nobody figures out what's going on, that's a different kind of disease—it's a drug-induced disease. But from the human perspective, it doesn't matter—it's suffering," said Ruaño. □