Pharmacogenomic Testing in Clinical Practice

GENETWORx

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Learning Objectives

1. Identify the areas of current and future potential applications of pharmacogenomics to tailor medication therapy.
2. Describe the impact of the following drug metabolizing phenotypes – extensive metabolizer, intermediate metabolizer, poor metabolizer, and ultra-rapid metabolizer – on medication efficacy and toxicity for both regular substrates and prodrugs.
3. Apply pharmacogenomic test results in a patient case to recommend appropriate doses for affected medications.
4. Predict the impact of a CYP450 inhibitor and inducer on metabolic capability of each metabolizing phenotype for both regular and prodrug substrates.

Introduction

Completed in April 2003, the Human Genome Project gave us the ability to, for the first time, to read nature's complete genetic blueprint for human beings. Since the completion of this project, the science of pharmacogenomics, the study of how an individual's genetic inheritance affects the body's response to medications, has made enormous advances. Pharmacogenomics combines traditional pharmaceutical sciences with knowledge of genes, proteins, and single nucleotide polymorphisms. Inherited variation in genes for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways can have major effects on the efficacy or toxicity of a drug. The focus of this program is the use of individual pharmacogenomic tests in clinical practice.

Pharmacogenomics holds the promise that medications will one day be tailor-made for individuals and adapted to each person's own genetic makeup. Environment, diet, age, lifestyle, other concurrent medications, and state of health all can influence a person's response to medicines, but understanding an individual's genetic makeup is thought to be the key to creating personalized medications with greater efficacy and safety.

Definitions

Before embarking on a discussion of pharmacogenomic testing, a few definitions are in order. These are presented below.[1] For additional background reading on genetics in general, genetic testing to identify disease, and pharmacogenomic testing refer to the resource listing at the end of this document.

- **Genetics** is the study of heritable biological variation. In the health-care setting, this concerns heritable variation that is related to health and disease.
- **Genomics** is the study of the constitution of entire genomes, that is, all of the genetic material in an organism.
- The **genotype** is the coding sequence of DNA base pairs for a particular gene.

- The **phenotype** is the expression of the genotype (e.g., disease or drug response) through the production of protein gene products. The general drug metabolizing phenotypes are poor, intermediate, extensive (normal), and ultra-rapid.
- **Personalized Medicine** refers to the use of genetic or other molecular biomarker information to improve the safety, effectiveness, and health outcomes of patients by risk stratification, prevention, and tailored management approaches.
- **Pharmacogenomics** refers to the general study of all of the many different genes that determine drug behavior.
- **Pharmacogenetics** refers to the study of inherited variation in drug metabolism and response.

Is there a difference between pharmacogenomics and pharmacogenetics?
The distinction between the two terms is considered arbitrary and the two terms are used interchangeably. The term pharmacogenomics will be used for this discussion.

- **Companion diagnostics** are tests used to help health care professionals determine whether a patient with a particular disease or condition should receive a particular medication therapy or how much to give. These may or may not be pharmacogenomic tests. Companion diagnostics are often being developed or identified during drug discovery by a drug manufacturer. Approval for the diagnostic is sought from the FDA in conjunction with the new drug approval.
- **Polymorphism** is an inter-individual variation within the human genome. In pharmacogenomics, the term is used to describe certain point mutations (changes in nucleotide sequence) in the genotype, which alter gene product function in carriers.
- **Single nucleotide polymorphism (SNP)** is a DNA sequence variation where a single nucleotide (A, T, C, or G) in the genome sequence is altered and is commonly referred to as "snip". About 80% of genetic variation in humans is accounted for by SNPs. SNP nomenclature is explained below:

  CYP2C19 681 G > A

  - The first few letters/numbers identify the gene (e.g., *CYP2C19*). The *CYP2C19* gene encodes for the CYP2C19 enzyme
  - Numbers following the gene indicate the nucleotide on the gene.
  - The first letter represents the original (or wild type) nucleotide.
  - The second letter represents the nucleotide that has changed to result in the SNP.

  rs4986893

  - The "rs" naming system is used in the SNP database (dbSNP), a database for all genetic variation information
  - Recommended by Human Genome Variation Society to be the standard nomenclature for SNPs
  - This SNP is the same as *CYP2C19* 636 G > A
- **Allele** is one of two or more forms of a gene. For example with CYP2C19, there are 28 known alleles. Alleles may result in functional, dysfunctional, or nonfunctional enzymes or proteins. Allele nomenclature is explained below:

CYP2C19*1

- The first few letters/numbers identify the gene (e.g., CYP2C19).
- The * (star) and number after the gene designate the allele (e.g., *1). Note: *1 is always the wild type (normal function).

- **Allelic variants** are alleles having one or more SNPs and are typically numbered sequentially (e.g., CYP2C19*2, CYP2C19*3, etc).
- **Haplotype** is a set of SNPs on a single chromosome of a chromosome pair that is statistically associated. An example is VKORC1*B/*B.
- **Homozygote** is a patient with two copies of the same allele. An example designation is CYP2C19*3/*3.
- **Heterozygote** is a patient with two different alleles. An example is CYP2C19*3/*1.
- **Cytochrome P450 superfamily** is a large and diverse group of enzymes that catalyze the oxidation of organic substances (lipids, steroidal hormones, medications and toxic chemicals). This superfamily is named on the basis of their cellular (cyto) location and spectrophotometric characteristics (chrome); these enzymes absorb light at wavelengths near 450 nm.

Use of Pharmacogenomic Tests

Pharmacogenomics can play an important role in maximizing effectiveness and minimizing toxicity, minimizing pharmacokinetic and pharmacodynamic variability of drug therapy, avoiding adverse events, avoiding unnecessary treatment, and optimizing dose. Information provided through these tests can be predictive to help providers choose the right medication and dosage for individual patients.

An additional use of pharmacogenomics includes drug development. Pharmaceutical companies are discovering potential therapies more easily using genome targets. Previously failed drug candidates may be revived as they are matched with the niche population they serve. The drug approval process could be enhanced as trials are targeted for specific genetic population groups. Targeting only those persons capable of responding to a medication will reduce the cost and risk of clinical trials.[2]

An interesting use of pharmacogenomics is in forensic toxicology.[3] Pharmacogenomics can be used postmortem in cases of incongruence between dose and plasma drug concentrations of a suspected medication to verify cause of death.

Certain aspects of pharmacogenomics have been around for decades. For example, through trial and error of dosing and adverse reactions, it was discovered that patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency should avoid certain medications due to the risk of hemolytic anemia. These include chloroquine, aspirin, nalidixic acid, nitrofurantoin, isoniazid, dapsone, and furazolidone.[4]

Clinical studies are now showing a wide range of benefits from pharmacogenomic testing. For example, a large prospective study evaluating the clinical utility of pharmacogenomics

showed a reduction in hospitalization rates by nearly a third when genetics are used to tailor warfarin therapy.[5] Another benefit will likely be reduced emergency room and other health care visits related to adverse effects.

An emerging benefit of pharmacogenomic testing is improved medication adherence and persistence. Arming patients with their genetic information may provide a unique way to change behavior. In one study (AKROBATS), patients who were informed of their KIF6 (a predictor of statin response) test results had significantly higher overall adherence to their statin treatment as measured by the proportion of days with medication on hand over a six-month period (77 percent of days covered versus 68 percent). They were also 83 percent more likely to be persistent, meaning they stayed on their statin therapy for the full six months.[6] More studies like this are under way.

Currently, the costs of pharmacogenomic testing are significant, but with new technology (next generation sequencers) testing costs are expected to dramatically decline. When considering costs, the fact that pharmacogenomic testing only has to be done once in a lifetime compared with other risk factor or disease management testing such as hemoglobin A1C testing in diabetes needs to be understood. Additionally, the results for one test can have implications for many medications. The cost effectiveness data currently available on this type of testing do not yet prove cost savings because of the elevated costs of the tests and limited outcomes data on selecting therapy or doses based on the test results.

Overall for patients, the benefits of pharmacogenomics are more effective disease treatment and management; better, safer medications the first time; more accurate determination of appropriate dosages; and the potential for decreased overall cost of health care. For providers, there are also numerous benefits including increased confidence with difficult to dose medications, decreased titration times, evidence to make the best medication choice in a therapeutic class, decreased overall health care cost for patients and their insurers, and decreased side effects to encourage better medication adherence and persistence in patients.

Caveats to Pharmacogenomic Testing

Although we can identify certain genetic variations within a given individual, it is important to realize that many medications are metabolized to varying degrees by more than one pathway, either within or outside of the Cytochrome (CYP) P450 enzyme system. In addition, interaction between different metabolizing genes, interaction of genes and environment, and interaction between different non-genetic factors also influence metabolizing functions. Identification of a variant in a single gene in the metabolic pathway may be insufficient to explain inter-individual differences in metabolism and consequent efficacy or toxicity.

FDA Labeling

The FDA has added black box warnings and other labeling to numerous medications stressing the importance of genetic information in determining patient benefit. The labeling may describe genetically related:

- Drug exposure and clinical response variability
- Risk for adverse events
- Genotype-specific dosing
- Mechanisms of drug action
- Polymorphic drug target and disposition genes

Only a few product labels incorporate genotype specific dosing but those that do are noted when a relevant test is discussed. For the most up-to-date list of genetic information labeling, please consult: http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ Pharmacogenetics/ ucm083378.htm

Biological Sample Used for Testing

At this time, DNA for pharmacogenomic testing can obtained from a blood, tissue, or buccal cell sample. With regulations related to blood samples and lack of personnel trained to collect the sample, some of the tests are not practical for certain practice settings such as a pharmacy or patient home. For settings already collecting blood samples, integration of this type of testing would be simple. The buccal cell sample tests, which utilize a cheek swab, lend themselves to easy collection at any point of care (pharmacy, physician's office, emergency room, health screening event). As technology evolves with next generation sequencers, most of these tests will only require a cheek swab.

Cytochrome P450 Tests

The CYP450 enzyme system are the major enzymes involved in drug metabolism and bioactivation, accounting for about 85-95% of total drug metabolism.[7,8] Although there are 270 different known CYP450 families, the table below lists the families that are important for drug metabolism.

Table 1: Selected Cytochrome P450 Enzymes	
CYP1 family	CYP1A1, CYP1A2, CYP1B1
CYP2 family	CYP2A6, CYP2A13, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2F1, CYP2J2, CYP2R1, CYP2S1, CYP2W1
CYP3 family	CYP3A4, CYP3A5, CYP3A7, CYP3A43
Reference: 9	

In a poll conducted by the American Association for Clinical Chemistry, five Cytochrome P450 genes (CYP2D6, CYP2C9, CYP2C19, CYP2B6, and CYP3A5) were identified among the top 10 pharmacogenomic tests.[10] Each of these and CYP3A4 are discussed in subsequent sections. For information on the other CYP450 enzymes, the reader should consult one of the resources listed at the end.

Polymorphisms in CYP450 genes can lead to altered drug metabolism action. Depending on the inherited alleles, an individual can be classified as ultra efficient or rapid, efficient or normal, intermediate, or poor metabolizers. If patients have a less active or inactive form of CYP450 enzymes, they are unable to inactivate and efficiently eliminate a medication from the body (i.e., poor or intermediate metabolizer), which can cause increased concentrations that lead to severe adverse events or overdose. On the other hand, patients with very active forms of CYP450 enzymes (i.e., ultra-rapid metabolizers) can cause the body to eliminate a medication too rapidly.

