Pharmacogenetic testing: not as simple as it seems

Susanne B. Haga, PhD[1], and Wylie Burke, MD, PhD[2]

Pharmacogenetics has the potential to help guide treatment decisions by tailoring appropriate drugs and dosages to patients most likely to benefit. This straightforward clinical goal has led some to suggest that pharmacogenetic testing is free of ethical concerns. However, a number of potential risks and clinical uncertainties arise in considering the use of these new tools in clinical care. We propose a classification of pharmacogenetic tests to identify and prioritize the policy issues that will need to be addressed to ensure appropriate delivery of pharmacogenetic testing. We use the classification framework to consider the benefits and risks associated with ancillary information, timing of testing, and storage and retrieval of pharmacogenetic test results among health professionals. These issues have implications for informed consent and genetic counseling requirements, and for the role of health professionals. *Genet Med* 2008:10(6):391–395.

Key Words: *pharmacogenetic tests, classification, policy, risks*

Pharmacogenetics represents one of the most promising clinical applications of genomic research. Testing for gene variants associated with drug response has the potential to improve both the safety and efficacy of drug treatment, by identifying the best patient candidates or most appropriate dosages for a particular drug.[1,2] Some have argued that pharmacogenetic tests pose risks similar to other genetic tests,[3] although others have suggested that the direct application of pharmacogenetic tests to improved health care represents a major difference, such that the ethical issues surrounding traditional genetic tests are not applicable to pharmacogenetic tests, or to a much lesser degree.[4–6] We propose a classification of pharmacogenetic tests to assist clinicians and policy makers to identify salient differences in the ethical and policy implications of different pharmacogenetic tests. This framework indicates that some pharmacogenetic tests raise ethical issues that warrant additional attention before their use.

CLASSIFICATION OF PHARMACOGENETIC TESTS

Although pharmacogenetic tests are likely to be used in a wide range of clinical settings, two distinctions are of particular importance: (1) the type of genetic variation identified by the test—either acquired or inherited and (2) the goal of testing—either to address a specific clinical question or to provide information for future clinical care. A third important distinc-

tion applies to tests detecting inherited variation—whether the test reveals ancillary clinical information. Ancillary information refers to information unrelated to drug response, such as predisposition to diseases for which the individual is not currently seeking treatment or does not manifest symptoms, or prognostic information that is not informative for treatment.[3,7,8] Our classification framework extends the analysis of Freund and Wilfond,[9] who identified four similar criteria in their discussion of the differences between traditional genetic tests and pharmacogenetic tests: the purpose of testing, scope of testing, predictive value, and potential collateral information. In considering policies for test use, the leading issues will differ in the categories of pharmacogenetic tests generated by these parameters (Fig. 1).

Testing of acquired variants

Pharmacogenetic testing of tumor or other disease tissue before prescription of a drug may allow the selection of the patients most likely to benefit from treatment. For example, testing for mutations in the epidermal growth factor receptor (*EGFR*) gene in non-small cell lung cancers will help to identify patients more likely to respond favorably to treatment with the tyrosine kinase inhibitor erlotinib (Tarceva). A genetic analysis found that patients who respond favorably usually had tumors carrying mutations in the *EGFR* gene (the drug target of Tarceva), whereas the tumors of nonresponsive patients had few or no mutations.[10,11]

Testing for inherited variation to improve current care

Variants in the genes coding for metabolic enzymes, transporters, receptors or other proteins involved in drug disposition can influence the efficacy of drug treatment or the likelihood of adverse drug responses. When a particular drug therapy is contemplated, testing for relevant gene variants may provide guidance for treatment decisions. For example, several polymorphisms in two genes, *CYP2C9* and *VKORC1*, have

From the [1]*Institute for Genome Sciences and Policy, Duke University, Durham, North Carolina; and* [2]*Center for Genomics and Healthcare Equality and Department of Medical History and Ethics, University of Washington, Seattle, Washington.*

