THE JOURNAL OF FAMILY PRACTICE

Personalized medicine: The promise, the reality

Genetic testing can tell us how a patient will metabolize warfarin, but no one can tell us how to adjust our dosing

Doug Campos-Outcalt, MD, MPA
Department of Family and Community Medicine, University of Arizona College of Medicine, Phoenix
dougco@u.arizona.edu

Genetic tests to guide warfarin dosing could avert 85,000 serious bleeding events and 17,000 strokes annually, according to a report from the AEI-Brookings Joint Center for Regulatory Studies, a Washington, DC, think tank. The report further suggests that by integrating genetic testing into warfarin therapy, American health care spending could be reduced by $1.1 billion annually.[1] Unfortunately, the promise of using genetic testing to guide such pharmacological treatment has largely gone unfulfilled.[2]

Case in point: Genetic testing can tell us whether a patient is likely to be an ultra-rapid metabolizer of warfarin (and need larger doses) or a poor metabolizer (and need lower doses), but there are no guidelines to tell us how to dose accordingly. International normalized ratios (INRs) still need to be ordered and the patient will likely have to pick up the tab for the genetic test ($250), since Medicare and private insurers don't cover the cost. (See **"Warfarin: An ideal, but far from ready, candidate"** on page 622.)

Hints that change may be on the horizon. The government—specifically the Department of Health and Human Services—created the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) to assess how genetic and genomic technologies are being integrated into health care and to identify opportunities and gaps in research. To that end, SACGHS issued a draft report earlier this year that notes that genetic-based treatment has "the potential to yield significant gains in personal health, population health, and cost-effective resource allocation." Among its many recommendations, SACGHS calls for greater collaboration between the public and private sectors to expand our knowledge of the clinical validity and utility of using genetics to guide treatment.[3]

A standard of care, potentially. Readying ourselves for the ways that genetics is likely to shape the way we prescribe such drugs as anticoagulants, antidepressants, and antiarrhythmics requires that we step back and assess the progress made so far, and the work that still needs to be done before genetic testing becomes a common occurrence, and perhaps even a standard of care.

The goal: Avert adverse events

The wide variation in the way different people respond to the same dose of medications is a major contributor to the problem of adverse drug reactions. Lazarou and colleagues estimated that 6.7% of hospitalized patients—over 2 million patients in the US—experienced

IN THIS ARTICLE

Warfarin: An ideal, but far from ready, candidate

It would appear that warfarin dosing would be a perfect candidate for the clinical use of a pharmacogenetic test. Studies have shown that about 7% of the Caucasian population are poor metabolizers and at increased risk of bleeding from over coagulation and 1% are ultra-rapid metabolizers.[4] Despite what we know about the polymorphisms to the CYP2C9 enzyme, which is the primary route of metabolism for warfarin, the package insert on Coumadin still doesn't contain a recommendation for determining a patient's genetic profile before initiating treatment.[30] Similarly, the chapter on anticoagulation in *Applied Therapeutics*, a commonly used medical textbook, says nothing about the use of CYP polymorphisms for dosing decisions.[13]

At issue: Genotyping to guide dosing has not been tested in comparison to the usual monitoring using the international normalized ratio (INR).[31] Specifically, the outcomes of bleeding complications and adequate anticoagulation of the 2 methods have not been compared in a clinical trial.

Here's what we do know: In one study, the presence of specific polymorphisms was associated with a lower maintenance warfarin dose, but not with over-anticoagulation.[32] In a review of 4 studies on CYP2C9 polymorphisms and warfarin daily dose, Lee and colleagues found that between the slowest and fastest metabolizers, the difference in dose was, at most, 4 mg/day. These studies did not explore if dosing decisions could accurately be made on genetic classifications and it is unlikely they could because of the wide overlap in maintenance dosages in the different classes.[7]

To complicate things further, the future use of warfarin in some conditions is problematic because fractionated heparin has been proven in many situations to be as effective and less risky than warfarin, and does not require frequent monitoring with blood tests. All of these unknowns make it unclear how useful genetic tests will be, and whether insurers will pay for them.

FAST TRACK

Polymorphisms were associated with a lower warfarin dose, but not with over-anticoagulation

an adverse drug reaction and 0.32% (106,000) had a fatal adverse drug reaction.[4]

Individual response to medications is determined by a host of factors including age, environment, other medications being taken, and genetic differences in drug absorption and metabolism. These genetic differences have spawned the fields of pharmacogenomics and pharmacogenetics.

