Pharmacogenetics: Using Genetic Information to Guide Drug Therapy

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Clinical pharmacogenetics, the use of genetic data to guide drug therapy decisions, is beginning to be used for medications commonly prescribed by family physicians. However, clinicians are largely unfamiliar with principles supporting clinical use of this type of data. For example, genetic variability in the cytochrome P450 2D6 drug metabolizing enzyme can alter the clinical effects of some opioid analgesics (e.g., codeine, tramadol), whereas variability in the *CYP2C19* enzyme affects the antiplatelet agent clopidogrel. If testing is performed, patients who are ultrarapid or poor metabolizers of *CYP2D6* should avoid codeine use (and possibly tramadol, hydrocodone, and oxycodone) because of the potential for increased toxicity or lack of effectiveness. Patients undergoing percutaneous coronary intervention for acute coronary syndromes who are known to be poor metabolizers of *CYP2C19* should consider alternate antiplatelet therapy (e.g., ticagrelor, prasugrel). Some guidelines are available that address appropriate drug therapy changes, and others are in development. Additionally, a number of clinical resources are emerging to support family physicians in the use of pharmacogenetics. When used appropriately, pharmacogenetic testing can be a practical tool to optimize drug therapy and avoid medication adverse effects. (***Am Fam Physician*****. 2015;92(7):588-594. Copyright © 2015 American Academy of Family Physicians.)**

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Clinical pharmacogenetics determines whether individual differences in the expression of a protein or enzyme affect the metabolism of a drug. These effects may lead to changes in the levels of active or inactive metabolites, possibly warranting the use of a different drug or dose.[1] Family physicians are usually the first resource for patient questions about genetics; however, quick and accurate use of pharmacogenetic data in a clinical environment is challenging.[2] Patients have increasing interest in and access to their own genetic information, including pharmacogenetic data from direct-to-consumer genetic testing companies (e.g., 23andMe).[3] With pharmacogenetic information on the labels of more than 150 drugs approved by the U.S. Food and Drug Administration (FDA), family physicians should have some knowledge of how to find and apply this information.[4] *eTable A* lists resources for more information.

Few primary care physicians are comfortable ordering a pharmacogenetic test or interpreting test results,[5,6] often citing a general lack of education in this area.[6] This article presents recommendations for two well-studied gene-drug pairs to illustrate the type of information and evidence needed to apply pharmacogenetic data clinically.

Basics of Pharmacogenetic Variability and Terminology

Table 1 includes definitions of commonly used pharmacogenetic terms.[7] Much of the available and clinically relevant pharmacogenetic information stems from variations in genes that code for drug metabolizing enzymes (e.g., cytochrome P450 2C19 and clopidogrel [Plavix]), or those that alter a drug's ability to act in the body or the body's response to a drug (e.g., *VKORC1* and warfarin [Coumadin]). The most common type of genetic variation (or polymorphism) is a single nucleotide polymorphism. The presence of specific variants at certain single nucleotide polymorphisms or other polymorphisms can lead to different versions of a gene, or alleles. As with many other genetic traits, individuals usually inherit one allele from each parent. These inherited alleles govern expression of the gene and the corresponding enzyme or protein.[8]

Pharmacogenetics employs a "star allele" naming system for many genes, in which the normal or reference allele is referred to as wild type and given a designation of *1. A variant allele is usually designated with a * followed by a number other than one to distinguish it from other variants. For example, a patient who carries two wild-type alleles for *CYP2C19* would be designated as having a *CYP2C19*1/*1* genotype, which is associated with normal *CYP2C19* activity (this activity level is the patient's phenotype).[8]

This genetic variability leads to clinical effects when it changes how drugs are processed or activated in the body. For some genes and drugs, there is evidence to support an association between genetic variability and changes in drug levels or effects. For example, carriage of two reduced-function (or loss-of-function) *CYP2C19* alleles, such as *CYP2C19*2/*2*, is associated with poor metabolization and relatively low *CYP2C19* activity. Clopidogrel is a prodrug and requires activation by *CYP2C19* to become a bioactive drug. Therefore, patients with this "poor metabolizer" phenotype have reduced active clopidogrel metabolites and higher on-treatment platelet aggregation compared with carriers of *CYP2C19*1/*1*.[8,9]