Susanne B. Haga, PhD, Institute for Genome Sciences and Policy, Duke University, 101 Science Drive, Box 3382, Durham, NC 27708. E-mail: susanne.haga@duke.edu.
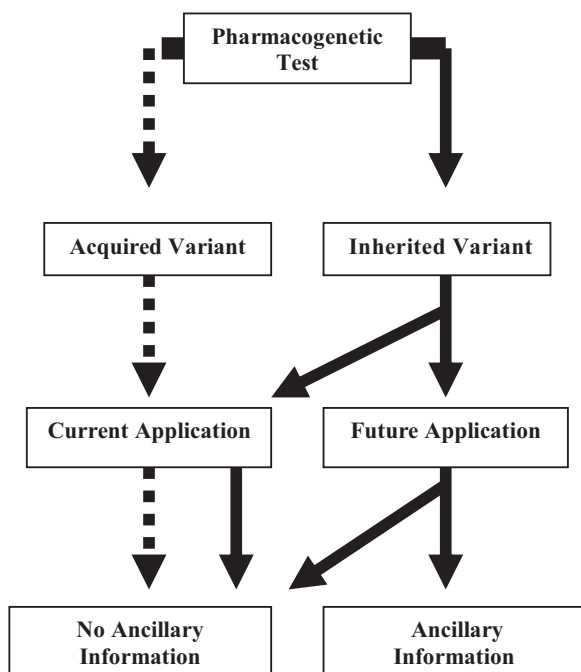
Fig. 1. Classification of pharmacogenetic tests according to heritability of variant, current/future application, and potential for ancillary information (dotted line, acquired variant; solid line, inherited variant).

been associated with higher bleeding complications or lower dose requirements for warfarin.[12,13] *CYP2C9* is involved in the metabolism of warfarin and *VKORC1* is a target of warfarin. Testing for variants in these genes may assist clinicians to choose the appropriate warfarin dose or treatment surveillance for patients diagnosed with venous thrombosis or other clinical conditions requiring anticoagulant therapy.

Testing for inherited variation to improve future care

Testing for inherited variations may also improve future care if pharmacogenetic information is routinely collected before any specific drug treatment. This approach assumes that most people who undergo testing will eventually require drug treatment for which pharmacogenetic testing will be informative, and that prospective testing will improve outcome by enabling immediate treatment decisions. Continued increases in prescription drug use may further encourage the use of prospective testing, as point-of-care testing may not be considered cost-effective.

Prospective testing is most likely to use pharmacogenetic profiles which test for variants in multiple genes involved in drug metabolism rather than single gene testing. Examples of general pharmacogenetic profiles include the Roche Ampli-Chip,[14] which tests for variants in *CYP2D6* and *CYP2C19* and Genelex's Drug Reaction Testing panel.[15] Gene selection for inclusion in a general pharmacogenetic profile can be based on several factors including functional significance of genetic variants, frequency of variants across different populations, prevalence of drug use affected by the chosen genes, severity of adverse drug response, and classification as a known valid biomarker by the Food and Drug Administration.[16]

Combination testing for inherited/acquired variants

A situation may arise where testing for both an inherited and acquired variant may be necessary. For example, erlotinib and other tyrosine kinase inhibitors are known to be metabolized by the highly variable CYP3A4 enzyme.[17,18] Therefore, in addition to testing lung tumors for EGFR mutations or expression level, testing to determine the level of CYP3A4 activity would be helpful to predict exposure to this class of drugs. Whereas the EGFR mutation represents an acquired variant, the CYP3A4 genotype is an inherited variant. The potential for ancillary information would be limited to CYP3A4.

POLICY CONCERNS

The test categories determined by these parameters help to identify and prioritize policies for pharmacogenetic testing in different clinical settings. The appropriate use of a test is based on the test's potential to improve treatment outcome and its cost-effectiveness (tests that are required for use of a particular drug as indicated on the drug label are a priori part of the drug treatment process). Additional concerns arise in tests for inherited variation.