Table 2: Phenotype and Genotype

Phenotype	Genotype
Extensive metabolizer (EM)	An individual carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced-function allele. The "normal" metabolizer or "wild" genotype has two fully functional alleles.
Intermediate metabolizer (IM)	An individual carrying one reduced and one nonfunctional allele for a particular enzyme
Poor metabolizer (PM)	An individual carrying no functional alleles for a particular enzyme
Ultra-rapid metabolizer (UM)	An individual carrying two copies of super functional alleles or extra copies of a functional allele

Effects of activity of the CYP450 enzymes will vary with medication. If a medication requires metabolism to be activated (prodrug), then someone with reduced or absent (i.e., IM or PM) metabolism would have lower concentrations of effective medication. Effects will also vary if inducers or inhibitors of that particular CYP450 enzyme are present.

CYP2C19

CYP2C19 is involved in phase I metabolism. Like other P450 enzymes, CYP2C19 performs hydroxylation, demethylation, and dealkylation of various substrates. It metabolizes approximately 10 to 15 % of all medications and variant alleles are common.[11] At least 28 alleles have been described with many subtypes and uncharacterized SNPs also described.[9] The various allelic variations of a CYP450 family are named sequentially with *1 always designating the so-called wild type or normal version. Thus, the CYP2C19 wild type allele is named CYP2C19*1 and so on through the 28 different variations.

Alleles CYP2C19*2 and CYP2C19*3 produce nonfunctional enzymes. A patient would be a poor metabolizer (PM) if they inherit two nonfunctional alleles (CYP2C19*3/*3). An

extensive metabolizer (EM) is an individual having at least one functional allele (e.g., CYP2C19*1/*2). CYP2C19*17 produces an enzyme that is super functional thus the person with this allele is termed an ultrametabolizer (UM).

The frequencies for various CYP2C19 variants are described in **Table 3**.

Table 3: Clinically Significant CYP2C19 Variants

	Predicted phenotype	Enzyme Function	Caucasian	African American	Asian
CYP2C19*2	PM or IM	nonfunctional	15%	17%	30%
CYP2C19*3	PM or IM	nonfunctional	0.04%	0.04%	3-7%
CYP2C19*17	UM	↑	18%	26%	~1%

Other nonfunctional alleles (CYP2C19*4, *6, *7, *8, *9, and *10) occur at less than 1% incidence but also denote PM status.
PM, poor metabolizer; IM, intermediate metabolizer, UM, ultrametabolizer
References: 11, 12

Twenty four percent of the Caucasian non-Hispanic population, 18% of Hispanics, 33% of African Americans, and 50% of Asians carry at least one loss-of-function allele. Homozygous carriers, poor metabolizers (PM), make up 3 to 4% of the population.[13]

Many drugs are metabolized by more than one CYP450 enzyme, and this is especially true for CYP2C19, where it is often a secondary pathway. Nonetheless, for some medications, CYP2C19 is known to be the primary pathway, and these are noted in **Table 4**. Additionally, several medications are prodrugs that are activated by CYP2C19.

Important Note: Table 4 and all subsequent substrate tables list the known major medications metabolized by that particular pathway and marketed in the U.S. These are not intended to be all-inclusive lists.

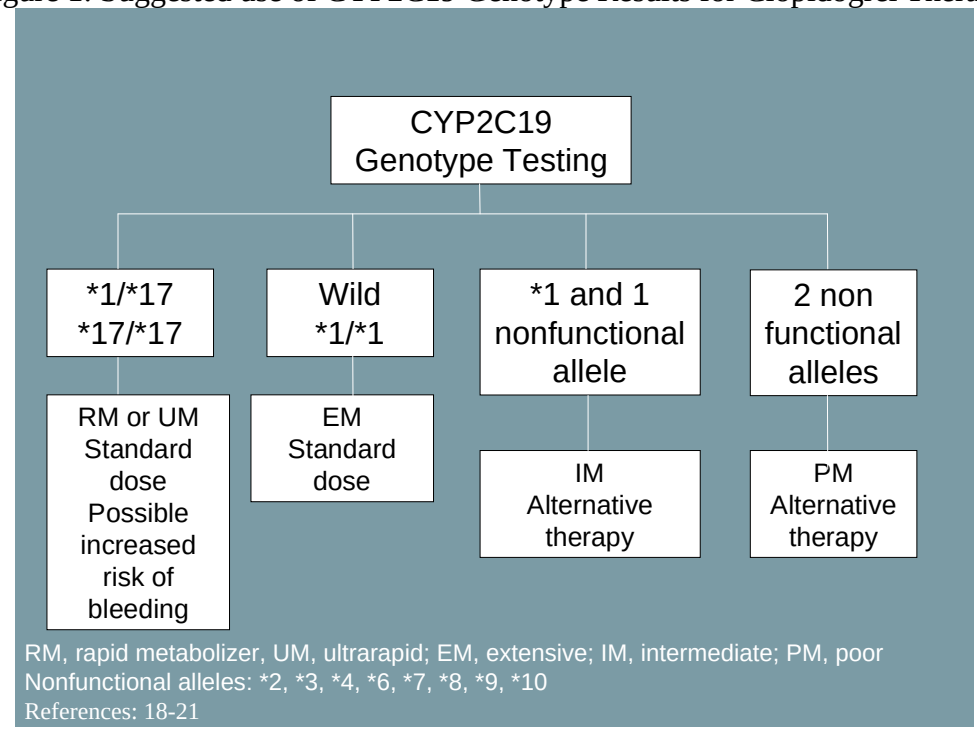
Table 4: Substrates for CYP2C19	
Amitriptyline	Nelfinavir
Aripiprazole	Nilutamide
Carisoprodol	Olanzapine
Chloramphenicol	Omeprazole [a]
Citalopram [a]	Pantoprazole [a]
Clomipramine	Pentamidine [a]
Clopidogrel [b]	Phenobarbital
Clozapine	Phenytoin
Cyclophosphamide [b]	Primidone
Desipramine	Progesterone
Diazepam [a]	Proguanil [a,b]
Doxepin	Propranolol
Escitalopram [a]	Rabeprazole
Fluoxetine	Sertraline [a]
Ifosfamide [b]	Thalidomide [a]
Imipramine	Teniposide
Indomethacin	Trimipramine
Lansoprazole	Voriconazole
Methadone	R-Warfarin
Moclobemide [a]	
a – primary metabolic pathway b - prodrug References: 11, 14, 15	

Clopidogrel (Plavix®)

The CYP2C19 gene is important in clopidogrel response as conversion of clopidogrel to its active metabolite depends principally on this enzyme. Carriers of at least one loss-of-function allele (PM and IM) have reduced plasma exposure to the active metabolite and a reduced platelet aggregation response as compared with noncarriers. Poor metabolizers treated with clopidogrel at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.[16,17] Patients with ultra-rapid metabolism have enhanced platelet inhibition with standard doses of clopidogrel but may be at increased risk for bleeding. Some sources classify both *17/*17 and *1/*17 as being ultra-rapid (UM) genotypes. Others label *1/*17 as a rapid metabolizer.

Therapy adjustments of clopidogrel based on CYP2C19 genotype test results are given in **Figure 1**.[18-21]

Figure 1: Suggested use of CYP2C19 Genotype Results for Clopidogrel Therapy



An appropriate dose regimen for the PM patient population has not been established in clinical outcome trials. Thus for the PM patient who is going to be treated with an antiplatelet agent, prasugrel (Effient®) is an alternative. For prasugrel, common functional CYP450 genetic variants in CYP2C19, CYP2C9, CYP2B6, CYP3A5, and CYP1A2 do not affect active drug metabolite levels, inhibition of platelet aggregation, or clinical cardiovascular event rates in persons treated with this agent.[22] However, it may not be a substitute for clopidogrel in all patients because of a higher associated risk of bleeding including fatal bleeding.

On March 12, 2010, the US Food and Drug Administration (FDA) added a boxed warning clopidogrel labeling alerting patients and health care professionals that the drug can be less effective in people who cannot metabolize it to its' active form.[23]

Proton Pump Inhibitors

CYP2C19 polymorphisms have been inconsistently associated with the efficacy of proton pump inhibitor (PPI)-based triple therapy for eradicating *Helicobacter pylori* infection.[24] Cure rates of *Helicobacter pylori* infection appear to be higher in poor metabolizers compared to heterozygous or homozygous extensive metabolizers because the poor metabolizers have higher serum concentrations of the PPIs resulting in lower stomach pH.[25-27] For omeprazole, lansoprazole, dexlansoprazole, and pantoprazole, plasma concentrations can increase 5 times

or higher in the PM phenotype compared with the EM phenotype.[28] For esomeprazole, the ratio of area under the curve (AUC) in PMs to AUC in EMs is approximately two fold.[28]

Using CYP2C19 genetic status to adjust doses can lead to better eradication rates. In one study, eradication rates following initial treatment were 96% in the pharmacogenomics-based treatment versus 70% in the standard therapy group ($p<0.001$).[29] When analyzed according to genetic status, the improvement in eradication rates in the pharmacogenomics group was greater for EM/UM patients (100% vs. 58%) and IM patients (95% vs. 72%), compared to PM patients (91% vs. 91%).

Patients with the CYP2C19*17/*17 ultrametabolizer phenotype are likely to fail therapy without dosage adjustments for most of the PPIs (see **Table 5**). Dosage adjustments are recommended for the UM phenotype but not for the PM, IM or EM phenotypes. It is important to remember that omeprazole and esomeprazole also inhibit the actions of CYP2C19.[30] There are conflicting data whether the other PPIs significantly inhibit CYP2C19 action.[14]

The clearance of rabeprazole is largely nonenzymatic and less dependent on CYP2C19 than other drugs in the PPI class.[28] Thus, rabeprazole is an alternative PPI for patients with the UM phenotype.

Table 5: Proton Pump Inhibitor Dose Adjustments Based on CYP2C19 Phenotype

	Percent of Standard Dose
Medication	**UM**
Esomeprazole	Helicobacter pylori eradication: increase dose by 50-100%. Be extra alert to insufficient response. Other indication: be extra alert to insufficient response. Consider dose increase by 50-100%.
Lansoprazole	Helicobacter pylori eradication: increase dose by 200%. Be extra alert to insufficient response. Other indication: be extra alert to insufficient response. Consider dose increase by 200%.
Omeprazole	Helicobacter pylori eradication: increase dose by 100-200%. Be extra alert to insufficient response Other indication: be extra alert to insufficient response. Consider dose increase by 100-200%
Pantoprazole	Helicobacter pylori eradication: increase dose by 400%. Be extra alert to insufficient response Other: be extra alert to insufficient response. Consider dose increase by 400%
Dexlansoprazole	No dosing recommendations have been published. This R isomer of lansoprazole is metabolized by CYP2C19 and results in significantly elevated serum levels in PM and IM patients. Be alert for insufficient response in UM patients and consider dose increase.
No dosage adjustments are recommended for PM, IM or EM phenotype References: 28, 31	

Antidepressants

Up to 60% of depressed patients do not respond completely to antidepressants and up to 30% do not respond at all. [32] Genetic factors are thought to contribute to 50% of the antidepressant response.[32] CYP2C19 and CYP2D6 are primary CYP450 enzymes involved in the metabolism of many selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. In addition to these two enzymes, many other factors which can be polymorphic have been identified as important to therapeutic response including P-glycoprotein (ABCB1), tryptophan hydroxylase, catechol-O-methyltransferase, monoamine oxidase A, serotonin transporter, norepinephrine transporter, dopamine transporter, variants in the 5-hydroxytryptamine receptors (5-HT1A, 5-HT2A, 5-HT3A, 5-HT3B, and 5-HT6), adrenoreceptor beta-1 and alpha-2, dopamine receptors, the G protein beta 3 subunit, the corticotropin releasing hormone receptors (CRHR1 and CRHR2), the glucocorticoid receptors, c-AMP response-element binding, and brain-derived neurotrophic factor.

Although the data are inconsistent, genetic polymorphisms of CYP2C19 and CYP2D6 appear to influence antidepressant treatment response.[32-38] Poor metabolizers exhibit a significantly lower level of depressive symptoms than extensive metabolizers but are at risk for concentration dependent adverse effects. Understanding a patient's CYP2C19 and CYP2D6 metabolizer status should be helpful in choosing an initial medication and dose that is most likely to be effective.