Clinical Implications of Pharmacogenetic Testing

The Clinical Pharmacogenetics Implementation Consortium provides guidance on interpreting genetic test results.[10] Additional recommendations are available from the Dutch Pharmacogenetics Working Group and the Evaluation of Genomic Applications in Practice and Prevention working group, and disease-specific guidance is provided in guidelines from various professional associations.[11,12]

CYP2D6 AND OPIOIDS

Codeine and morphine exert their analgesic effects through interaction at the μ-opioid receptor. The affinity of codeine for this receptor is approximately 200-fold weaker than that of morphine.[13,14] As a result, codeine's analgesic properties primarily come from its bioactivation in the liver to morphine via the *CYP2D6* enzyme.[13,15]

CYP2D6 enzyme activity is highly variable because of single nucleotide polymorphisms

Table 1. Definitions of Common Pharmacogenetic Terms

Term	*Definition*
Allele	One of two or more versions of a gene; an individual inherits two alleles for each gene, one from each parent; if the two alleles are the same (e.g., *CYP2C19*1/*1*), the individual is homozygous for that gene; if the alleles are different (e.g., *CYP2C19*1/*2*), the individual is heterozygous
Gene	Basic physical and functional unit of heredity
Genotype	An individual's collection of genes
Pharmacogenetics (also called pharmacogenomics)	Study of how genes affect the way a person responds to medications; pharmacogenetics is being used to determine ahead of time the best drug or dose for an individual patient
Phenotype	Clinical presentation or observable characteristics of an individual with a particular genotype
Polymorphism	Natural variation in a gene, DNA sequence, or chromosome
Single nucleotide polymorphism	Type of polymorphism involving variation of a single base pair in the human genome
Star allele nomenclature	Common format used to represent variability of a specific gene; signified as gene symbol, *allele number/*allele number (e.g., *CYP2C19*1/*2*)

CYP = cytochrome P450.

Information from reference 7.

and other alterations of the *CYP2D6* gene.[13,14] In approximately 90% of patients, codeine metabolism by *CYP2D6* results in expected amounts of morphine formation. However, approximately 1% to 2% of patients are ultrarapid metabolizers, in whom the expected increased formation of morphine leads to a higher toxicity risk. Conversely, the approximately 5% to 10% of patients who are classified as poor metabolizers are at risk of insufficient pain relief with normal codeine dosages.[13]

A 2006 case report described the death of a breastfed infant of a mother taking codeine.[16] The mother was an ultrarapid *CYP2D6* metabolizer, and the infant's death was attributed to opioid toxicity secondary to morphine excretion into breast milk. Childhood deaths with normal codeine dosages have been attributed to *CYP2D6* polymorphism and resulted in an FDA warning against codeine use for postoperative pain control in children undergoing tonsillectomy or adenoidectomy.[17] Adverse effects have also been reported in adults with variant *CYP2D6* metabolism.[18] FDA-approved prescribing information for codeine warns that even at approved dosages, persons who are ultrarapid metabolizers may have life-threatening or fatal respiratory depression or experience signs of overdose, including extreme sleepiness, confusion, and shallow breathing.[19]

Other opioids such as tramadol, hydrocodone, and oxycodone are also metabolized through *CYP2D6* to their active forms. Of these agents, evidence supporting clinically relevant effects of genetic variability is strongest with use of tramadol in poor metabolizers of *CYP2D6*. In patients undergoing abdominal surgery, those who were poor metabolizers were more likely to be nonresponsive to tramadol and required significantly more rescue pain medications postoperatively compared with non–poor metabolizers.[20,21]

Clinicians should consider *CYP2D6* testing in patients who have no response to codeine or tramadol (possible poor metabolizers) or who have unexpected adverse effects (possible ultrarapid metabolizers). Although evidence is limited, clinicians should keep in mind that hydrocodone and oxycodone may not be good alternatives in these patients because they are also activated by this enzyme.[13,22] Other factors that may influence optimal drug therapy choices need to be considered, such as concomitant use of drugs that inhibit *CYP2D6* (e.g., paroxetine [Paxil]) and risk factors for respiratory depression.[13] Numerous other drugs have also been associated with genetic variability in *CYP2D6* expression and altered clinical effects *(Table 2)*.[9,13,23-30]

