

EDITORIAL



Pharmacogenomics — Ready for Prime Time?

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It cannot be emphasized too strongly that treatment of each patient is a highly individualized matter.

— FDA-approved labeling for warfarin (Coumadin) NDA 9-218/5-105

Pharmacogenomics is receiving a great deal of attention in scientific circles and, increasingly, in the popular press because of the promise of personalized medicine. Short of being able to cure an illness or to prevent one, every clinician's dream is to offer patients a precisely targeted drug at a precisely calibrated dose to address a specific ailment — and to do so without wreaking havoc on the rest of the body. We have ample reason to anticipate that pharmacogenomics will get us there, but it is a promise that has yet to be fulfilled. Therefore, many clinicians are left wondering whether pharmacogenomics represents great hope, overblown hype, or something in between.

Although the term pharmacogenomics, which describes a field of study in which genetics explains individual differences in drug responses, has been used for decades by research scientists, only recently have health care providers and consumers begun to stand up and take notice. Technological advances that make it possible to identify millions of DNA sequence variations rapidly and inexpensively, and to correlate them with phenotypic characteristics, have fueled an explosion of knowledge in this exciting area.^{1,2} The long-term vision of uncovering new targets for pharmacologic intervention and, ultimately, of creating a broad selection of custom-made agents for individualized treatment glimmers tantalizingly, if distantly, on the horizon. Much closer to near-term application is the use of information about how genetic variations affect the efficacy

of drugs to guide prescribing decisions for agents currently on the market. Indeed, it is not much of a stretch to imagine that someday soon DNA sequencing will be a routine part of the workup for patients, at the very least to identify a patient's sensitivity to drugs that are likely to produce adverse effects.

Achieving effective and safe administration of warfarin therapy has been both an urgent concern for clinicians and an outstanding opportunity for researchers to explore the potential of pharmacogenomics. The administration of warfarin is tricky because of the drug's narrow therapeutic range and the large variations in dose requirements from one patient to another. The drug is also relatively easy to study because we have what we think is a good measure, the prothrombin-time international normalized ratio (INR), to track a patient's response to the drug. Research has focused on polymorphisms of genes encoding two proteins: the cytochrome P-450 2C9 enzyme (CYP2C9), which is involved in the metabolic clearance of warfarin, and the vitamin K epoxide reductase enzyme (VKORC1), which recycles reduced vitamin K and is essential for the post-translational gamma-carboxylation of vitamin K-dependent clotting factors II (prothrombin), VII, IX, and X. Studies have shown that patients with CYP2C9*2 and CYP2C9*3 allelic variants and the VKORC1 haplotype A/A require lower doses of warfarin to achieve an appropriate state of anticoagulation with a minimal risk of bleeding.^{3,4} In August 2007, the Food and Drug Administration (FDA) deemed that the accumulation of pharmacogenomic information was sufficient to warrant a modification in the labeling of warfarin to highlight the potential relevance of genetic information to prescribing decisions.⁵

The study by Schwarz et al. in this issue of

the *Journal* adds to these observations by providing important prospective data on variability in the INR response to initial warfarin therapy on the basis of *CYP2C9* genotypes and *VKORC1* haplotypes.⁶ The investigators examined the effects of variants of *CYP2C9* and *VKORC1* on initial warfarin dose requirements in a cohort of 297 patients who were undergoing anticoagulation therapy for a variety of typical indications. The investigators found that the early INR response to warfarin was more strongly influenced by *VKORC1* haplotypes than by *CYP2C9* genotypes. Specifically, patients with the A/A *VKORC1* haplotype had a decreased time to the first INR within the therapeutic range and to an INR of more than 4, as compared with patients who did not have the A/A haplotype. In contrast, *CYP2C9* genotypes did not affect the time to the first INR within the therapeutic range but did predict the time to the first INR of more than 4. Variants of both genes were associated with warfarin dose requirements after the initial 2 weeks of therapy but not with the incidence of bleeding episodes.

These findings add important information to the body of knowledge about the pharmacogenetics of warfarin, but they also remind us that the warfarin story is far from complete. Fortunately, much basic research is under way to elucidate the pathways by which *CYP2C9* genotypes and *VKORC1* haplotypes — acting alone, with other genes, or in combination with environmental factors — influence sensitivity to warfarin. Moreover, a number of efforts are making sense of emergent findings in the context of potential clinical applications. One example involves activities of the Pharmacogenetics Research Network (PGRN), a consortium of scientists who are supported by the National Institutes of Health and who are studying how genetic variation contributes to differences in drug response among patients. The collected information about specific proteins, genes, and pathways is being integrated into the Pharmacogenetics and Pharmacogenomics Knowledge Base (www.nigms.nih.gov/Initiatives/PGRN/). Several PGRN investigators have joined with non-PGRN investigators to form the International Warfarin Pharmacogenomics Consortium (www.pharmgkb.org/views/project.jsp?pld=56), a group of research centers around the world that are sharing their clinical and genetic data to develop a consensus model for drug administration that is consistent with all avail-

able data. The Collaborative Cardiovascular Drug Safety and Biomarker Research Program, a partnership between the Critical Path Institute and the University of Utah that is funded by a grant from the FDA, is evaluating genetic tests for their ability to predict safer and more effective doses of warfarin. Other researchers who are conducting ancillary pharmacogenomic studies in ongoing or completed clinical research projects supported by the National Heart, Lung, and Blood Institute (NHLBI) have developed a free Web-based tool for health care professionals to estimate the beginning dose for patients who are starting warfarin therapy (www.warfarindosing.org).⁷ And, most recently, the NHLBI is awarding contracts to conduct a large, multicenter, double-blind, randomized trial of genotype-guided administration of warfarin therapy.⁸

We are still a long way from the day when a patient presents a DNA “chip,” a key-chain tag bearing the patient’s electronic health record, and an insurance card to a physician and gets a dose of personalized medicine. Considerable basic and clinical research needs to be done, including investigations of gene–gene and gene–environment interactions. Evidence from various clinical and population studies suggests that patients of Asian, European, and African ancestry require, on average, lower, intermediate, and higher doses of warfarin, respectively; additional studies involving larger numbers of patients of African and Asian descent are needed to confirm these associations.⁹

After strong associations between genotype and drug sensitivity have been identified, trials must be conducted to evaluate the clinical efficacy of the gene-based prescribing strategy and to determine whether the increment in efficacy or safety warrants the cost of genetic testing. Moreover, genetic stratification in clinical trials will be needed to evaluate new drugs — and indeed, genetic information will be invaluable for the design of new agents to serve as alternatives to existing drugs that are likely to produce adverse effects in genetically susceptible patients.

The merits of pharmacogenomics will probably be an active area of research for some time to come. However, the study by Schwarz et al. of the relative role of genetic variants in the administration of warfarin confirms the importance of genetic variation in influencing drug metabolism and response to therapy. Ready for

prime time? Perhaps not quite yet, but with gene-based clinical studies in place or planned for the near future, we can expect to have a clearer understanding of the relative merits of pharmacogenomics in everyday clinical practice.

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