Recommendations for dose adjustments based on CYP2C19 and CYP2D6 phenotypes have been published (**Table 6**, see CYP2D6 section for those dose adjustments).[39] Alternative antidepressants for CYP2C19 PM, IM or UM phenotype patients include paroxetine and mirtazepam.

One antispychotic agent, clozapine, is primarily metabolized by CYP2C19. Dosing recommendations for this agent are included in **Table 6**.

Table 6: Psychiatric Medication Dose Adjustments Based on CYP2C19 Phenotype				
	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Antidepressants				
Amitriptyline	53-59	81-94	104-109	-
Citalopram	61	84	108	Max 150
Clomipramine	62-71	79-88	106-110	-
Doxepin	48	91	105	-
Escitalopram	-	-	-	Max 150
Fluoxetine	39	72	113	-
Fluvoxamine	93	97	101	-
Imipramine	70	83-91	105-108	-
Sertraline	50-75	90	105	-
Trimipramine	31-58	48-73	100-114	-
Antipsychotics				
Clozapine	78	91	104	-
- no data available These dosage adjustments are based on an analysis of published pharmacogenomic studies with these medications. References: 31, 39				

CYP2C19 Related Adjustments For Other Medications

Recommendations for other medications metabolized by CYP2C19 are general. For poor metabolizers, the dose can be reduced by 20-60% of the standard dose. For IM, the lowest typically effective dose should be started. In the case of the IM, medications which inhibit this pathway should be avoided (see **Table 7**). An inhibitor can convert an IM individual into a PM. The UM patient may require a higher dose of a given medication. No more specific guidelines are available for how much to increase the dose.

In addition to clopidogrel, proguanil and cyclophosphamide are the other two known prodrugs which are metabolized to active compounds by CYP2C19.[14] No dosing recommendations related to CYP2C19 phenotypes have been published for these two agents but consideration should be given to avoiding them in PM patients because of possible lack of efficacy.

Induction of CYP2C19 activity by concomitant medications also has to be considered but there are currently no specific recommendations on dosage adjustments. An inducer may convert an IM to normal metabolism. Because a CYP2C19 PM has no functional enzyme activity, inducers and inhibitors will not have any effect.

Table 7: Effects on CYP2C19 Activity	
Inhibitors	
Chloramphenicol Cimetidine Delaviridine Efavirenz Esomeprazole Felbamate Fluoxetine Fluvoxamine [a] Fluconozole Indomethacin	Ketoconazole Lansoprazole[b] Modafinil Omeprazole Oxcarbazepine Pantoprazole[b] Probenicid Rabeprazole[b] Ticlopidine [a] Topiramate
Inducers	
Rifampin	Ginkgo biloba St John's Wort
a – potent inhibitor b-conflicting references, some list these as inhibitors, others do not References: 14, 30, 40	

Case Study

Mr P. is a 68-year-old male with a past medical history of hypertension, diabetes mellitus, seizures, and coronary artery disease. His current medications include lisinopril 20 mg daily, metoprolol 100 mg daily, felbamate 1200 mg/day, aspirin 81 mg daily, atorvastatin 80 mg daily, and metformin 1000 mg twice a day. He had an episode of acute chest pain and was admitted to the hospital for evaluation. After evaluation and follow-up, Mr. P's cardiologist recommends angioplasty and stent placement; hence, he will be started on an additional antiplatelet agent so pharmacogenomic testing for CYP2C19 variants is ordered.

Result	*Reference Range/Comment*
*CYP450 2C19 *17/*17*	*Ultra Rapid Metabolizer*

Based on his genetic information, would a standard 75 mg dose of clopidogrel be sufficient? He carries two super functional alleles which makes him an ultra-rapid metabolizer of medications predominately metabolized by CYP2C19. For clopidogrel, this means he should have improved platelet inhibition with a usual dose but this improved efficacy does increase his risk of bleeding.

Are there any complicating factors in predicting the impact of his genetics on clopidogrel efficacy and adverse effects? The complicating factor is the felbamate, which is an inhibitor of CYP2C19. Because he does not have a history of bleeding related conditions and he is taking an inhibitor, a standard dose should be acceptable. If he were to stop taking the felbamate, his bleeding risk would have to be reevaluated.

How might you explain the need for genetic screening to him and what does his finding mean? When first discussing the need for genetic testing, he needs to be reassured that he is only being screened to determine his likelihood of responding to a medication (clopidogrel). He will need to be assured that only genes involved in drug response are being screened and not his susceptibility to disease, inheritable risk factors, or other biomarkers. The discussion should include how genetic screening can help to save his life, decrease side effects and maybe save him money. His genetic screening results should be explained to him, such that he understands what they mean for clopidogrel efficacy and possible adverse effects. He also needs to understand that he can eliminate certain medications from his body faster than other people and may require higher than normal doses of some medications.

CYP2C9

CYP2C9 is the major CYP450 2C enzyme found in the human liver and is involved in the metabolism of several clinically important medications including phenytoin and warfarin, which both have narrow therapeutic ranges. In addition, this enzyme metabolizes nonsteroidal anti-inflammatory drugs (NSAID), angiotension receptor blockers (ARB), sulfonylureas, and torsemide. Approximately 15% of all medications are metabolized by CYP2C9 (**Table 8**).[11]

Table 8: Substrates for CYP2C9

Angiotensin II blockers	**NSAIDs**
Candesartan [a]	Flurbiprofen
Irbesartan [a]	Celecoxib [a]
Losartan [b]	Diclofenac
	Ibuprofen
Antidepressants	Indomethacin
Amitriptyline	Mefenamic acid [a]
Fluoxetine	Meloxicam
Sertraline	S-naproxen
	Piroxicam [a]
Hypoglycemics, oral	Valdecoxib
Chlorpropamide [a]	
Glimepiride [a]	**Other drugs**
Glipizide	Bosentan
Glyburide	Dapsone
Tolbutamide [a]	Fluvastatin
Nateglinide	Mestranol [b]
Rosiglitazone	Phenobarbital [a]
	Phenytoin
	Tetrahydrocannabinol
	Tamoxifen
	Torsemide
	S-Warfarin
	Valproic acid

a – primary metabolic pathway
b - prodrug
Reference: 11, 14, 41

Thirty-four different alleles have been identified for the CYP2C9 gene.[9] Three that have shown clinical importance are *2, *3, and *5. The CYP2C9*2 and *3 alleles result in significantly decreased CYP2C9 metabolic activity. This has been reported to be 50% and 90% decreases, respectively but the effect varies by medication.[42] For warfarin, CYP2C9*2 only produces 12% of the activity of the normal gene and CYP2C9*3 produces 5%.[43,44] Phenytoin metabolism is reduced by as much as a third in patients with at least one CYP2C9*2 or CYP2C9*3 allele. Like other CYP450 enzymes there are important interethnic differences in frequency (**Table 9**).

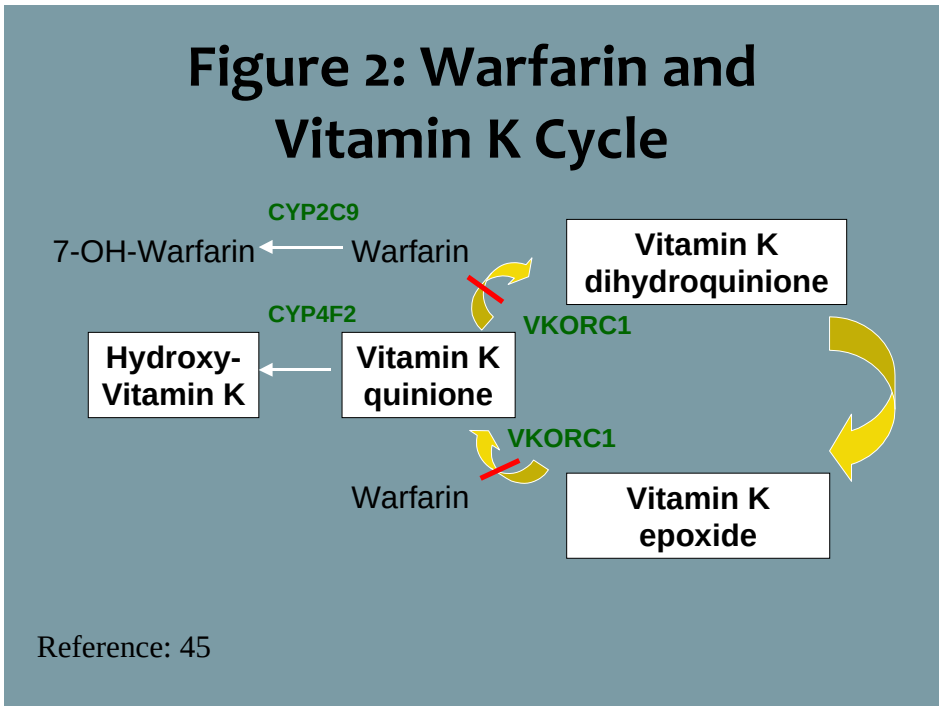
Table 9: Clinically Significant CYP2C9 Variants					
	Predicted phenotype	**Enzyme Function**	**Caucasian**	**African American**	**Asian**
CYP2C9*2	PM or IM	Altered affinity	13-22%	3%	0%
CYP2C9*3	PM or IM	↓	4-6%	1%	4%
CYP2C9*5	PM or IM	↓	0%	2%	0%
Other PM alleles (CYP2C9*4, *6, and *11) occur at less than 1% incidence but also denote PM status. PM, poor metabolizer; IM, intermediate metabolizer References: 11, 12					

Warfarin (Includes VKORC1 test)

Warfarin therapy is associated with significant complications because of its narrow therapeutic index and large interpatient dosage variation necessary to achieve an optimal therapeutic response. This variation is due to both genetic and environmental factors.

Warfarin is metabolized by CYP2C9 (**Figure 2** below).[45] Variants of CYP2C9 account for 10-15% of warfarin dosage variability. Individuals carrying certain variants in the CYP2C9 gene (CYP2C9*2, CYP2C9*3, CYP2C9*5, and CYP2C9*6) have reduced metabolism of warfarin, and those with 2 copies of variant alleles are at high risk of life-threatening side effects.

As shown in the figure, Vitamin K epoxide reductase complex subunit 1 (VKORC1) is the enzyme that activates Vitamin K. In humans, mutations in VKORC1 are associated with deficiencies in vitamin-K-dependent clotting factors. A particular VKORC1 variant (-1939G>A) leads to increased sensitivity to warfarin. VKORC1 mutation accounts for 25-44% of warfarin dose variability and is typically tested for at the same time as CYP2C9 when warfarin is being considered.[11]



VKORC1 and CYP2C9 polymorphisms, together with clinical factors, account for 50% to 60% of the variability in an individual's response to warfarin.[11] **Table 10** illustrates the distribution of poor warfarin metabolizer alleles by ethnicity.

Table 10: Distribution of Poor Metabolizer Alleles by Ethnicity			
Poor Metabolizer Allele	*Proportion Carrying Poor Metabolizer Allele, %*		
	Caucasians	African-Americans	Asians
VKORC1 -1639G>A	42	14	95
CYP2C9*2, *3, *5, or *6	35	3-13	2-8
References: 46, 47			

The prescribing information for warfarin (Coumadin) was updated in 2007 to include specific dose recommendations utilizing genetic information. These dosing guidelines based on CYP2C9 and VKORC1 are shown in **Table 11.**

Table 11: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Pharmacogenetic Results[a]						
VKORC1 Haplotype	**CYP2C9 Genotype**					
	*1/*1	*1 and *2, *4, *5, or *11	*1/*3, *1/*6	Any 2 of *2, *4, *5, *6, *11	*3 and *2, *4, *5, or *11	*3/*3 or *3/*6
*B/*B	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
*A/*B	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
*A/*A	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg
[a] Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the table. VKORC1 –1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 *1/*3, *2/*2, *2/*3, and *3/*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen. Reference: 48						

CYP2C9 Related Adjustments For Other Medications

For poor metabolizers, the initial dose of a medication predominately metabolized by CYP2C9 can be reduced by 20-60% of the standard dose. The few medications for which dosing adjustment guidelines have been published are included in **Table 12**. For IMs, the lowest typically effective dose should be started. For prodrugs such as losartan, which require activation by CYP2C9, an alternative agent or increased dose should be considered in IM and PM patients.