CYP2C19 AND CLOPIDOGREL

Clopidogrel is a prodrug that is activated in the liver to exert its antiplatelet effects by a two-step process that largely involves the *CYP2C19* enzyme.[31] The *CYP2C19* gene is highly polymorphic, with many variations occurring naturally. Most patients (up to 80%) have normal *CYP2C19* activity based on their genotype, but approximately 18% to 45% and 2% to 15% of patients have intermediate or poor *CYP2C19* enzyme activity, respectively.[9,31]

Clopidogrel-induced inhibition of platelet aggregation varies widely among different patient groups. This variable response has been linked in part to genetic alterations in the *CYP2C19* enzyme function.[9] A number of studies have documented decreased formation of active clopidogrel metabolites and higher on-treatment platelet aggregation in patients who carry one or two copies of a reduced-function *CYP2C19* allele.[31-34]

Although clopidogrel has numerous uses, *CYP2C19* genetic variability has been linked to adverse clinical outcomes primarily in patients undergoing percutaneous coronary intervention for acute coronary syndromes.[9,31,35] Meta-analyses have found that patients undergoing percutaneous coronary intervention for acute coronary syndromes who are poor *CYP2C19* metabolizers (carriers of two reduced-function alleles) and taking clopidogrel have a significantly increased risk of a composite outcome of cardiovascular death, myocardial infarction, or stroke (hazard ratio = 1.76; 95% confidence interval, 1.24 to 2.50; $P = .002$) or stent thrombosis (hazard ratio = 3.97; 95% confidence interval,

Table 2. Interpreting Pharmacogenetic Test Results for Selected Medications Used in Family Practice

Allele	*Medications*	*Test results* and clinical implications†*	*Comments*
Pain			
CYP2D6	Codeine, hydrocodone, oxycodone, tramadol	Ultrarapid metabolizer: Avoid codeine because of potential for toxicity[13,23] Poor metabolizer: Avoid codeine and possibly tramadol because of possible lack of effectiveness[13,23]	CPIC guidance limits genotype-guided dosing recommendations to codeine.[13] Alternative analgesics not affected by *CYP2D6* variability include morphine, oxymorphone, and nonopioid analgesics.[13] Oxycodone may also have reduced effectiveness in poor *CYP2D6* metabolizers.[11,13,23]
Cardiovascular (percutaneous coronary intervention)			
CYP2C19	Clopidogrel (Plavix)	Intermediate metabolizer: Use alternative antiplatelet therapy if no contraindications[9] Poor metabolizer: Use alternative antiplatelet therapy if no contraindications[9]	Clopidogrel prescribing information states that *CYP2C19* tests can be used as an aid to determine therapeutic strategy in patients with acute coronary syndromes who are undergoing percutaneous coronary intervention.[24] CPIC guidance limits genotype-guided dosing recommendations to patients undergoing percutaneous coronary intervention for acute coronary syndromes (excluding medical management of acute coronary syndromes, stroke, and peripheral artery disease).[9] ACCF/AHA guidelines state that genotyping may be considered in patients with unstable angina/non-ST segment elevation myocardial infarction (or after percutaneous coronary intervention for acute coronary syndromes) if test results could alter management.[25] Alternative antiplatelet therapy not affected by *CYP2C19* variability includes prasugrel (Effient) and ticagrelor (Brilinta).[9]
Depression/psychiatry			
CYP2C19	Amitriptyline	Poor metabolizer: Consider 50% reduction in recommended starting dose[26]	CPIC guidance is available for *CYP2D6*- and *CYP2C19*-genotype guided tricyclic antidepressant therapy.[26] Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline (Pamelor).[26]
CYP2C19	Citalopram (Celexa), escitalopram (Lexapro)	Ultrarapid metabolizer: Consider alternative Poor metabolizer: Consider 50% starting dose reduction and titrate to response, or use alternative[27]	CPIC guidance is available for *CYP2C19*-genotype guided citalopram and escitalopram therapy.[27] FDA label for citalopram states that 20 mg per day is the maximum recommended dosage for patients older than 60 years, patients with hepatic impairment, and *CYP2C19* poor metabolizers or patients taking cimetidine (Tagamet) or another *CYP2C19* inhibitor.[28]

continues

1.75 to 9.02; $P = .001$).[9,35,36] Conversely, meta-analyses show no clinical benefit for testing patients with lower clinical risks (e.g., clopidogrel use in atrial fibrillation).[9,35,37,38] In 2010, the FDA added a boxed warning to the clopidogrel drug label about higher rates of cardiovascular events in patients undergoing percutaneous coronary intervention for acute coronary syndrome who are poor metabolizers of *CYP2C19*, compared with patients who have normal *CYP2C19* function, and recommended that clinicians consider alternative treatments in these patients."[24]