Pharmacogenomics is the biotechnological science that combines the techniques of medicine, pharmacology, and genomics and is concerned with developing drug therapies to compensate for genetic differences in patients, which cause varied responses to a single therapeutic regimen.

- A good example of pharmacogenomics at work is the use of trastuzumab in addition to chemotherapy for breast cancer patients who are positive for the human epidermal growth factor receptor 2 (HER2) oncogene.[5]

Pharmacogenetics is the branch of pharmacology that examines the relation of genetic factors to variations in response to drugs.

The use of pharmacogenetics to predict individualized responses to medi-

cations and to prevent adverse drug reactions through individualized dosing regimens or avoidance of certain medications hinges on our knowledge of genetic polymorphisms, that is, gene-based differences in drug absorption, distribution, metabolism, or excretion.

Polymorphisms of the cytochrome P450 family of drug metabolizing enzymes have been the most extensively studied. The names of these enzymes are abbreviated by using CYP and then a series of letters and numbers to describe individual enzymes. The 4 most extensively studied CYP enzymes are CYP2A6, CYP2C9, CYP2C19, and CYP2D6. These 4 metabolize an estimated 40% of all drugs; the distributions of polymorphisms of each vary considerably by race/ethnicity.[6–8]

A sampling of medications and classes of medications where polymorphisms play a significant role in drug metabolism is listed in the **TABLE**. Three with significant potential for prevention of adverse drug reactions are the antipsychotics, because of the severity of a specific drug adverse reaction, tardive dyskinesia;[6,9] warfarin, because of the risk of bleeding complications and its narrow therapeutic index;[7,10] and chemotherapeutic agents because of the serious nature of the disease and the potential for tailoring individualized therapies to maximize tumor response to medication and to minimize adverse reactions of very toxic drugs.[11]

TABLE

Polymorphisms to these enzymes affect drug metabolism

DRUG/CLASS	ENZYMES
Antiarrhythmmics[7]	CYP2D6
Antidepressants[7]	CYP2D6
Antipsychotics[6,9]	CYP2D6, CYP1A2, CYP2C19, CYP3A4
Beta-blockers[7]	CYP2D6
Cancer chemotherapy[11]	Varies by the agent
HMG-CoA reductase inhibitors (statins)[29]	CYP2D6, CYP2C9, CYP2C19
Losartan[7]	CYP2C9
Neuroleptics[7]	CYP2D6
NSAIDs[29]	CYP2C9
Phenytoin[7]	CYP2C9, CYP2C19
Proton pump inhibitors[29]	CYP2C19
Tolbutamide[7]	CYP2C9
Warfarin[7,10]	CYP2C9

Clinical resources reflect an information gap

In spite of the potential for improved patient care, there remains very little clinical application of pharmacogenetic information in primary care practice. Zineh and colleagues reviewed prescribing information in the electronic version of the *Physicians' Desk Reference* (PDR) in 2004 and found that only 76 package inserts out of 3382 contained pharmacogenetic information.[12] In only 25 was there enough information to affect treatment decisions. Just 5 inserts mentioned that the chance of successful response to treatment could be predicted by genetic testing, and only one insert mentioned that a specific genetic subgroup should not take a drug.

The authors concluded that, generally, the pharmacogenetic information was inadequate to guide drug therapy and the majority of information was available for drugs that are not commonly prescribed. The FDA is addressing this issue by requiring the inclusion of pharmacogenetic information in package inserts more frequently.

Consider, too, the 2005 edition of *Applied Therapeutics*, a commonly used medical textbook.[13] In it there is no mention of the use of pharmacogenetics in managing pharmacological therapies, which tells us that very little teaching on this topic is going on in medical schools and residencies.

But why? Why are clinicians and the tools we rely on so out of sync with the recommendations and expectations of personalized medicine advocates?

CONTINUED

FAST TRACK

The potential is great to prevent adverse drug reactions with antipsychotics, warfarin, and chemotherapeutic agents

Will litigation be the tipping point?