Table 12: Dose Adjustment Chart for IM and PM CYP2C9 Genotypes	
Glipizide and other sulfonylureas	**PM**: Reduce dose to 20 - 60% of standard dosages **IM**: Start at lowest efficacious dose, avoid multiple drug therapy that inhibits or activates through the same pathway.
Phenytoin (CYP2C19 status should also be considered)	**PM**: Standard loading dose. Reduce maintenance dose by **50%.** Evaluate response and serum concentration after 7-10 days. Be alert for adverse effects (e.g., ataxia, nystagmus, dysarthria, sedation). **IM**: Standard loading dose. Reduce maintenance dose by **25%.** Evaluate response and serum concentration after 7-10 days. Be alert for adverse effects.
Celecoxib	**PM**: Consider a dose reduction by 50% (or alternative management for Juvenile Rheumatoid Arthritis patients) in patients who are known or suspected to be PM.

Table 12: Dose Adjustment Chart for IM and PM CYP2C9 Genotypes	
Flurbiprofen	Labeling recommends, but does not require, genetic testing prior to initiating or reinitiating treatment. No guidelines on adjusting dose are given.
Fluvoxamine	Labeling recommends, but does not require, genetic testing prior to initiating or reinitiating treatment. No guidelines on adjusting dose are given.
References: 49-51	

In the case of the IM patient, medications which inhibit this pathway should be avoided (see **Table 13**). A moderate to potent inhibitor of CYP2C9 can essentially make an IM patient into a PM. Induction of CYP2C9 activity also has to be considered but there are currently no specific recommendations on dosage adjustments.

Table 13: Effects on CYP2C9 Activity	
Inhibitors	
5-Fluorouracil Amiodarone [b] Anastrozole Cimetidine Delavirdine Efavirenz Fenofibrate Fluconazole [a] Fluoxetine Fluvastatin Fluvoxamine Isoniazid	Ketoconazole Leflunomide Miconazole Modafinil Sertraline Sulfamethoxazole Tamoxifen Teniposide Valproic acid Voriconazole Zafirlukast
Inducers	
Aprepitant, long term Barbiturates Bosentan Carbamazepine	Rifampin Ritonavir St. John's Wort
a – potent inhibitor b – moderate inhibitor References: 14, 41	

CYP2D6

Like the other CYP2 family enzymes already discussed, CYP2D6 is highly polymorphic; in this case with 75 identified variant alleles.[9] **Table 14** lists the clinically significant variants. Interestingly, some people carry multiple copies (2-16) of the CYP2D6 gene (*1XN, *2XN) which makes them ultra-rapid metabolizers.[52]

Table 14: Clinically Significant CYP2D6 Variants

	Predicted phenotype	Enzyme Function	Caucasian	African American	Asian
CYP2D6*2XN	UM	↑	1-5%	2%	0-2%
CYP2D6*3	PM or IM	nonfunctional	1-2	0	<1
CYP2D6*4	PM or IM	nonfunctional	12-21	2-8	<1
CYP2D6*5	PM or IM	nonfunctional	2-7	6	4-6
CYP2D6*6	PM or IM	nonfunctional	1	<1	0
CYP2D6*10	PM or IM	↓	1-2	3-9	38-70
CYP2D6*17	PM or IM	↓	<1	20-35	<1
CYP2D6*41	PM or IM	↓	8-10	11-14	0-2
PM, poor metabolizer; IM, intermediate metabolizer; UM, ultra-rapid metabolizer					
References: 11,12					

Like the other CYP450 enzymes, there are significant ethnic variations in expression of the various phenotypes (**Table 15**).

Table 15: CYP2D6 Genetics

Phenotype	Example diplotypes	CYP2D6 Activity	Ethnic Differences (approximate)
PM	*4/*4, *4/*5, *5/*5, *4/*6	None	Caucasians 6-10% Mexican Americans 3-6% African Americans 2-5% Asians ~1%
IM	*4/*10, *5/*41	Low	~ 2-11% of people
EM	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10	Normal	Most people (~77-92%)
UM	*1/*1xN, *1/*2xN	High	Finns and Danes 1% North American Caucasians 4% Greeks 10% Portuguese 10% Saudis 20% Ethiopians 30%
Reference: 53			

Although it only accounts for 2-4% of CYP450 protein content in the liver, CYP2D6 metabolizes 25-30% of all clinically used medications.[11] **Table 16** lists the major substrates.

Table 16: Substrates for CYP2D6	
Antidepressants	**Beta Blockers**
Amitriptiline	Carvedilol
Clomipramine	Metoprolol
Desipramine	Propranaolol
Duloxetine	Timolol
Doxepin	
Fluoxetine	**Serotonin (5-HT 3) Receptor**
Fluvoxamine	**Antagonists**
Imipramine	Dolesetron [a]
Nortriptyline	Ondansetron
Paroxetine	Palonesetron
Protriptyline	
Trazodone	**Pain Medications**
Venlafaxine	Codeine [a]
	Hydrocodone [a]
Antipsychotics	Oxycodone [a]
Aripiprazole	Tramadol [a]
Chlorpromazine	
Haloperidol	**Other drugs**
Risperidone	Amphetamine
Perphenazine	Atomoxetine
Thioridazine	Benztropine
	Chlorpheniramine
Antiarrhythmics	Diphenhydramine
Encainide	Dexfenfluramine
Flecainide	Dextromethorphan
Mexiletine	Doxorubicin
Propafenone	Hydroxyzine
	MDMA (Ecstasy)
	Metoclopromide
	Tamoxifen [a]
	Tolterodine
a - prodrug Reference: 11, 14, 53, 54	

Inhibitors and Inducers of CYP2D6

Unlike other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction. It is technically considered a noninducible enzyme although clearance of many medications predominately metabolized by CYP2D6 is increased by dexamethasone and rifampin.[11] There

are numerous inhibitors of CYP2D6 (**Table 17**) which should be avoided in those who are IM phenotype.

Table 17: Effects on CYP2D6 Activity	
Inhibitors	
Amiodarone Buproprion [a] Chloroquine Cimetidine Cinacalcet [a] Diphenhydramine Duloxetine Fluoxetine [a] Fluvoxamine	Haloperidol Imatinib Paroxetine [a] Propafenone Quinidine [a] Sertraline Terbinafine Thioridazine Venlafaxine
Increased Clearance	
Clearance increased by dexamethasone and rifampin by unknown mechanism which is not induction.	
a – potent inhibitor References: 11, 14, 53, 54	

Tamoxifen

Tamoxifen is prescribed as adjuvant endocrine therapy to prevent estrogen receptor-positive breast cancer recurrence, as treatment of metastatic breast cancer, and to prevent breast cancer in high-risk populations and women with ductal carcinoma in situ (DCIS). Tamoxifen is metabolized by a number of CYP450 enzymes including 2D6, 3A4, 2C9, 2C19, and 2B6 to active metabolites – N-desmethyl tamoxifen and 4-hydroxytamoxifen. N-desmethyl tamoxifen is further metabolized to endoxifen by CYP2D6. Endoxifen has 100-fold greater affinity for the estrogen receptor and is 30-100 fold more potent than tamoxifen in suppressing estrogen-dependent cell proliferation.[55]

Because tamoxifen metabolism is complex, CYP2D6 variation does not appear to account for all variability in endoxifen levels. Some investigators propose that polymorphisms in additional genes encoding non-CYP450 enzymes in the tamoxifen metabolic and elimination pathways (e.g., SULT1A1 and UGT2B15) also need to be considered to account adequately for interindividual variation in medication response.[55]

Co-administration of a potent CYP2D6 inhibitor to CYP2D6 homozygous wild type patients (EMs) is associated with endoxifen levels near those of patients who are poor metabolizers.[56] Evidence from two higher-quality trials of adjuvant tamoxifen suggests that women who are CYP2D6 IMs or PMs, whether by genotype or by co-medication with CYP2D6 inhibitors, treated with tamoxifen have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to EMs.[57,58] The strength of these associations was marginal and might be stronger and more convincing if PMs alone could be compared to

EMs, but PM numbers were insufficient in the trials. Thus, individuals with poor-metabolizer phenotype of CYP2D6 should be treated with alternatives to tamoxifen such as aromatase inhibitors.[57,58]

Take Away Message

Women who are PMs probably won't get benefit from tamoxifen - recommend an aromatase inhibitor. Women who are taking tamoxifen need to avoid potent inhibitors of 2D6 metabolism (especially the SSRIs).

Pain Medication

Codeine, hydrocodone, and oxycodone are metabolized to active metabolites (i.e., codeine – morphine, hydrocodone – hydromorphone, oxycodone – oxymorphone) by CYP2D6, CYP3A4, and CYP3A5. Genetic variations in these enzyme systems have been shown to significantly affect response to these opioids and alter clinical outcomes, including pain relief and likelihood of overdose.[59,60] CYP3A4 and CYP3A5 are discussed later. If clinical genotyping identifies a patient as a CYP2D6 PM, current evidence suggests that the above analgesics be avoided because of the possibility of lack of effect due to insufficient active metabolite; an alternative analgesic should be used. [59]

Patients who are UMs have increased formation of active metabolites leading to higher risk of toxicity. In a patient identified as a CYP2D6 UM, an alternative analgesic should be chosen to avoid the risk of severe toxicity associated with a "normal" dose of these agents. [59] The FDA issued a public health advisory warning that the use of codeine by nursing mothers who are CYP2D6 UMs may increase the risk of serious adverse events, including death, in breastfed infants.[61]

Tramadol is metabolized to the active metabolite O-desmethyltramadol (M1) by CYP2D6. The M1 metabolite has a 200-fold greater affinity for opioid receptors compared with tramadol. CYP2D6 PMs have shown an increase in tramadol levels by 20% and decreased O-desmethyltramadol (M1) by 40%.[28]

Table 18 provides some guidelines on using pain medications affected by CYP2D6 polymorphisms. The primary alternative agent for use in the PM or UM patient for pain relief requiring an opioid would be morphine.

Table 18: CYP2D6 Pain Medication Recommendations		
Codeine, hydrocodone, oxycodone		
Phenotype	Implications for metabolism	Recommendations for therapy
UM	Increased formation of metabolites leading to higher risk of toxicity	Avoid use due to potential for toxicity. Consider alternative analgesics such as morphine or a non-opioid. Consider avoiding tramadol
EM	Normal metabolite formation	Usual doses (e.g., 15-60 mg q 4h for codeine) as needed for pain.
IM	Reduced metabolite formation, possible reduced analgesia	Begin with usual doses. If no response, consider alternative analgesics such as morphine or a non-opioid. Monitor tramadol use for response.
PM	Greatly reduced metabolite formation leading to insufficient pain relief.	Avoid use due to lack of efficacy. Consider alternative analgesics such as morphine or a non-opioid. Consider avoiding tramadol.
Tramadol		
UM	Increased formation of active metabolite O-desmethyltramadol leading to higher risk of toxicity	Reduce dose by 30% and be alert to ADEs (e.g., nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) or select alternative drug (e.g., acetaminophen, NSAID, morphine).
EM	Normal active metabolite formation	Usual dose.
IM	Reduced active metabolite formation.	Be alert to decreased efficacy. Consider dose increase. If response is still inadequate, select alternative drug or be alert to symptoms of insufficient pain relief.
PM	Greatly reduced active metabolite formation leading to insufficient pain relief.	Select alternative drug or be alert to symptoms of insufficient pain relief.
References: 28, 62, 63		

Psychiatric Medications

A large portion of the available antispychotic and antidepressant agents are primarily metabolized by CYP2D6. It has been reported that psychiatric inpatients with poor or ultra-rapid metabolism cost on average $4000– $6000 more per year to treat than EM patients when prescribed medications that are metabolized by the CYP2D6 enzyme.[64] This translates to an estimated $112,000– $168,000 per year in added health care expenses at a single psychiatric hospital directly related to this single gene.