Physicians should consider *CYP2C19* testing to guide antiplatelet therapy selection in patients undergoing percutaneous coronary intervention for acute coronary syndromes.[9] When evaluating the expected response to clopidogrel, clinicians should keep in mind other factors that may affect clopidogrel response and/or clinical outcomes. These factors include underlying risk factors (e.g., diabetes mellitus, age) and concomitant medications (e.g., omeprazole [Prilosec], a *CYP2C19* inhibitor).[9,25]

Considerations in Ordering and Using Pharmacogenetic Tests

CLINICAL UTILITY AND PRACTICE-BASED RESOURCES

Although a randomized controlled trial is the preferred method for establishing

Table 2. Interpreting Pharmacogenetic Test Results for Selected Medications Used in Family Practice
(continued)

Test	*Medications*	*Test results* and clinical implications†*	*Comments*
Depression/psychiatry			
CYP2C19	Sertraline (Zoloft)	Ultrarapid metabolizer: If patient does not respond to recommended dose, consider alternative Poor metabolizer: Consider 50% dose reduction or alternative[27]	CPIC guidance is available for *CYP2C19*-genotype guided sertraline therapy.[27]
CYP2D6	Amitriptyline, nortriptyline	Ultrarapid metabolizer: Avoid because of possible lack of effectiveness[26] Poor metabolizer: Avoid because of possible adverse effects; if use is warranted, consider 50% reduction in recommended starting dose[26]	CPIC guidance is available for *CYP2D6*- and *CYP2C19*-genotype guided tricyclic antidepressant therapy.[26] Although limited data exist for other tricyclic antidepressants, most supporting evidence of clinically relevant gene-drug effects is for amitriptyline and nortriptyline.[26]
CYP2D6	Aripiprazole (Abilify)	Poor metabolizer: Decrease dose[29]	Quality of supporting evidence is classified as low by PharmGKB.‡ FDA label for aripiprazole states that in poor metabolizers, the usual dose should initially be reduced to 50% and then adjusted to achieve a favorable clinical response; in poor metabolizers receiving a strong *CYP3A4* inhibitor, the usual dose should be reduced to 25%.[29]
CYP2D6	Atomoxetine (Strattera)	Poor metabolizer: Adjust dose[30]	Quality of supporting evidence is classified as moderate (Level 2a) by PharmGKB.‡ FDA label for atomoxetine states that in poor metabolizers, the initial dosage should be 0.5 mg per kg per day and then increased to the the usual target dosage of 1.2 mg per kg per day only if symptoms do not improve after 4 weeks and the initial dose is well tolerated.[30]
CYP2D6	Paroxetine (Paxil)	Ultrarapid metabolizer: Select alternative because of possible lack of effectiveness. Poor metabolizer: Select alternative or if use is warranted, consider 50% starting dose reduction[27]	CPIC guidance is available for *CYP2D6*-genotype guided paroxetine therapy.[27]

ACCF/AHA = American College of Cardiology Foundation/American Heart Association; CPIC = Clinical Pharmacogenetics Implementation Consortium; CYP = cytochrome P450; FDA = U.S. Food and Drug Administration; PharmGKB = Pharmacogenomics Knowledgebase.

**—The format for reporting pharmacogenetic test results varies by laboratory and institution. Complete information on interpreting test results, including other genotypes associated with each metabolizer phenotype, is available in CPIC guidelines for each gene-drug pair (available at http://www.pharmgkb.org/page/cpic or from the reference laboratory).*

†—Dosing guidance is supported by CPIC guidelines and FDA prescribing information. If CPIC guidelines are unavailable, the quality of evidence supporting clinically relevant effects of genetic variability as rated by the PharmGKB is provided.

‡—PharmGKB evidence levels are defined at https://www.pharmgkb.org/page/clinAnnLevels.