Certain conditions will need to exist before testing for CYP polymorphisms will become the standard of care in dosing certain drugs, such as warfarin. (See **"Warfarin: An ideal, but far from ready, candidate"** on page 622.) The most important is that this clinical approach needs to be proven superior to existing methods, such as INR monitoring. Should this occur, guidelines that are evidence-based will include it as a recommendation, physician continuing education courses will cover it, and it will enter into the curricula of medical schools and residency programs. But the process of adopting new, evidence-based best practices has historically been slow.[32–36]

One variable that may play a part in facilitating more rapid acceptance of genetic testing before warfarin use is litigation. Marchant and colleagues describe potential legal pressures that may drive medicine to adopt more personalized medicine.[37] If genetic testing before warfarin use results in better outcomes (fewer catastrophic events or very bad outcomes) and there is plausible evidence that a catastrophic outcome (massive bleeding) could have been avoided with genetic information, then litigation will surely be close behind.

As news of successful litigation spreads, one of two results will likely occur: Either the use of the CYP polymorphism testing will increase, or the movement to use alternative medications, such as fractionated heparin, will accelerate.

There are 5 likely culprits:

1. A lack of clinically useful pharmacogenetic tests.
2. A lack of test standardization and availability.
3. A lack of coverage by third-party payers.
4. A low level of physician knowledge about genetic testing.
5. A lack of evidence of improved outcomes.

How useful are pharmacogenetic tests?

For a laboratory test to be clinically useful, it should provide information that will influence a therapeutic decision. Decisions that could be influenced by this information include the dose of a particular drug and the potential use of an alternative because of a contraindication or likelihood of a poor outcome based on a particular genetic polymorphism.

The use of pharmacogenetic laboratory information can place a patient into one of several groups:

- **ultra-rapid metabolizers**, who need a larger dose of medication
- **normal metabolizers,** often called extensive metabolizers, who do not need dose modifications
- **poor metabolizers**, who need lower doses.[9]

Most medications have a wide therapeutic margin of effectiveness and safety. This means that the medication works within a wide range of serum drug levels and is safe at these different levels, making refinement in dosing based on genetic information unnecessary. In medications with narrower therapeutic windows for effectiveness or adverse reactions, there are frequently alternative means of drug level monitoring.

In many instances, the genetic test predictability of a patient's actual metabolic responses—and resulting drug levels—is poor, leading to the need to monitor drug levels anyway.[14–16] This occurs because there is often a great deal of overlap in the response to a medication dose among the different metabolism classifications.[9,14,16–18] All of these realities have limited the clinical usefulness of pharmacogenetics up to this point.

Test standardization: Poised to improve?

Genotyping, the determination of the actual genetic makeup of the patient is not always predictive of an individual patient's metabolic response. In other words, genotype does not always equate to a phenotype. Further complicating matters is the fact that many of the pharmacogenetic studies have been performed at research laboratories and have used tests that are not standardized, or widely available.[19–21]

The recent commercial availability of pharmacogenetic tests by well-established and reputable laboratories will probably improve both standardization and availability.

An example is the AmpliChip CYP450 test by Roche Diagnostics.[22] This microassay-based test identifies 29 CYP-2D6 polymorphisms and 2 CYP-2C19 polymorphisms. These genes affect the metabolism of 25% of currently prescribed drugs. Using this test, patients can be classified as poor, intermediate, extensive, or ultra rapid metabolizers of CYP-2D6 affected drugs, including antidepressants, antiarrhythmics, and antipsychotics. They can also be classified as poor or extensive metabolizers of CYP-2C19 affected drugs, including phenytoin and proton pump inhibitors.

How costly?

The cost of genetic testing will also affect availability. Tests will be widely available only if covered by third-party payers. The AmpliChip test costs between $300 and $500. Clearly, then, both cost and insurance coverage are issues that impede the adoption of pharmacogenetic testing, though there is little written about this in the medical literature.[19,23]

AAFP explores ways to teach genomics

Physicians who are currently in practice received little or no training in the clinical use of pharmacogenetics or other genetic tests, such as genetic testing for the prediction of cancer risk.[24,25] The main resources of pharmacological information for practicing physicians do not contain much, if any, useful genomic information. A recent continuing education monograph for family physicians on clinical genetics mentioned pharmacogenetics only as a promising future technology.[26]

For its part, the American Academy of Family Physicians has formed a genomics work group and is exploring how to educate family physicians on clinically useful genomic topics.