In general, the policy issues involving pharmacogenetic testing for acquired variants are likely to be similar to the issues raised with any other clinical biomarker used to characterize disease state. By definition, this testing occurs after diagnosis, for the purpose of identifying disease subtypes through analysis of disease tissue. Additional tests similar to *EGFR* mutation testing of non-small cell lung cancers can be cited: for example, the detection of genetic amplification of the *ERBB2* (also known as *HER2/NEU*) gene in breast cancer biopsies provides clinical guidance about use of the targeted drug trastuzumab (Herceptin).[19]

Pathogen testing would also be considered in the category of testing for an acquired genetic change. For example, human immunodeficiency virus resistance testing can inform the selection of which antiretroviral drugs to use.[20]

Arguably, these tests would provide no greater risks than other nongenetic tests used to characterize an infectious agent to further refine treatment choice (e.g., an antibiotic sensitivity test on a lung culture from a patient with pneumonia). Like tests for acquired changes in disease tissues, pathogen testing would not yield ancillary risk information or information about inherited risk because any risk information would be related directly to the disease (infection) and not the individual. Potential psychosocial risks associated with the nature of the disease would be no greater than with other nongenetic pathogen testing.

Ancillary information

Pharmacogenetic testing may divulge risk information unrelated or un-informative to current treatment.[3,7,8] Although it is possible to detect inherited variants in tumor tissue samples, they will be rare relative to acquired mutations and distinguishing them would require confirmatory testing. Information about prognosis may be revealed by the pharmacogenetic

test, but this information will usually be relevant to treatment options, as is the case with testing for *HER2/NEU* amplification.[19]

By contrast, testing for *inherited* changes may pose a substantial risk of ancillary information. For example, a variant in the guanine nucleotide binding protein beta polypeptide 3 (*GNB3*) gene may predict response to antidepressants.[21] Although *GNB3* testing could help guide drug selection, it would also provide information about the risk of essential hypertension[22] and type 2 diabetes.[23] The A1/A2 variant of the dopamine receptor D2 (*DRD2*) gene has been associated with response to bupropion and nicotine replacement therapy[24]; in addition, some studies suggest an association with risk for alcoholism.[25] The E4 variant in the *APOE* gene is associated with warfarin[26] and statin[27] response as well as Alzheimer disease[28] and coronary heart disease.[29] The ancillary information provided in these examples may be unwelcome or stigmatizing, and could be a reason *not* to test—or even to exclude certain gene variants from testing panels unless the pharmacogenetic information is deemed critical to safe or effective drug therapy. The proportion of pharmacogenetic tests that will yield such information is unclear, and is largely understudied. However, one study reported more than a third of the 42 inherited pharmacogenetic variants reviewed were associated with a disease unrelated to the pharmacogenetic indication.[30]

The greatest risk of ancillary information will likely occur with a prospective pharmacogenetic profile. This testing approach involves measurement of many gene variants to inform future treatment decisions, amplifying the potential for ancillary risk information. In addition, the harm of ancillary information can occur any time after testing is performed whereas the benefits will only occur at some unspecified time in the future when information from the profile is used to inform drug treatment.

The potential for ancillary information is relevant in determining practice guidelines and informed consent procedures for pharmacogenetic tests. By extension, investigation of the potential for clinically relevant ancillary information is an important component of pharmacogenetic test evaluation, to insure that information about this test property is available to policy-makers. The validity and utility of the ancillary information must be weighed against the validity and utility of the intended pharmacogenetic information. If the evidence to support ancillary disease associations is poor, the issue may not be of significant concern in light of the benefit of testing to guide treatment selection or prevent adverse responses. Careful scrutiny is particularly important when a variant is proposed for inclusion in a pharmacogenetic profile.

Informed consent/genetic counseling

The scope of information needed by patients to allow adequately informed consent pivots on the potential risks of testing. With tests for inherited variation, the potential for ancillary risk information becomes an important factor in considering the appropriate scope of informed consent. When the test is likely to reveal clinically important risks unrelated to the purpose of testing, an explicit and formal informed consent process should be considered, whereas in the absence of such information, incorporation of pharmacogenetic testing under a general consent for care may be reasonable.

Building on the issue of informed consent is the question of who is best able to inform patients of the risks and benefits associated with pharmacogenetic testing.

