# Pharmacogenetics: Using DNA to Optimize Drug Therapy

DAVID E. LANFEAR, MD, MS, *Henry Ford Hospital, Heart and Vascular Institute, Detroit, Michigan*
HOWARD L. MCLEOD, PharmD, *Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina*

**Pharmacogenetics is a growing field of research that focuses on the interaction between genetics and drug therapy. Relationships between genetic variation and drug effect have been observed for a growing number of commonly used drugs. Validation studies may soon define the use of these relationships in clinical practice, moving the field toward routine application. Currently, there are only a few pharmacogenetic diagnostic tests available, and clinical guidelines for pharmacogenetically tailored therapy are lacking. It is likely that guidelines for pharmacogenetic dosing of certain commonly used drugs such as warfarin, codeine, and inhaled beta agonists will become available within the next few years.** (Am Fam Physician 2007;76:1179-82. Copyright © 2007 American Academy of Family Physicians.)

One of the many reasons that pharmacology remains as much art as science is the extraordinary variation in patient response to medications. It is clear that many nongenetic factors (e.g., age, organ function, drug interactions) influence the effects of medications. However, genetic variation can account for as much as 95 percent of variability in drug disposition and effects.[1] There are numerous examples of interindividual differences in drug response caused by common genetic variations (called polymorphisms) in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets.[2-4]

Genetic determinants of drug response can supplement other predictors and have the additional advantage of remaining stable for a person's lifetime, making them potentially useful for rational drug prescription strategies. This is especially relevant today when there often are many medications available for a given condition but no single best therapeutic strategy.[5]

Inherited differences in drug effects in terms of drug metabolism were first documented in the 1950s,[6,7] creating a field of research and medicine that is concerned with the interaction of drug therapies and genetic variation (i.e., pharmacogenetics). Because most drug effects are determined by the interplay of multiple gene products throughout the entire drug pathway, the field has now extended to all aspects of drug disposition (i.e., absorption, distribution, and excretion)[8] and drug targets, as well as downstream effect mediators. Pharmacogenetics also has been rediscovered by a broader spectrum of academia and industry, creating the term "pharmacogenomics." This term applies when genome-wide approaches, rather than just one or two genes of interest, are used to identify genetic variations that govern response to medications.

The genetic sequence variants of interest come in many forms: single nucleotide polymorphisms (SNPs) are the most common, with possibly 15 million in the human genome. SNPs are caused by a difference in one base-pair in the DNA sequence, which may or may not result in a change in function or amount of resulting protein depending on the nucleotide change and the location.

Recent advancements in technology and genomic knowledge have opened vast opportunities to expand and refine understanding of pharmacogenetics. The human genes involved in many pharmacogenetic traits have been identified, and polymorphisms within these genes are in various stages of becoming molecular diagnostics in medicine *(Table 1)*.[9-16] At present, clinical applications are mostly limited to medications with narrow therapeutic indices (e.g., anticancer agents, some antidepressants, warfarin [Coumadin]). As additional pharmacogenetic relationships are explained, increased use of a broader range in medications can be anticipated.

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**Table 1. Examples of Pharmacogenetic Traits with Clinical Testing**

| *Gene* | *Drug(s)* | *Consequence of variant genotype* |
|---|---|---|
| Thiopurine methyltransferase *(TPMT)** | Mercaptopurine (Purinethol) or azathioprine (Imuran) | Lower dose requirement; increased risk of bone marrow toxicity[9,10] |
| *CYP2D6** | Codeine | Nonresponse or toxic overdose depending on allele[11,12] |
| Vitamin K epoxide-reductase *(VKORC1)** | Warfarin (Coumadin) | Higher dose requirement[13] |
| *CYP2C9** | Warfarin | Lower dose requirement; increased risk of supratherapeutic International Normalized Ratio[14] |
| $Beta_2$ adrenoreceptor *(ADRB2)*† | Beta agonists | Nonresponsive to chronic stimulation, possibly detrimental[15,16] |