The Royal Dutch Pharmacists Association - Pharmacogenetics Working Group and Kirchheiner and colleagues have published dosing guidelines for affected antidepressants and antipsychotics medications based on CYP2D6 phenotypes (**Tables 19**).[39,65] As an example, nortriptyline is dosed for depression as 75-150 mg per day. But in poor CYP2D6 metabolizers, the suggested dose would be 40 - 80 mg per day. UM patients metabolize the medication so extensively that they may require a dose increase to more than 225 mg to achieve therapeutic effect.

Table 19: Psychiatric Medication Dose Adjustments Based on CYP2D6 Phenotype

	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Antidepressants				
Amitriptyline	75	75-90	105	130
Bupropion	90	95	105	110
Clomipramine	50-60	90	110	145
Desipiramine	40	80	125	170
Doxepin	35-40	80	130	175-200
Imipramine	30	70-80	130	170-180
Mirtazipine	40	60	-	160
Nortriptyline	55	95	120	150
Paroxetine	65	85	115	135
Trimipramine	35	90	130	180
Venlafaxine	70	80	105	130-150
Antipsychotics				
Aripiprazole	67	-	-	-
Haloperidol	50-75	95	100	115
Olanzapine	60	105	120	150
Perphenazine	30	80	125	175
Risperidone	85	90	100	110

- no data available
These dosage adjustments are based on an analysis of published pharmacogenomic studies with these medications.
References: 39, 65

Because there are wide ranging recommendations for dosage adjustments and the possibility of treatment failure or adverse effects, it may be easiest to avoid using the affected antidepressants and antipsychotics in CYP2D6 PM and UM patients. Alternative antidepressants are citalopram and sertraline but a patient's other genetic polymorphisms must also be considered in choosing an agent. Alternative antipsychotics for the CYP2D6 PM and UM patient include pimozide, fluphenazine, quetiapine, and clozapine. Remember the patient's other CYP450 polymorphisms, if tested for, will have to be considered in selecting an alternative agent.

CYP2D6 Related Adjustments For Other Medications

In general, if a medication predominately metabolized by CYP2D6 cannot be avoided in a patient with IM or PM phenotype and is a normal substrate, a dosage reduction of 20-25% in IM and 50% in PM should be used unless the package insert provides other recommendations. For example, because atomoxetine has a wide therapeutic range, the usual starting dose is suggested in the PM patient with dose increases to the standard target dose of 1.2 mg/kg/day only if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.[66] For prodrugs, the usual dose should be used for IM patients but efficacy should be monitored. PM patients are unlikely to benefit from a prodrug.

Patients with UM phenotype are at risk for treatment failure from low serum concentrations so consider starting with a higher dose. They are at risk for adverse effects from excessive active metabolite with prodrugs. For prodrugs, reduce usual starting dose and monitor for adverse effects and efficacy.

Case Study

Mrs B. is a 45 year old, new patient at a pain clinic. Her medical history includes hypertension, type 2 diabetes, and hyperlipidemia. Current medications are irbesartan, glipizide, insulin, rosuvastatin, and fenofibrate.

She has chronic pain and disability from an industrial accident 5 years ago. She was referred to the pain clinic because of difficulty with pain control and a history of unusual reactions to pain medications in the past. She states some pain medications do not work for her and some incapacitate her even at small doses. Unfortunately she is unable to specifically name which results in which reaction. In addition, she has significant symptoms of depression.

The decision was made to conduct pharmcogenomic testing for several CYP polymorphisms. Her results are below.

Result	*Reference Range/Comment*
*CYP 450 2C9 *1/*3*	*Intermediate metabolizer*
*CYP 450 2C19 *1/*1*	*Normal metabolizer*
*CYP450 2D6 *4/*4*	*Poor metabolizer*
*CYP450 3A4 *1/*1*	*Normal metabolizer*
*CYP450 3A5 *1/*1*	*Normal metabolizer*

Based on her genetic information, would oxycodone be an appropriate choice for managing her pain? She carries two nonfunctional alleles for 2D6, a primary metabolic route for oxycodone. It is also metabolized by 3A4 for which she is a normal metabolizer. She is likely to have inadequate pain relief from oxycodone, codeine, hydrocodone, and tramadol.
If she requires an opioid for pain management, what would be an appropriate choice? Morphine (and its derivatives hydromorphone and oxymorphone) is not significantly metabolized by CYP enzymes. Thus based on these results alone, it would be the opioid of choice. There are some other genetic variations that can impact morphine efficacy and tolerance which were not tested including UGT2B7. Given her history, a low dose of morphine could be initiated and titrated to effect.
What impact do these test results have for her other medications or future medications? Given her 2D6 PM status, medications predominately metabolized by this route should be avoided if prodrugs because they will not be converted to the active form. For other medications, she may require a significant dosage adjustment (~50%) if they cannot be avoided. Because she is a 2C9 IM, she should not be prescribed inhibitors of this enzyme, which would functionally make her a poor metabolizer (Table 13). Inhibitors may lead to adverse effects from glipizide (hypoglycemia) or irbesartan (hypotension). Additionally, starting doses for new medications metabolized by 2C9 likely should be reduced by 25%.
Which antidepressant would be appropriate, based on genetics, to initiate in this patient for depressive symptoms and pain management? Because she is a 2D6 PM, alternative agents such as citalopram and sertraline could be initiated or an adjusted dose of one of the affected agents (Table 19).

CYP3 Family

The CYP3 family includes three genes - 3A4, 3A5, and 3A7 - that are considered the most important in drug metabolism because CYP3A4 and CYP3A5 alone account for 37 to 46 percent of drug metabolism. Altogether the CYP3 family is responsible for the metabolism of almost 50% of currently marked medications.[11] Because the CYP3A enzymes constitute 82% of the CYP450 enzyme content in the human intestine, they play an important role in the first-pass metabolism of medications. CYP3A4 and CYP3A5 account for 40% of the liver CYP450 content.[11]

CYP3A4 is the most abundant and clinically significant of the CYP3 family. CYP3A5 is second most important; it is only expressed in 20% of Caucasians and about 70% of African Americans. 3A7 is third most important and only occurs in about 11 percent of adults. There is a fourth CYP3 gene, *CYP3A43*, which is of unknown relevance to drug metabolism.[11]

Like all the other previously discussed CYP450 enzymes, the CYP3 family has a high degree of genetic variability.[9] The identified variants which have been shown to impact medications are shown in **Table 22**.

Table 22: Clinically Significant CYP3 Variants

	Predicted phenotype	Enzyme Function	Caucasian	African American	Asian
CYP3A4*1B	PM or IM	↓	-	-	-
CYP3A4*2	PM or IM	↓	-	-	-
CYP3A4*12	PM or IM	↓	-	-	-
CYP3A4*17	PM or IM	↓	-	-	-
CYP3A4*20	PM or IM	nonfunctional	0.06	-	-
CYP3A5*3	PM or IM	nonfunctional	85-98%	27-48%	60-75%
CYP3A5*6	PM or IM	nonfunctional	0	13-17	0
CYP3A7*1C	EM or UM	↑ expression	3	6	0
CYP3A7*2	EM or UM	↑	7-12	55	31

- Prevalence data not available.
Routine testing for all known variants may not be available.
PM, poor metabolizer; IM, intermediate metabolizer; EM, extensive metabolizer; UM, ultra-rapid metabolizer

Reference: 11,67-69

CYP3A4

Twenty two different variants of CYP3A4 have been identified.[11] The CYP3A4*17 allele results in minimal function compared with wild type.[67] Alleles with moderately decreased functionality include: CYP3A4*2, *8, *11, *12, *13, *16, and *18.[68] A rare nonfunctional allele (CYP3A4*20) has been identified in less than 0.06% of Caucasians.[69] Routine testing

for all these variants may not be available. Induction and inhibition by interacting medications appear to be a very important factor contributing to variability in CYP3A4 activity.

One genetic CYP3A4 variant may play a vital role in determining response to statin therapy. Carriers of a newly identified CYP3A4 polymorphism (rs35599367) required significantly lower statin doses (0.2–0.6 times less) for optimal lipid control. The analysis which identified this polymorphism included atorvastatin, simvastatin, and lovastatin, and the association was robust (P = .019).[70]

Another CYP3A4 polymorphism of importance may be CYP3A4*1B in select cases. Because the majority of the Caucasian population would demonstrate nonexistent or lowered CYP3A5 enzyme, a Caucasian with CYP3A4*1B variant, especially the homozygous variant, may not be able to efficiently metabolize medications typically metabolized by CYP3A4 and CYP3A5 resulting in increased toxicity. One of these medications is fentanyl. In a case series of fentanyl related deaths, 88% of the decedents were Caucasian but not all carried this variant.[71]

CYP3A5

In addition to those listed in **Table 22**, additional CYP3A5 variants with known reduced activity include *2, *3B, *7, *8, and *9.

There is significant overlap in the medications metabolized by CYP3A5 and CYP3A4. The impact of CYP3A5 polymorphisms appears to be drug-dependent to some extent (i.e., some medications are preferentially metabolized by CYP3A5). For example, vincristine is preferentially metabolized by CYP3A5 and results in a much higher rate of neurotoxicity in Caucasians who have a much lower expression rate than in African Americans.[72]

Tacrolimus is extensively used for immunosuppression after various transplants. Its clearance is significantly affected by CYP3A5 polymorphisms. Several studies in kidney, heart and liver transplant recipients have reported homozygous carriers of a CYP3A5*3 variant allele (*3/*3) require a significant dose reduction compared with heterozygous or homozygous carriers of a CYP3A5*1 wild type allele.[73]

Pharmacogenomic testing can be used in combination with serum trough concentrations to target dosing of tacrolimus post transplant to reach target levels earlier. The European Science Foundation has published initial dosing guidelines of 0.15 mg/kg/day for the CYP3A5*3/*3 phenotype, 0.20 mg/kg/day for CYP3A5*3/*1, and 0.25 mg/kg/day for CYP3A5*1/*1.[74] The current FDA approved package labeling for tacrolimus does not include any information on CYP3A5 and the dosing guidelines list a maximum dose of 0.20 mg/kg/day.[75] Presence of CYP3A4 inhibitors and inducers must also be taken into account when selecting an initial dose.

CYP3 Related Adjustments For Medications

Table 23 lists selected substrates of CYP3A4 and CYP3A5. At this time, no specific dose adjustments, other than for tacrolimus, are recommended related to CYP3A4 or CYP3A5 polymorphisms. When selecting a dose, consideration has to be given to the individual patient's phenotype for both CYP3A4 and CYP3A5 since both metabolize the same medications except in a few cases. Presence of inducers or inhibitors must also be considered (**Table 24**).