Pharmacogenetic testing would likely not be feasible in many clinical settings if genetic counseling were routinely recommended or required; uptake would likely be discouraged, costs increased, and an already limited workforce would be further strained. Yet some tests may generate complex risk information that would require detailed pretest counseling to assure informed consent. This concern emphasizes the need to consider formal counseling requirements for some tests so that the risks are appropriately disclosed to the patient; the counseling could be provided by genetics professionals or by other clinicians who had received appropriate professional education as part of the introduction of pharmacogenetic tests.[8]

Timing of pharmacogenetic testing

With tests used to improve current care, the timing of testing arises primarily as a question about the efficacy of the testing protocol, specifically whether the test turnaround time is sufficiently rapid to inform treatment decisions. However, for prospective pharmacogenetic profiling, timing has broader implications. Several possible scenarios can be envisioned: a pharmacogenetic profile could be routinely performed as a part of pediatric care; offered as part of routine adult primary care; or offered the first time an individual requires drug therapy for which pharmacogenetic testing is likely to be useful.

Pharmacogenetic profiling of children raises particular ethical concerns regarding the benefit of early testing in the absence of an immediate benefit and the potential for ancillary information.[31] In general, genetic tests are not recommended for children unless the benefits clearly outweigh the risks for the child's immediate health, in large part because the child cannot participate fully in the informed consent process.[32] A child with a chronic illness might derive greater benefit from prospective pharmacogenetic testing than a healthy child. If drug treatment is required for a child, pharmacogenetic testing relevant to current care may be the preferred option.[31]

In addition, several companies offer pharmacogenetic profiling direct to consumers, allowing consumers the option to decide when testing is most appropriate for them. Despite the flexibility provided by these companies and the ability to be tested without having the results entered into the medical record to protect patient privacy, test interpretation and appropriate adjustment of drug treatment requires professional expertise and consideration of additional clinical measurements, respectively. Therefore, the benefit of direct-to-consumer testing may be outweighed by the limited application of test results.

Storage/retrieval/portability of test results

Storage, retrieval, and portability of pharmacogenetic information is also a greater concern for pharmacogenetic testing of inherited variants, particularly those ordered for future care, than for acquired variants. The more in advance of treatment testing is performed, the greater the need for an effective and secure storage and retrieval system is required. Because the use of information about inherited variants will span an individual's lifetime, an individual's pharmacogenetic profile must be stored securely but easily retrieved when needed. An effective solution for both retrieval and privacy protection will be a prerequisite for using pharmacogenetic testing as part of routine preventive care.

Results of pharmacogenetic tests will become a part of the patient's medical record, with access to this information protected under medical privacy laws, including the Health Insurance Portability and Accountability Act and any relevant state laws or regulations. Typically, multiple providers caring for the patient share this information. For example, when a diabetic patient is being treated for vascular insufficiency, the primary care provider, endocrinologist, and cardiologist are all likely to have access to the patient's record and information. Appropriately, neither Health Insurance Portability and Accountability Act nor most state laws prohibit sharing of medical information among treating providers; the benefits of pharmacogenetic testing would be diminished if they were not readily available whenever medications were prescribed.

As a result, portability is an important concern for information derived from pharmacogenetic testing for inherited variants for both current and future care. The benefits of this information are derived in part from its relevance to many drug classes that a patient may need during his/her lifetime; the nondisclosure or inability to retrieve pharmacogenetic information may result in redundant testing or adverse responses if other physicians are unaware of a patient's genetic predisposition. This situation may arise when a pharmacogenetic test is ordered to assist treatment in a specific clinical situation and the test result is not available to a different treating physician for a subsequent condition. The patient may not know to inform the second physician of the pharmacogenetic test result since s/he may not be aware of its relevance to a different class of drugs.

One approach to facilitating portability of pharmacogenetic information would be to develop mechanisms that make it easy for patients to carry this information with them. A digital electronic record could be stored on a magnetic strip card or in an online database that is password-protected but accessible to health professionals granted permission by the patient.