Information from references 9, 13, and 23 through 30.

utility of a new drug, there are challenges in designing and executing these trials for pharmacogenetic testing.[39-42] Clinical use of pharmacogenetic testing is based largely on observational and retrospective trials conducted in targeted patient populations. Although proponents of pharmacogenetic testing cite challenges in demonstrating the benefit of an intervention that largely benefits patient outliers (e.g., poor metabolizers, nonresponders), the lack of supporting randomized controlled trials remains a limitation in the clinical adoption of these tests.[10,40,41,43,44]

ORDERING AND REIMBURSEMENT

Although availability varies, *CYP2D6*, *CYP2C19*, and other pharmacogenetic tests can be used as stand-alone tests or within broader pharmacogenetic panels. Further

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Codeine should be avoided in *CYP2D6* ultrarapid metabolizers because of the potential for toxicity.	C	13, 23	Consensus guideline based on observational studies and case reports
Codeine, and possibly tramadol, should be avoided in *CYP2D6* poor metabolizers because of possible lack of effectiveness.	C	13, 23	Consensus guideline based on observational studies
In poor *CYP2C19* metabolizers who are undergoing percutaneous coronary intervention for acute coronary syndromes, ticagrelor (Brilinta) or prasugrel (Effient) should be considered as an alternative to clopidogrel (Plavix) for antiplatelet therapy.	B	9, 36, 37	Consensus guideline based on observational studies; meta-analyses of observational studies show conflicting results

CYP = cytochrome P450.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.

information on test availability and ordering is available through the National Institutes of Health Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/) and the Pharmacogenomics Knowledgebase (https://www.pharmgkb.org/). Because clinical reimbursement rates vary, clinicians should consider contacting the laboratory or the patient's insurance provider for details before ordering.

Data Sources: A PubMed search was completed in Clinical Queries using the key terms pharmacogenetic, pharmacogenomic, *CYP2D6*, and *CYP2C19*. The search included clinical trials, randomized controlled trials, systematic reviews, and guidelines. We also searched the National Guideline Clearinghouse database, the Agency for Healthcare Research and Quality evidence reports, DynaMed, and UpToDate. Search dates: September 15, 2014, and June 8, 2015.

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eTable A. Resources for More Information About Clinical Pharmacogenetics

Resource	*Comments*
American Family Physician — AFP By Topic http://www.aafp.org/afp/topicModules/viewTopicModule.htm?topicModuleId=56	Collection of previously published content related to genetics, including pharmacogenetics
American Medical Association http://www.ama-assn.org/ama/pub/physician-resources/medical-science/genetics-molecular-medicine/current-topics/pharmacogenomics.page	Overview of pharmacogenetics
Clinician-focused content from health systems or educational institutions engaged in clinical pharmacogenetics: Duke Center for Personalized and Precision Medicine http://dukepersonalizedmedicine.org Mayo Clinic Center for Individualized Medicine http://mayoresearch.mayo.edu/center-for-individualized-medicine/ St. Jude Children's Research Hospital http://www.stjude.org/pg4kds University of Florida Health Personalized Medicine Program (includes SNP•its, a clinician focused pharmacogenetics e-newsletter) http://www.personalizedmedicine.ufhealth.org Vanderbilt Medical Center http://www.pharmacogenomics.mc.vanderbilt.edu/	Various resources, including educational tools, presentations, patient education materials, and descriptions of the clinical use of gene-drug pair information
Evaluation of Genomic Applications in Practice and Prevention http://www.egappreviews.org/default.htm	Primarily focused on genomic medicine implementation; evidence reports for a limited number of pharmacogenetic gene-drug pairs
Genetics/Genomics Competency Center http://g-2-c-2.org	Categorized educational resources in genetics/genomics and pharmacogenetics for health care educators and clinicians
Global Genetics and Genomics Community http://g-3-c.org/en	Online learning portal, including interactive cases demonstrating the link between genetics and genomics and health
National Human Genome Research Institute http://www.genome.gov	Information for health care professionals and patients on genetics and pharmacogenetics, including terminology, videos, and illustrations
Pharmacogenomics Knowledgebase http://www.pharmgkb.org/	Database of research findings about the impact of genetic variation on drug response for clinicians; links to other subspecialty society guideline recommendations (e.g., Dutch Pharmacogenetics Working Group); the Clinical Pharmacogenetics Implementation Consortium (http://www.pharmgkb.org/page/cpic) provides free peer-reviewed guidelines with supplemental information and updates