*CYP = cytochrome P.*

**—Genotyping currently available.*
†*—Expected to be available in the near future.*

*Information from references 9 through 16.*

## Drug Metabolism

Nearly all members of the more than 30 families of drug-metabolizing enzymes are polymorphic; many such genetic variants translate into functional changes in the encoded proteins.[3] One of the best-developed examples of pharmacogenetics applied to clinical practice is the enzyme thiopurine methyltransferase *(TPMT)*.[9,10,17] *TPMT* is responsible for the degradation of azathioprine (Imuran) and mercaptopurine (Purinethol), which are commonly used to treat acute leukemia, inflammatory bowel disease, rheumatoid arthritis, and transplant immune suppression. Although family physicians rarely prescribe these medications, they are still likely to see patients who are being treated with them.[6]

Patients who inherit complete *TPMT* deficiency (i.e., two nonfunctional alleles) are at very high risk (near 100 percent) of severe and potentially fatal hematologic toxicity,[9,10,18,19] whereas patients who are heterozygotes are at intermediate risk (35 percent).[10] *TPMT* genotyping is available from reference laboratories as a Clinical Laboratory Improvement Act–certified molecular diagnostic tool. There also are clear dosing guidelines based on *TPMT* genotype.[10]

*CYP2D6* is probably the most extensively studied polymorphic drug-metabolizing enzyme in humans.[6] More than 30 medications are substrates for this enzyme, including analgesics, antidepressants, and antiemetics. *CYP2D6* genetic polymorphisms can cause exaggerated or diminished drug effects, depending on whether the medication is inactivated (e.g., nortriptyline [Pamelor], fluoxetine [Prozac], 5-hydroxytryptamine inhibitors) or activated (e.g., codeine).[20] For example, approximately 10 percent of patients will receive no pain relief from codiene becaues of the absence of a functional *CYP2D6* enzyme, which is responsible for producing the active agent from the prodrug.[11,12,20,21] This has led to the suggestion that genotype should influence rational prescribing, with poor or ultrarapid metabolizers not being prescribed this particular agent.

There is a U.S. Food and Drug Administration–approved, commercially available test (Amplichip) for determining *CYP2D6* genotype. This test is available through commercial laboratories (e.g., Labcorp) and, although the Centers for Medicare and Medicaid Services has not published a specific ruling, it is reimbursable through Medicare using current procedural terminology codes for DNA diagnostic tests. Private insurance companies are taking varied approaches to reimbursement, with some covering it on a case-by-case basis and others denying coverage.[22,23] Widely accepted guidelines for genetically guided dosing of a specific drug or for genotype testing in general are still lacking.

## Genetic Polymorphisms of Drug Targets

Genetic variation in drug targets (e.g., receptors) also can have a profound effect on drug effectiveness.[2,4,24] One example of this that is nearing clinical use is the $beta_2$-adrenoreceptor gene *(ADRB2)*. *ADRB2* interacts with catecholamines and various medications, including inhaled beta agonists. Several SNPs in *ADRB2* that are associated with altered trafficking and down-regulation of the receptor have been identified.[25-28] Clinical studies have shown differential effect of beta-agonist therapy, depending on genotype at the 46G>A polymorphism (46 refers to the location of the variation within the gene, and G>A refers to the two alternative nucleotides at that site).

Use of chronic inhaled beta-agonist therapy in patients with the 46 AA genotype resulted in a gradual decline in morning peak expiratory flow (PEF), whereas no change was observed in patients with the 46 GG genotype.[29] In a subsequent randomized study, change in morning PEF with chronic inhaled beta-agonist therapy again

depended on patient genotype, with the authors concluding that withholding albuterol (Proventil) therapy from patients with the 46 AA genotype may be appropriate.[15]

These data suggest that the *ADRB2* 46 AA genotype identifies patients at risk of deleterious or nonbeneficial effects of regularly scheduled inhaled beta-agonist therapy. In the near future, it is likely that published guidelines will address this; however, further studies may be needed to develop a strategy for patients that are heterozygous at this locus (i.e., those with the GA genotype).

## Comprehensive Pathway Assessment

The use of warfarin illustrates the need to look at the entire drug pathway and to integrate genetic and nongenetic factors when prescribing. It is widely known that many clinical and demographic factors such as age, sex, drug interactions, and diet impact warfarin dosing.[30] In addition, there is strong evidence that genetic variation contributes to interindividual variability in warfarin dosing. *CYP2C9* is the major metabolizing enzyme that inactivates warfarin, and vitamin K epoxide reductase complex *(VKORC1)* is its primary target.