Another approach would involve pharmacy practice. Pharmacists' access to patient pharmacogenetic information could ensure review of this information before the prescription being filled.[33] Pharmacists already play an important role in assuring the safety of drug therapy by assessing potential adverse drug interactions when a new drug is prescribed, and by providing information about appropriate substitutions for patients with drug allergies and concomitant medications that should be avoided. In some clinical settings, pharmacist scope of practice has expanded to incorporate identification of alternative therapies to reduce cost or increase safety (e.g., avoid drug-drug interactions), as well as other services such as case management for patients with complex drug regimens.[34,35] Pharmacists have also taken on broader public health responsibilities in some settings, including the provision of vaccinations, health screening (e.g., blood pressure, bone density), and, in some states, prescriptive authority to administer emergency contraception. Despite success with expanded pharmacy practice at some institutions, largely in inpatient settings, the structure of an appropriate collaborative partnership between pharmacist and physician is not yet well-defined and warrants further exploration as the use of pharmacogenetic tests increases.[36]

CONCLUSION

The classification of pharmacogenetic tests presented here provides a framework for identifying and prioritizing the policy issues that will need to be addressed in the delivery of testing. Although the clinical validation of testing will be critical to the development of evidence-based guidelines, policy-makers must also consider the benefits and risks of prospective versus point-of-care testing including the economics of each type of testing, identification and disclosure of ancillary information, mechanisms to securely store and retrieve test results, and sharing of pharmacogenetic results among health professionals. These issues are factors in weighing the overall risks and benefits of testing, and will influence judgments about, the appropriate scope of informed consent, and the potential need for genetic counseling. As a result, pharmacogenetic tests likely fall in between traditional genetic tests and routine clinical tests with respect to their appropriate use and delivery in clinical practice.

References

1. Evans WE, McLeod HL. Pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med* 2003;348:538–549.
2. Spear BB, Heath-Chiozzi M, Huff J. Clinical application of pharmacogenetics. *Trends Mol Med* 2001;7:201–204.
3. Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. *Bioethics* 2004;18:344–360.
4. Roses AD. Pharmacogenetics and the practice of medicine. *Nature* 2000;405:857–865.
5. Moldrup C. Ethical, social and legal implications of pharmacogenetics: a critical review. *Community Genet* 2001;4:204–214.
6. Wertz DC. Ethical, social, and legal issues in pharmacogenomics. *Pharamacogenomics J* 2003;3:194–196.
7. Buchanan A, Califano A, Kahn J, McPherson E, et al. Pharmacogenetics: ethical issues and policy options. *Kennedy Inst Ethics J* 2002;12:1–15.
8. Robertson JA. Consent and privacy in pharmacogenetic testing. *Nat Genet* 2001;28:207–209.
9. Freud CL, Wilfond BS. Emerging ethical issues in pharmacogenetics: from research to clinical practice. *Am J Pharmacogenomics* 2002;2:273–281

10 Tsao MS, Sakurada A, Cutz JC, Zhu CQ, et al. Erlotinib in lung cancer—molecular and clinical predictors of outcome. *N Engl J Med* 2005;353:133–144.

11. Jackman DM, Yeap BY, Sequist LV, Lindeman N, et al. Exon 19 deletion mutations of epidermal growth factor receptor are associated with prolonged survival in non-small cell lung cancer patients treated with gefitinib or erlotinib. *Clin Cancer Res* 2006;12:3908–3914.

12. Higashi MK, Veenstra DL, Kondo LM, Wittkowsky AK, et al. Association between CYP2C9 genetic variants and anticoagulation-related outcomes during warfarin therapy. *JAMA* 2002;287:1690–1698.

13. Rieder MJ, Reiner AP, Gage BF, Nickerson DA, et al. Effect of *VKORC1* haplotypes on transcriptional regulation and warfarin dose. *N Engl J Med* 2005;352:2285–2293.

14. Roche AmpliChip Package Insert. Available at: http://www.amplichip.us/documents/AmpliChip_CYP450_Test_Package_Insert.pdf.