Table 23: Selected Substrates for CYP3A4/5

Benzodiazepines:	**Pain**	Imatinib
Alprazolam	Codeine	Irinotecan
Diazepam	Fentanyl	Lidocaine
Midazolam	Methadone	Nateglinide
Triazolam	**Psychiatric**	Ondansetron
Calcium Channel Blockers:	Buspirone	Paclitaxel
Amlodipine	Haloperidol	Progesterone
Diltiazem	Pimozide	Propranolol
Felodipine	Quetiapine	Quinidine [a]
Nifedipine	Risperidone	Quinine
Nisoldipine	Trazodone	Salmeterol
Nitrendipine	Ziprasidone	Sildenafil
Verapamil	**Miscellaneous:**	Sirolimus
HIV Antivirals:	Alfentanil	Sorafenib
Indinavir	Aprepitant	Sunitinib
Nelfinavir	Aripiprazole	Tamoxifen
Ritonovir	Boceprevir	Telaprevir
Saquinavir	Caffeine	Testosterone
HMG CoA Reductase	Chlorpheniramine	Vincristine
Inhibitors:	Cilostazol	Zaleplon
Atorvastatin	Dapsone	Zolpidem
Lovastatin	Dexamethasone	
Simvastatin	Dextromethorphan	
Immune Modulators:	Docetaxel	
Cyclosporine	Domperidone	
Tacrolimus	Eplerenone	
Macrolide antibiotics:	Estradiol	
Clarithromycin	Finasteride	
Erythromycin [a]	Hydrocortisone	

a – NOT CYP3A5
References: 11, 14, 76

Table 24 presents inhibitors and inducers of the CYP3 family.

Table 24: Effects on CYP3A4/5/7 Activity	
Inhibitors	**Inducers**
Amiodarone [a]	Aprepitant (long term)
Atazanavir [a]	Bosenten
Aprepitant [b]	Carbamazepine
Boceprevir	Dexamethasone
Cimetidine	Efavirenz
Ciprofloxacin	Felbamate
Clarithromycin [a]	Griseofulvin
Delavirdine	Methylprednisolone
Diltiazem [b]	Nafcillin
Erythromycin [b]	Nelfinavir
Flucoazole [b]	Nevirapine
Fluvoxamine	Oxcarbazepine
Grapefruit juice constituents [b]	Phenobarbital
Imatinib	Phenytoin
Indinavir [a]	Prednisone
Itraconazole [a]	Primidone
Ketoconazole [a]	Rifabutin
Miconazole	Rifampin
Mifepristone	Rifaximin
Nefazodone [a]	Ritonavir (long term)
Nelfinavir [a]	St John's Wort
Norfloxacin	Topiramate (>200mg/d)
Norfluoxetine	
Ritonavir (short term)[a]	
Saquinavir [a]	
Telaprevir	
Telithromycin [a]	
Verapamil [b]	
Voriconazole	
a – potent inhibitor (80% decrease in clearance) b – moderate inhibitor (50-80% decrease in clearance) References: 11, 14, 76	

CYP2B6

CYP2B6 is a minor drug metabolizer, accounting for approximately 4% of medications (see **Table 20**).[11] Twenty nine different allelic variations have been identified.[9] The significance of 2B6 polymorphisms for clinical drug treatment is just beginning to emerge.

Table 20: Substrates/Inhibitors/Inducers for CYP2B6		
Substrates	**Inhibitors**	**Inducers**
Bupropion	Clopidogrel [c]	Lopinavir/ritonavir
Efavirenz [a]	Efavirenz	Phenobarbital
Ifosphamide	Fluoxetine	Phenytoin
Methadone	Fluvoxamine	Rifampin
Sorafenib	Memantine	
Cyclophosphamide [b]	Nelfinavir	
Meperidine	OC and HRT	
Methadone	Paroxetine	
Nevirapine [a]	Ritonavir	
Nicotine	Sertraline	
Propofol	Thiotepa	
Selegiline	Ticlopidine [c]	
Sertraline		
Tamoxifen		
Testosterone		
a – primary metabolic pathway b – prodrug c - potent inhibitor OC, oral contraceptives; HRT, hormone replacement therapy References: 11, 14, 77		

CYP2B6 is the primary enzyme involved in the metabolism of efavirenz (Sustiva®). Efavirenz has a narrow therapeutic window with severe CNS side effects associated with high plasma concentrations and treatment failure associated with low concentrations. Variants CYP2B6:516G>T and CYP2B6:983T>C as well as CYP2B6*4 and CYP2B6*6 have been associated with adverse effects of efavirenz treatment.[11] Clinical significance of CYP2B6 variants has also been implicated in cyclophosphamide therapy and smoking cessation in response to bupropion. **Table 21** lists clinically significant variants of CYP2B6.

Table 21: Clinically Significant CYP2B6 Variants					
	Predicted phenotype	**Enzyme Function**	**Caucasian**	**African American**	**Asian**
CYP2B6*4	UM	↑	2-4	0	7
CYP2B6*6	PM or IM	↓	16-26	33-50	16
CYP2B6*9	PM or IM	↓	13	0	0
CYP2B6*18	PM or IM	↓	0	4-7	0
PM, poor metabolizer; IM, intermediate metabolizer; UM, ultra-rapid metabolizer					
Reference: 11					

At this time, no specific dose adjustments are recommended related to CYP2B6 polymorphisms. Although several important variants and haplotypes have been identified, the drug-variant interactions for CYP2B6 still need further investigation.

Oncology Specific Pharmacogenomic Tests

In oncology, a therapeutic arena in which medications may cost a single patient (and their respective third party payer) hundreds of thousands of dollars a year, understanding the complex genetic pathways that will identify whether a patient will respond to a particular therapy is becoming an essential component of care. This aspect of medical practice is truly personalized to the individual. The numerous pharmacogenomic tests commonly used in oncology are summarized in **Table 25**.

Table 25: Oncology Focused Pharmacogenomic Tests

Test	Medication	Effect/Comments
ALK (anaplastic lymphoma kinase)	Crizotinib (Xalkori®)	▪ Crizotinib is indicated for late-stage (locally advanced or metastatic), non-small cell lung cancers that express an abnormal ALK gene.
BRAF (v-raf murine sarcoma viral oncogene homolog B1)	Vemurafenib (Zelboraf®)	▪ BRAF is a human gene that makes a protein called B-Raf, a signal conductor for cell growth. ▪ > 30 mutations of the BRAF gene associated with human cancers have been identified. ▪ V600E (1799T>A) mutation is associated with papillary thyroid carcinoma, colorectal cancer, melanoma, hairy cell leukemia, and non-small-cell lung cancer. ▪ Tumor DNA is extracted from fixed tumor tissue for this testing. ▪ Other codon 600 BRAF mutations, beside the most common V600E, may not be detected by this test. ▪ Vemurafenib is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAFV600E mutation as detected by an FDA-approved test (companion diagnostic). ▪ It is not recommended for use in patients with wild type BRAF melanoma.
C-KIT (cytokine receptor)	Imatinib (Gleevec®)	▪ Imantinib is indicated for the treatment of patients with KIT (CD117)-positive unresectable tumors or metastatic malignant gastrointestinal stromal tumors (GIST).

Table 25: Oncology Focused Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
DPYD (dihydropyrimidine dehydrogenase)	Capecitabine (Xeloda®) 5-flurouracil (5-FU)	▪ Capecitabine, an oral prodrug of 5-FU, and 5-FU are both contraindicated in patients with DPD deficiency (PM phenotype). ▪ IM patients should have their dose decreased 50%.
EGFR (epidermal growth factor receptor)	Cetuximab (Erbitux®) Panitumumab (Vectibix®) Gefitinib (Iressa®) Erlotinib (Tarceva®)	▪ Cetuximab and panitumumab are effective in EGFR-expressing metastatic colorectal cancer. ▪ Tyrosine kinase inhibitors (gefitinib and erlotinib) have been shown to improve response and progression-free survival in patients with EGFR-mutated non-small cell lung cancer.
G6PD (glucose-6-phosphate dehydrogenase)	Rasburicase (Elitek®)	▪ Rasburicase is a recombinant version of urate oxidase for prevention and treatment of tumor lysis syndrome. ▪ Testing for G6PD deficiency is recommended in high-risk populations (e.g., African or Mediterranean ancestry) before starting treatment with this agent.
HER2 (human epidermal growth factor receptor 2)	Trastuzumab (Herceptin®)	▪ Traztuzumab is highly effective in the 15-25% of breast cancers that have a genetic variant that causes an overexpression of the HER2 protein (a cell growth promoter) and is not effective against breast tumors lacking HER2 overexpression.
KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog)	Cetuximab (Erbitux®) Panitumumab (Vectibix®)	▪ The agents listed do not work for treatment of colorectal cancer in KRAS mutation positive patients.
Philadelphia (Ph) chromosome and BCR-ABL	Dasatinib (Sprycel®) Imatinib (Gleevec®) Nilotinib (Tasigna®)	▪ The agents listed are effective for treating Philadelphia chromosome positive leukemias. ▪ BCR-ABL is a fusion gene that results from the translocation of two chromosomes, 9 and 22 (Ph chromosome) ▪ Treatment response to these medications is monitored using peripheral blood counts to determine hematologic response, Ph chromosome to determine cytogenetic response, and BCR-ABL expression to determine molecular response.

Table 25: Oncology Focused Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
TPMT (thiopurine methyltransferase)	6-mercaptopurine (Purinethol®) Mercaptopurine Azathioprine (Imuran®)	▪ TPMT testing is recommended before starting treatment with these agents. ▪ See next section for additional discussion
UGT1A1 (UDP glucuronosyltransferase 1 family, polypeptide A1)	Irinotecan (Camptosar®)	▪ Individuals with UGT1A1*28/*28 are at increased risk for neutropenia from irinotecan. ▪ Patients with UGT1A1 *28/*28 who would typically get > 250 mg/m^2 should have initial dose reduced by 30%. Increase dose in response to neutrophil count. Dose <250mg/m^2: no dose adjustment.

Other Pharmacogenomic Tests

This section includes tests that are not widely available or apply to fewer medications. Some of them also currently use blood or tissue samples, which make them less amenable to some point of care settings. In a practice setting without access to phlebotomy, patients could be referred for this testing. For tests, which are conducted at a limited number of laboratories, testing can be referred to these laboratories. As technology evolves with next generation sequencers many of the blood-based tests will be able to be accomplished with the much smaller quantity of DNA obtained from a buccal sample and will be available at more laboratories. Additionally, patients may ask questions about their test results from some other sources so providers need to be knowledgeable of all available tests.

A few of these tests are spotlighted here. The rest are briefly described in **Table 26**.

HLA-B*5701

One well established use of a pharmacogenomic test is HLA-B*5701 testing prior to prescribing the antiretroviral abacavir (Ziagen®). HLA-B (human leukocyte antigen B) is a human gene that provides instructions for making a protein that plays a critical role in the immune system and is part of the major histocompatibility complex which helps the immune system distinguish the body's own proteins from foreign proteins

Approximately 8% of those treated with abacavir experience a hypersensitivity reaction which occurs only in those people carrying at least one HLA-B*5701 allele, although people lacking this marker can have other types of adverse reactions. The prevalence of the HLA-B*5701 marker varies around the world. Approximately 5-7% of people with European ancestry carry this marker. In India, 20-50% of people are HLA-B*5701 positive, while this marker is virtually absent in Japan. The package labeling states abacavir should not be used in HLA-B*5701 positive patients.[78]

TPMT

In the poll conducted by the American Association for Clinical Chemistry mentioned earlier, thiopurine methyltransferase (TPMT) was identified as the second most important pharmacogenomic test following CYP2D6 in the list of top 10 pharmacogenomic tests.[10]

Thiopurines - azathioprine, mercaptopurine, and 6-mercaptopurine - are most commonly used to treat nonmalignant conditions such as rheumatoid arthritis but are also critical anticancer agents. The thiopurines are converted to inactive metabolites by the phase II drug-metabolizing enzyme TPMT. Of the more than 20 identified TPMT allelic variants, three (*2, *3A, and *3C) are common and collectively account for more than 95% of the inherited variation in enzyme activity. The resultant proteins from these allelic variants are nonfunctional because they produce an enzyme with an increased susceptibility to cellular degradation. About 0.3% of Caucasians have low TPMT activity, 6% to 11% have intermediate activity, and 89% to 94% have high activity. Patients with homozygous variant TPMT genotype (i.e., two alleles conferring low TPMT activity) are at high risk of developing hematopoietic toxicity after treatment with standard thiopurine doses. Conversely, standard doses in patients with high TPMT activity may not achieve an optimal therapeutic effect.