Evidence-based outcomes are needed

To date there has not been a head-to-head comparison of the outcomes of using clinical pharmacogenetics with those obtained from standard drug level monitoring practices. The CDC has formed a committee modeled after the USPSTF, the Evaluations of Genomics Applications in Practice and Prevention (EGAPP), which will evaluate the effectiveness of genomic clinical tests and make recommendations to physicians on their use.[27] The group's first report, on the use of CYP450 testing in depression, concluded that there is a paucity of good quality data that addresses whether testing for CYP450 polymorphisms in adults entering SSRI treatment leads to improved outcomes.[28]

In addition, SACGHS, the Department of Health and Human Services' Committee, recommends in its draft report that HHS "provide resources to identify and address evidentiary gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics."[3]

Outcomes data will undoubtedly be key. With it, pharmacogenetic testing has the potential to grow by leaps and bounds—perhaps even becoming a standard of care in guiding pharmacological therapy. Without it, such testing will remain a promising, but as yet unrealized advance in personalized medicine. ■

Correspondence

Doug Campos-Outcalt, MD, MPA, 550 E. Van Buren, Phoenix, AZ 85004; dougco@u.arizona.edu.

Disclosure

No potential conflict of interest relevant to this article was reported.

References

1. McWilliam A, Lutter R, Nardinelli C. Health care savings from personalized medicine using genetic testing: The case of warfarin. [Working Paper 06-23]. November 2006. Available at: www.aei-brookings.org/admin/authorpdfs/page.php?id=1337&PHPSESSID=7b3a3ae4b30d77cb76223e29535e7590. Accessed on June 27, 2007.

FAST TRACK

A CDC committee will evaluate the effectiveness of genomic clinical tests and make recommendations on their use