15. Genelex's drug reaction testing panel. Available at: http://www.healthanddna.com/drugreactiontest.html.

16. Food and Drug Administration. Table of valid genomic biomarkers in the context of approved drug labels. Available at: http://www.fda.gov/cder/genomics/genomic_biomarkers_table.htm.

17. Li J, Zhao M, He P, Hidalgo M, et al. Differential metabolism of gefitinib and erlotinib by human cytochrome P450 enzymes. *Clin Cancer Res* 2007;13:3731–3717.

18. Li J, Karlsson MO, Brahmer J, Spitz A, et al. CYP3A phenotyping approach to predict systemic exposure to EGFR tyrosine kinase inhibitors. *J Natl Cancer Inst* 2006;98:1714–1723.

19. Cobleigh MA, Vogel CL, Tripathy D, Robert NJ, et al. Multinational study of the efficacy and safety of humanized anti-HER2 monoclonal antibody in women who have HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. *J Clin Oncol* 1999;17:2639–2648.

20. Hirsch MS, Brun-Vezinet F, Clotet B, Conway B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society—USA Panel. *Clin Infect Dis* 2003;37:113–128.

21. Wilkie MJ, Smith D, Reid IC, Day RK, et al. A splice site polymorphism in the G-protein beta subunit influences antidepressant efficacy in depression. *Pharmacogenet Genomics* 2007;17:207–215.

22. Bagos PG, Elefsinioti AL, Nikolopoulos GK, Hamodrakas SJ. The GNB3 C825T polymorphism and essential hypertension: a meta-analysis of 34 studies including 14,094 cases and 17,760 controls. *J Hypertens* 2007;25:487–500.

23. Kiani JG, Saeed M, Parvez SH, Frossard PM. Association of G-protein beta-3 subunit gene (GNB3) T825 allele with type II diabetes. *Neuro Endocrinol Lett* 2005;26:87–88.

24. Lerman C, Jepson C, Wileyto EP, Epstein LH, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of two randomized clinical trials. *Neuropsychopharmacology* 2006;31:231–242.

25. Sasabe T, Furukawa A, Matsusita S, Higuchi S, et al. Association analysis of the dopamine receptor D2 (DRD2) SNP rs1076560 in alcoholic patients. *Neurosci Lett* 2007;412:139–142.

26. Sconce EA, Daly AK, Khan TI, Wynne HA, et al. APOE genotype makes a small contribution to warfarin dose requirements. *Pharmacogenet Genomics* 2006;16:609–611.

27. Gerdes LU, Gerdes C, Kervinen K, Savolainen M, et al. The apolipoprotein ϵ4 allele determines prognosis and the effect on prognosis of simvastatin in survivors of myocardial infarction. *Circulation* 2000;101:1366–1371.

28. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* 1993;261:921–923.

29. Stengard JH, Pekkanen J, Ehnholm C, Nissinen A, et al. Genotypes with the apolipoprotein epsilon4 allele are predictors of coronary heart disease mortality in a longitudinal study of elderly Finnish men. *Hum Genet* 1996;97:677–684.

30. Henrikson NB, Burke W, Veenstra DL. Ancillary risk information and pharmacogenetic tests: social and policy implications. *Pharmacogenomics J* 2008;8:85–89.

31. Freund CL, Clayton EW. Pharmacogenomic and children: meeting the ethical challenges. *Am J Pharmacogenomics* 2003;3:399–404.

32. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. American Society of Human Genetics Board of Directors, American College of Medical Genetics Board of Directors. *Am J Hum Genet* 1995;57:1233–1241.

33. Morley KI, Hall WD. Using pharmacogenetics and pharmacogenomics in the treatment of psychiatric disorders: some ethical and economic considerations. *J Mol Med* 2004;82:21–30.

34. ACP/ASIM Position paper. Pharmacist scope of practice. *Ann Intern Med* 2002;136:79–85.

35. Hinthorn DR, Generali JA, Godwin HN. Pharmacist scope of practice: response to position paper. *Ann Pharmacother* 2002;36:718–720.

36. Clemerson JP, Payne K, Bissell P, Anderson C. Pharmacogenetics, the next challenge for pharmacy? *Pharm World Sci* 2006;28:126–130.