FDA labeling for the thiopurines recommends TPMT testing before starting treatment with these agents and consideration of dosage reduction in patients heterozygous for a nonfunctional allele and alternative treatment in patients with a homozygous variant genotype. Recommendations for adjusting doses based on TPMT genotype are currently lacking in the product labeling but have been published by the Clinical Pharmacogenetics Implementation Consortium.[79] In PM patients, these guidelines recommend alternative agents. If one of these agents must be used, drastically reduced doses are indicated. In IM patients, starting doses should be 30-70% of target dose and titrated based on tolerance.

Table 26: Additional Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
ABCB1 (ATP binding cassette subfamily B, member 1)	Clopidogrel Colchicine Doxorubicin Etoposide Tacrolimus Quinidine Vinblastine and potentially many others	▪ The gene that codes for the ubiquitous intestinal efflux transporter P-glycoprotein. ▪ Increased intestinal expression of P-glycoprotein can reduce bioavailability of drugs that are substrates for P-glycoprotein.[80] ▪ Supratherapeutic plasma concentrations and drug toxicity may result because of decreased P-glycoprotein expression ▪ Overexpression can lead to multidrug resistance in cancer treatment and other diseases.
ApoE (Apolipoprotein E)	Statins	▪ ApoE alleles include ApoE2, ApoE3, and ApoE4 ▪ ApoE3 is the "normal" genotype ▪ ApoE2 is associated with hyperlipoproteinemia type III ▪ The ApoE4 allele has been implicated in patients with higher levels of LDL cholesterol and a higher risk of both cardiovascular disease and Alzheimer's disease. ▪ Several studies have shown that individuals who carry one or more copies of ApoE4 don't have as large a reduction in LDL as would be expected after statin treatment. ▪ Studies indicate that ApoE4 carriers receiving regular simvastatin or pravastatin treatment who experience myocardial infarction actually have improved outcomes compared to ApoE4 carriers who do not take a statin. Effect appears to be independent of cholesterol lowering, but rather may be due to these statins' other properties.

Table 26: Additional Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
CCR5 (C-C chemokine receptor type 5)	Maraviroc (Selzentry®)	▪ CCR5 is one of the receptors HIV initially uses to enter and infect host cells. A few individuals carry a mutation known as CCR5 delta 32 in the CCR5 gene, protecting them against these strains of HIV. ▪ Maraviroc is effective only against CCR5-tropic HIV. ▪ Patients with viruses using both the CXCR4 (chemokine receptor type 4) and CCR5 receptors (dual/mixed tropic) or just CXCR4-tropic do not respond. ▪ Testing should be done before initiating therapy and in cases of treatment failure.[81] ▪ Other CCR5 inhibitors are under study.
G551D-CFTR (cystic fibrosis transmembrane conductance regulator)	Ivacaftor (Kalydeco®)	▪ People with cystic fibrosis (CF) with the G551D mutation have a defective protein, CFTR ▪ The defective protein moves to the right place at the surface of the cell but does not function correctly to allow fluids and electrolytes to flow. ▪ About 4 % of the CF population in the US has this mutation. ▪ Ivacaftor is a potentiator of CFTR protein; facilitates increased chloride transport by potentiating the channel-open probability of the G551D-CFTR protein. ▪ Ivacaftor improves lung function, lowers sweat chloride levels, and helps patients gain weight. ▪ Ivacaftor is only FDA approved for patients >6 years old with this specific mutation.

Table 26: Additional Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
GRK (G protein-coupled receptor kinase)	Beta blockers	▪ GRKs regulate and desensitize beta adrenergic receptors. ▪ A specific GRK5 gene variant (Gln41Leu), common in African Americans, reduces beta-AR signaling, essentially acting as an endogenous beta blocker. ▪ Patients with this GRK5 variant respond less well to beta blocker treatment after heart failure. This may explain why clinical trials of beta blockers in heart failure have generally shown less promising results in African-American populations than in European-Americans. ▪ About 60 % of African Americans have an unaltered version of the gene and thus may actually benefit from beta blocker treatment. ▪ With this test, genotype, rather than race or ancestry, can be used to optimize beta blocker use in African Americans.
HLA-B*1502 (human leukocyte antigen)	Carbamazepine Phenytoin Allopurinol	▪ HLA-B*1502 is a risk factor for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Han Chinese from carbamazepine. The FDA recommends genotyping all Asians for the allele before using carbamazepine.[82] ▪ Risk factor for SJS & TEN in Asian patients treated with phenytoin. ▪ Risk factor for SJS, TEN, drug-induced hypersensitivity syndrome (DHIS) or drug rash with eosinophilia and systemic symptoms (DRESS) with allopurinol in Caucasian and Asian patients.[83] ▪ HLA-B*1502 is largely absent in individuals not of Asian origin.
KIF6 (kinesin-like protein 6)	Statins	▪ Trp719Arg polymorphism influences the effect of LDL cholesterol on the risk of CVD ▪ KIF6 Trp719Arg carriers experienced a 13% greater reduction in the risk of CVD per mmol/L decrease in LDL cholesterol than non-carriers.[84] ▪ In the AKROBAT study, knowing KIF6 results improved adherence and persistence with statins.[6]

Table 26: Additional Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
LPA (Lipoprotein(a)) Buccal or blood	Aspirin	▪ A SNP (LPA rs3798220) has been identified in the LPA gene that has been associated with both elevated levels of LPA and an increased risk of cardiovascular disease. ▪ LPA-Aspirin genotype test predicts increased CVD risk and event reduction during aspirin therapy. ▪ LPA carriers have at least two-fold higher risk of CVD events than noncarriers. ▪ In women, the number needed to treat (NNT) to prevent 1 CVD event is significantly less for carriers (37) than noncarriers (625). ▪ The allele was present in 3.7% of the female population, 3.6% who were heterozygotes and 0.06% who were homozygotes.[85-87]
NAT2 (N-acetyltransferase)	Rifampin Isoniazid Pyrazinamide Isosorbide dinitrate Hydralazine Docetaxel Thalidomide Caspofungin Dapsone Procainamide Zonisamide Sulfonamides	▪ ~50% of people in U.S are slow acetylators (50% of African Americans and Caucasians) ▪ ~40% are intermediate ▪ ~10% are rapid acetylators (majority of Eskimos and Asians) ▪ NAT2*5, NAT2*6, NAT2*7, and NAT2*14 – slow ▪ NAT2*4 – rapid ▪ Rapid acetylators (RA, two active NAT2 alleles) represent the norm for metabolic capacity. ▪ Intermediate acetylators (IA, one active and one inactive NAT2 allele) may require lower than average drug dosages for optimal therapeutic response. ▪ Slow acetylators (SA, no active NAT2 alleles.) are at increased risk of drug-induced side effects due to diminished drug elimination or lack of therapeutic effect resulting from failure to generate the active form of the drug. ▪ Isoniazid: standard dose for IA, a 50% decrease in dose for SA and a 50% increase for RA. ▪ Acetaminophen – inhibitor of NAT2 ▪ Retinoic acid – inducer of NAT2

Table 26: Additional Pharmacogenomic Tests		
Test	**Medication**	**Effect/Comments**
SLC01B1[a] (solute carrier organic anion transporter family member 1B1)	Statin	▪ *SLCO1B1* gene encodes for a membrane-bound sodium-independent organic anion transporter protein that is involved in active cellular influx of many endogenous and xenobiotic compounds. ▪ SLC01B1*5 significantly increases risk of statin induced myopathy particularly with high doses. ▪ Homozygotes (*5/*5) have 18 fold increased risk; Heterozygotes have 3%.[88] ▪ SLC01B1 regulates the uptake of statins into the liver and the genetic variant seems to cause higher statin serum concentrations that may lead to myopathy.
SLC6A4 [solute carrier family 6 (neurotransmitter transporter, serotonin), member 4]	SSRIs	▪ Polymorphisms of the serotonin transporter appear to influence the treatment response and side-effect profiles of selective serotonin reuptake inhibitors (SSRIs). ▪ Carriers of the SLC6A4 L alleles have fewer side effects and better response to SSRI treatment; carriers of the S allele have a higher incidence of antidepressant induced mania and poorer response to SSRI treatment.[89-91]
Serotonin (5-HT) receptors	SSRIs	▪ Polymorphisms in serotonin receptors (2A and 2C subtypes) appear to influence SSRI response and side effects. ▪ Carriers of 5-HT 2A C alleles had more severe adverse effects from paroxetine, but another 5-HT 2A polymorphism common to Asians is associated with better response to antidepressant therapy.[92-93]
UGT2B7 (uridyl glucuronosyl-transferase)	Morphine Efavirenz Carbamazepine Fluribiprofen Valproic acid Mycophenolate	▪ Metabolizes morphine to morphine-3-glucuronide and morphine-6-glucuronide (active). ▪ Individuals homozygous for the UGT2B7*2 allele have higher morphine-6-glucuronide/morphine ratios than those homozygous for the wild type allele.
References: In addition to those in the table, 11 and http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022128s004lbl.pdf. a – has implications for other medications including mycophenolate, rifampin, repaglinide, lopinavir, and methotrexate SSRI, selective serotonin inhibitor		

Case Study

Mr D. is a 38 year old Asian American with a history of seizures after an automobile accident 5 years ago. His current seizure medication is valproic acid but he has been having breakthrough seizures.

His neurology specialist has requested a pharmacogenomic consultation before initiating additional therapies. The decision was made to conduct pharmacogenomic testing for several CYP polymorphisms and for HLA. His results are below.

Result	*Reference Range/Comment*
*CYP 450 2C9 *1/*1*	*Normal metabolizer*
*CYP 450 2C19 *2/*3*	*Poor metabolizer*
*CYP450 3A4 *1/*1*	*Normal metabolizer*
*CYP450 3A5 *1/*1*	*Normal metabolizer*
*HLA-B*1502 Positive*	*Hypersensitivity*

Based on his genetic information, would carbamazepine be an appropriate choice for managing his seizures?
Carbamazepine would not be an appropriate choice because of his HLA-B*1502 allele status. He is at risk for Stevens-Johnson syndrome and toxic epidermal necrolysis from the carbamazepine.

Given his HLA-B*1502 status, what other medications should he avoid?
Phenytoin and allopurinol because HLA-B*1502 is a predictor of adverse effects (Stevens-Johnson syndrome and toxic epidermal necrolysis for both medications and drug-induced hypersensitivity syndrome (DHIS) and drug rash with eosinophilia and system symptoms (DRESS) with allopurinol.

What is another reason he should not be given phenytoin? He is a CYP2C19 poor metabolizer and thus is at risk for significant adverse effects. Phenytoin is also metabolized by CYP2C9, which is normal in him.

What effect does the valproic acid have on his metabolic capability? Valproic acid is a CYP2C9 inhibitor. Without the valproic acid, he is a normal metabolizer of CYP2C9 substrates. While on the valproic acid, his CYP2C9 metabolic activity is probably more like an intermediate metabolizer. Thus he may need lower doses of CYP2C9 substrates such as NSAIDs or angiotension receptor blockers.

Because carbamazepine and phenytoin are not appropriate choices in him, he was placed on topiramate (Topomax) in addition to the valproic acid to control his seizures. Topiramate (> 200 mg/day) is an inducer of CYP3A4/5 which should be considered if any additional medications are initiated.