FAST TRACK

With outcomes data, pharmacogenetic testing could become a standard of care

2. Tucker G. Pharmacogenetics—expectations and reality. *BMJ* 2004; 329:4-6.
3. Department of Health and Human Services. Realizing the promise of pharmacogenomics: Opportunities and Challenges [Draft report of the Secretary's Advisory Committee on Genetics, Health, and Society]. Available for public comment March 23–June 1, 2007. Available at: www4.od.nih.gov/oba/sacghs/SACGHS_PGx_PCdraft.pdf. Accessed on June 27, 2007.
4. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients. *JAMA* 1998; 279:1200–1205.
5. Dent R, Clemons M. Adjuvant trastuzumab for breast cancer. *Br Med J* 2005; 331:1035–1036.
6. Wolf CR, Smith G. Pharmacokinetics. *Br Med Bull* 1999; 55:366–386.
7. Lee CR, Goldstein JA, Pieper JA. Cytochrome P450 2C9 polymorphisms: a comprehensive review of the in-vitro and human data. *Pharmacogenetics* 2002; 12:251–263.
8. Bachman K. Genotyping and phenotyping the cytochrome P450 enzymes. *Am J Ther* 2002; 9:309–316.
9. Dahl ML. Cytochrome P450 phenotyping/genotyping in patients receiving antipsychotics. *Clin Pharmacokinet* 2002; 41:453–470.
10. Daly AK, King BP. Pharmacogenetics of oral anticoagulants. *Pharmacogenetics* 2003; 13:247–252.
11. Van Schaik RHN. Implications of cytochrome P450 genetic polymorphisms on the toxicity of antitumor agents. *Ther Drug Monit* 2004; 26:236–240.
12. Zineh I, Gerhard T, Aquilante CL, Beitelshees AL, Beasley BN, Hartzema AG. Availability of pharmacogenomics-based prescribing information in drug package inserts for currently approved drugs. *Pharmacogenomics J* 2004; 4:354–358.
13. Koda Kimball M, ed. *Applied Therapeutics.* 8th ed. Baltimore, Md: Lippincott, Williams and Wilkins; 2005.
14. Furuya H, Fernandez-Salguero P, Gregory W, et al. Genetic polymorphism of CYP2C9 and its effect on warfarin maintenance dose requirement in patients undergoing anticoagulation therapy. *Pharmacogenetics* 1995; 5:389–392.
15. Arthur H, Dahl ML, Siwers B. Polymorphic drug metabolism in schizophrenic patients with tardive dyskinesia. *J Clin Psychopharmacology* 1995;15:211–216.
16. Mulder AB, Van Lijf HJ, Bon MAM, et al. Association of polymorphism in the cytochrome CYP2D6 and the efficacy and tolerability of simvastatin. *Clin Pharmacol Ther* 2001; 70:546–551.
17. Takahashi H, Ehizen H. Pharmacogenetics of warfarin elimination and its clinical implications. *Clin Pharmakinetics* 2001; 40:587–603.
18. Caraco J. Genetic determinants of drug responsiveness and drug interactions. *Ther Drug Monit* 1998; 20:517–524.
19. Logue LJ. Genetic testing coverage and reimbursement: a provider's dilemma. *Clin Leadersh Manag Rev* 2003; 17:346–350.
20. Schwartz MK. Genetic testing and the clinical laboratory improvement amendments of 1988: present and future. *Clin Chem* 1999; 45:739–745.
21. US Food and Drug Administration. Guidance for industry: Pharmacogenomic data submissions 2003. Available at: www.fda.gov/cber/gdlns/pharmdtasub.pdf. Accessed on July 3, 2007.
22. Howard RH. Personalized drug therapy with pharmacogenetics. Part I; pharmacokinetics. *J Psychosoc Nurs Ment Health Serv* 2006; 44:13–16.
23. Veenstra DL, Higashi MK, Phillips KA. Assessing the cost effectiveness of pharmacogenics. *AAPS PharmSci* 2000; 2:E29.
24. Gramling R, Trask P, Nash J, Culpepper L. Family physicians' beliefs about genetic testing. *Fam Med* 2004; 36:691–692.
25. Caulfield TA. The informed gatekeeper? A commentary on genetic tests, marketing pressure and the role of primary care physicians. *Health Law Rev* 2000; 9:14–17.
26. Mueller C, Feero WG. Clinical genetics. AAFP Home Study Self Assessment Program No 317. Leawood, Kan: AAFP; 2005
27. CDC Activities page. Programs in Brief: Evaluations of Genomics Applications and Prevention (EGAPP). Available at: www.cdc.gov/genomics/activities/pib/egapp.htm. Accessed on June 27, 2007.
28. Agency for Healthcare Research and Quality. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs) [AHRQ Publication No. 07-E002]. Available at: www.ahrq.gov/downloads/pub/evidence/pdf/cyp450/cyp450.pdf. Accessed on July 3, 2007.
29. Vermes A, Vermes I. Genetic polymorphisms in cytochrome P450 enzymes. Effect on efficacy and tolerability of HMG-CoA reductase inhibitors. *Am J Cardiovasc Drugs* 2004; 4:247–255.
30. Yasar U, Eliasson E, Dahl ML, Johansson I, Ingelman-Sundberg M, Sjöqvist F. Validation of methods for CYP2C9 genotyping of mutant alleles in a Swedish population. *Biochem Biophys Res Commun* 1999; 254:628–631.
31. Aithal GP, Day CP, Kesteven PJL, Daly AK. Association of polymorphisms in the cytochrome p450 CYP2C9 with warfarin dose requirement and risk of bleeding complications. *Lancet* 1999; 353:717–719.
32. Taube J, Halsall D, Baglin T. Influence of cytochrome P450 CYP2C9 polymorphisms on warfarin sensitivity and risk of over anticoagulation in patients on long-term therapy. *Blood* 2000; 96:1816–1819.
33. Reeves MJ, Bohm SR, Korzeniewski SJ, Brown MD. Asthma care and management before an emergency department visit in children in western Michigan: how well does care adhere to guidelines? *Pediatrics* 2006; 117:118–126.
34. Rastogi D, Shetty A, Neugebauer R, Harijith A. National heart, lung, and blood institute guidelines and asthma management practices among inner-city pediatric primary care providers. *Chest* 2006; 129:619–623.
35. Bishop PB, Wing PC. Knowledge transfer in family physicians managing patients with acute low back pain: a prospective randomized control trial. *Spine J* 2006; 6:282–288.
36. Bauchner H, Marchant CD, Bisbee A, et al. Effectiveness of centers for disease control and prevention recommendations for outcomes of acute otitis media. *Pediatrics* 2006; 117:1009–1017.
37. Marchant GE, Milligan RJ, Wilhelmi B. Legal pressures and incentives for personalized medicine. *Personalized Medicine* 2007; 3:391–399.