*CYP2C9* has been linked to toxicity and altered dosage requirements despite being able to titrate warfarin dosing to a clear effect end point (i.e., International Normalized Ratio [INR]). Patients with a variant *CYP2C9* genotype take a median of 95 days longer to achieve stable dosing compared with patients who have a wild-type genotype.[31] They also have a higher risk of acute bleeding complications.[30-32] Patients with the two most common variant alleles require 15 to 30 percent lower maintenance doses of warfarin to achieve the target INR.[14,30,32]

When added to clinical factors that are known to impact warfarin dosing, *CYP2C9* genotype has been shown to incrementally improve prediction of warfarin dose maintenance.[33] Recently, *VKORC1* was identified as the therapeutic target site for warfarin.[13] Subsequently, polymorphisms within this gene have been associated with significant differences in warfarin dose requirements (6.2 mg versus 3.5 mg; $P < .001$).[34] A larger study recently confirmed the importance of *VKORC1* genetic variants, even after accounting for *CYP2C9* polymorphism.[32]

Putting all these factors together may allow for the construction of a clinically useful tool to improve warfarin therapy. Clinical and demographic variables account for roughly 20 percent of interindividual variability in warfarin dosing, whereas *CYP2C9* genotype makes up 15 to 20 percent of variability[13,30,34,35]; *VKORC1* can account for an additional 14 percent.[14] Together, 50 to 60 percent of the total variation in warfarin dosing is predictable before administration, which would be clinically useful information to have when prescribing.

Several authors have already produced formulas for determining initial warfarin dosing based on *CYP2C9* genotype.[36,37] Ongoing intervention studies comparing genotype-driven initial warfarin dosing versus standard dosing will be able to show definitively whether patients reach their INR goal more quickly and with less toxicity through a pharmacogenetic dosing scheme. It also should allow for the creation of clear testing and dosing guidelines.

## Current Limitations and Future Challenges

Recent advances in technology have contributed to increasingly rapid and affordable analysis of genotype.[24] The greatest challenge going forward will not be the technology for determining genotype but rather precisely defining clinical drug response phenotypes in well-powered trials and practically incorporating genetically guided therapy into routine clinical care. There also are societal factors (e.g., acceptance, privacy issues) that have not been fully explored and confronted. Security of patient information is already an important issue, but it is likely to be even more so once genetic information is included. Further education about and acceptance of genetic testing may be required before genetically guided therapy can become more widely used. Added concerns, such as insurability, and liability in the postgenomics era have yet to be fully scrutinized. These issues will also need to be explored and addressed before the vision of genetically customized medicine can become a reality.

## The Authors

DAVID E. LANFEAR, MD, MS, is a member of the Advanced Heart Failure and Cardiac Transplantation section at the Henry Ford Hospital, Heart and Vascular Institute and an assistant professor of medicine at Wayne State University, both in Detroit, Mich. Dr. Lanfear received his medical degree from the University of Michigan Medical School in Ann Arbor, completed an internal medicine residency and cardiovascular disease fellowship at Washington University in St. Louis, Mo., and received a master's degree in clinical research design and statistical analysis from the University of Michigan School of Public Health.

HOWARD L. McLEOD, PharmD, is the Fred N. Eshelman Distinguished Professor and the director of the University of North Carolina at Chapel Hill Institute for Pharmacogenomics and Individualized Therapy. Dr. McLeod received his doctor of pharmacy degree from the Philadelphia (Pa.) College of Pharmacy and Science (now called the University of the Sciences) and completed a clinical research fellowship at St. Jude Children's Research Hospital in Memphis, Tenn. He also is the principal investigator for the CREATE Pharmacogenetics Research Network, which is a member of the National Institutes of Health Pharmacogenetics Research Network.

*Address correspondence to Howard L. McLeod, PharmD, UNC Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina at Chapel Hill, Campus Box 7360, Kerr Hall, Chapel Hill, NC 27599-7360. Reprints are not available from the authors.*

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