Interpreting Testing Results for Patients and Health Care Providers

Pharmacogenomic tests are predictions based on information about the specific genetic variations being tested and on information about the associated diseases, adverse drug reactions, and patient outcomes that have been gathered during studies and clinical trials. In many cases, the predictions will be very accurate, but they cannot say with 100% certainty what will happen with an individual patient (i.e., Steven's Johnson Syndrome with carbamazepine). Nor do the test results, for the majority of the tests, mean that patients must absolutely avoid the affected medications. Also, not all possible genetic variants are included in the tests. Additionally, the test results do not incorporate or make allowances for the other factors in a patient's life related to the disease condition or to the individual that may also affect their response to treatment. This is one of the reasons why the results should be used in conjunction with other relevant clinical findings.

In addition to understanding the results of their testing and their limitations, the patient needs to know how to communicate this information to anyone who prescribes medications for them. Interpretive copies of the results that list likely affected medications and potential inducers and inhibitors should be incorporated into a patient's medical records. Given current regulations related to sharing laboratory results, patients have to request a copy of their test results, which they will need to give to all current health care providers who could potentially be prescribing for them. Patients will have to be educated how to advocate for pharmacogenomic based prescribing with current and future health care providers.

Future of Pharmacogenomic Testing

The use of genotyping to inform clinical decisions about medication use is just beginning to enter clinical practice. Routine testing is currently limited to a few clinical scenarios. However, additional applications are just around the corner. Knowledge of a person's genetic makeup particularly for the major CYP450 enzymes already predicts metabolism of the majority of all medications metabolized by the liver.

Pharmaceutical companies will be able to create drugs based on the proteins, enzymes, and RNA molecules associated with genes and diseases. This will facilitate drug discovery and allow drug makers to produce a therapy more targeted to specific diseases. This is already occurring in cancer treatment. This accuracy not only will maximize therapeutic effects but also decrease damage to nearby healthy cells.

The goal of personalized medicine will be manifested when medications and dosages are more efficacious and safer because a patient's genetic information is used in the therapeutic decision making process. With pharmacogenomic-guided personalized medicine, the idea of "one-drug-fits-all" will give way to "the right drug for the right patient at the right dose and time". However, each patient will not be treated completely different from every other patient. Instead, patients can be placed into groups based on genetic markers that can be utilized to

predict outcomes. Through personalized medicine, medication therapy issues such as lack of response and adverse events can be reduced.

Staying Up-To-Date

Keeping up with the rapidly evolving world of pharmacogenomics specifically and genetics in general can be a monumental task. Subscribing to email news lists is one way to know what has recently been published or discovered. Consult the resource section for various web-based resources. The Pharmacogenomics Knowledgebase (www.PharmGKB.org) is a particularly useful site because of the vast amount of information in one central location.

Summary

Use of pharmacogenomic testing in clinical practice is a rapidly evolving area. Tests for CYP450 polymorphisms are the most useful because they influence metabolism of the majority of all medications. Tests are available for CYP2C19, 2C9, 2D6, 2B6, and 3A4/5. In general, these tests will identify a patient's ability to metabolize substrates for a given enzyme. This will usually be reported as normal, intermediate, poor, or rapid/ultra-rapid depending on the enzyme. A patient with normal metabolism does not require any dosage adjustments based on genetics but may require adjustments for other reasons such as inhibitors or inducers. In poor metabolizers, it is best to avoid use of medications which are substrates for the particular CYP enzyme. If a medication cannot be avoided, a significantly reduced dose should be initiated and the patient monitored. Patients who are rapid metabolizers may require larger doses than "normal" in order to achieve adequate response. The situation is less clear for patients who are intermediate metabolizers; many times a reduced dose can be used. Inhibitors and inducers of a particular enzyme system are also important considerations in choosing medications and doses. Patients who are intermediate metabolizers should not receive a potent inhibitor because they will then be a poor metabolizer and at risk for adverse effects or lack of efficacy. Inducers can potentially covert a patient into an extensive metabolizer.

There are also numerous other pharmacogenomic tests, besides the CYP450 polymorphisms, which have a significant impact on medication use, particularly in oncology practice. FDA approved package labeling for many medications includes genetic information along with dosing recommendations for a few products. Published dosing recommendations are available for a wide range of drugs (see **Quick Reference Guide** at the end of this document). For those medications for which dosing guidelines are not available, the clinician must use their best clinical judgment along with the pharmacogenomic testing results to determine whether to initiate a given medication and an appropriate dose.

Resources for Additional Information

Books

- Pharmacogenomics: Applications to Patient Care, Second Edition. ISBN: 978-1-932658-69-9; 2009; 485 pages; softbound, available at accp.com/bookstore
- Pharmacogenomics Handbook, 2nd Edition. SBN 1-59195-124-0; 2006; 419 pages; softbound, available at accp.com/bookstore
- Brazeau DA, Brazeau GA. Principles of the Human Genome and Pharmacogenomics. ISBN: 978-1-58212-124-6; 2011; 124 pages; softbound, available at pharmacist.com/shop_apha

Web Based Resources

Cytochrome P450 Drug Interaction Table
Website: http://medicine.iupui.edu/clinpharm/ddis/table.aspx
Includes comprehensive information regarding substrates, inhibitors, and inducers of drug metabolizing CYP450 enzymes.

Evaluation of Genomic Applications in Practice and Prevention
Website: www.egappreviews.org
The EGAPP Working Group was established in 2005 to support the development of a systematic process for assessing the available evidence regarding the validity and utility of rapidly emerging genetic tests for clinical practice. This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios.

Food and Drug Administration Genomics Group
Website: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/
The Genomics Group, in FDA's Office of Clinical Pharmacology, works to advance the application of genomics in the discovery, development, regulation, and use of medication.

Genomic Applications in Practice and Prevention Network (GAPPNet™)
Website: www.gappnet.org
GAPPNet aims to accelerate and streamline effective and responsible use of validated and useful genomic knowledge and applications, such as genetic tests, technologies, and family history, into clinical and public health practice.

Global Genetic/Genomics Community (G3C)
Website: www.g-3-c.org
G3C is a bilingual collection of unfolding case studies for use with students and practicing healthcare providers learning basic genetic/genomic concepts. When faced with a patient and their needs, there may be multiple ways to meet those needs. Yet, too often education requires learners to follow a linear path to form a solution – negating the multi-dimensional nature of

human beings. An Unfolding Case Study (UCS) can address this deficiency by offering the student a self-guided learning experience which allows for nuanced experiential learning.

Medscape Genomic Medicine Resource Center
Website: www.medscape.com/resource/genomic-medicine
This site compiles various resources for genomics and provides research updates.

National Center for Biotechnology Information (NCBI)
Website: www.ncbi.nlm.nih.gov
The NCBI advances science and health by providing access to biomedical and genomic information.

National Human Genome Research Institute
Website: www.genome.gov
The National Human Genome Research Institute began as the National Center for Human Genome Research (NCHGR), which was established in 1989 to carry out the role of the National Institutes of Health (NIH) in the International Human Genome Project (HGP). In 1997 the United States Department of Health and Human Services renamed NCHGR the National Human Genome Research Institute (NHGRI), officially elevating it to the status of research institute - one of 27 institutes and centers that make up the NIH.

Pharmacogenomics Knowledgebase (PharmGKB)
Website: www.pharmgkb.org
The PharmGKB is a pharmacogenomics knowledge resource that encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations, and genotype-phenotype relationships. PharmGKB collects, curates and disseminates knowledge about the impact of human genetic variation on drug responses.

University of California PharmGenEd™
Website: www.pharmacogenomics.ucsd.edu
Offers live and online continuing education focusing on pharmacogenomics primer concepts and clinical applications in concentrated therapeutic areas for pharmacists and physicians, pharmacy and medical students, and other healthcare professionals.

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Quick Reference Table

The table below contains all the dosing adjustments for CYP450 phenotypes presented in this document for use as a quick reference tool. These guidelines are based on published information but clinicians must still use their clinical judgment in making dosing decisions based on pharmacogenetic testing. Patient response to therapy still needs to be monitored and dosing may need to be adjusted. No available recommendation for a particular phenotype is denoted as "-". It is important to note that the dosing recommendations are a percentage of a standard dose.

Dosing Recommendations Based on CYP Phenotypes				
CYP2C19				
	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Antidepressants				
Amitriptyline	53-59	81-94	104-109	-
Citalopram	61	84	108	Max 150
Clomipramine	62-71	79-88	106-110	-
Doxepin	48	91	105	-
Escitalopram	-	-	-	Max 150
Fluoxetine	39	72	113	-
Fluvoxamine	93	97	101	-
Imipramine	70	83-91	105-108	-
Sertraline	50-75	90	105	-
Trimipramine	31-58	48-73	100-114	-
Other Substrates				
Clopidogrel	Alternative agent	Alternative agent	Usual dose	Usual dose
Clozapine	78	91	104	-
Esomeprazole	Usual dose	Usual dose	Usual dose	100-150 for *H. pylori*, consider for other indications
Lansoprazole	Usual dose	Usual dose	Usual dose	200 for *H. pylori*, consider for other indications
Omeprazole	Usual dose	Usual dose	Usual dose	100-200 for *H. pylori*, consider for other indications
Pantoprazole	Usual dose	Usual dose	Usual dose	400 for *H. pylori*, consider for other

				indications
CYP2C19				
	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Prodrugs	Avoid	Consider avoiding	Usual dose	Usual dose
Other CYP2C19 substrates, not prodrugs	20-60	Lowest typically effective dose	Usual dose	May require higher dose
CYP2C9				
	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Glipizide and other sulfonylureas	20-60	Lowest typically effective dose	Usual dose	Usual dose
Phenytoin (CYP2C19 status should also be considered)	Standard loading dose, reduce maintenance dose by **50%**	Standard loading dose, reduce maintenance dose by **25%**	Usual dose	Usual dose
Celecoxib	Consider a dose reduction by 50%	Usual dose	Usual dose	Usual dose
Warfarin	See separate table below			
Other substrates				
Prodrugs	Avoid	Consider avoiding	Usual dose	Usual dose
Other CYP2C9 substrates, not prodrugs	20-60	Lowest typically effective dose	Usual dose	May require higher dose

Warfarin Dosing

VKORC1 Haplotype	**CYP2C9 Genotype**					
	*1/*1	*1 and *2, *4, *5, or *11	*1/*3, *1/*6	Any 2 of *2, *4, *5, *6, *11	*3 and *2, *4, *5, or *11	*3/*3 or *3/*6
*B/*B	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
*A/*B	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
*A/*A	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

References: 48

CYP2D6				
	Percent of Standard Dose			
Medication	**PM**	**IM**	**EM**	**UM**
Antidepressants				
Amitriptyline	75	75-90	105	130
Bupropion	90	95	105	110
Clomipramine	50-60	90	110	145
Desipiramine	40	80	125	170
Doxepin	35-40	80	130	175-200
Imipramine	30	70-80	130	170-180
Mirtazipine	40	60	-	160
Nortriptyline	55	95	120	150
Paroxetine	65	85	115	135
Trimipramine	35	90	130	180
Venlafaxine	70	80	105	130-150
Antipsychotics				
Aripiprazole	67	-	-	-
Haloperidol	50-75	95	100	115
Olanzapine	60	105	120	150
Perphenazine	30	80	125	175
Risperidone	85	90	100	110
Other substrates				
Codeine, hydrocodone, oxycodone	Avoid	Usual dose, may need alternative	Usual dose	Avoid
Tamoxifen	Avoid	Consider avoiding	-	-
Tramadol	Avoid	Usual dose, may need dose increase	Usual dose	70
Prodrug	Avoid	Usual	Usual	Reduce usual dose
Other CYP2D6 substrates, not prodrugs	50	75-80	Usual	Consider dose increase
CYP2B6, CYP3A4, CYP3A5				
No specific dose adjustments recommended at this time				

References for all dose recommendation tables can be found in the main document.