Chapter e7: Clinical Pharmacogenomics

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KEY CONCEPTS

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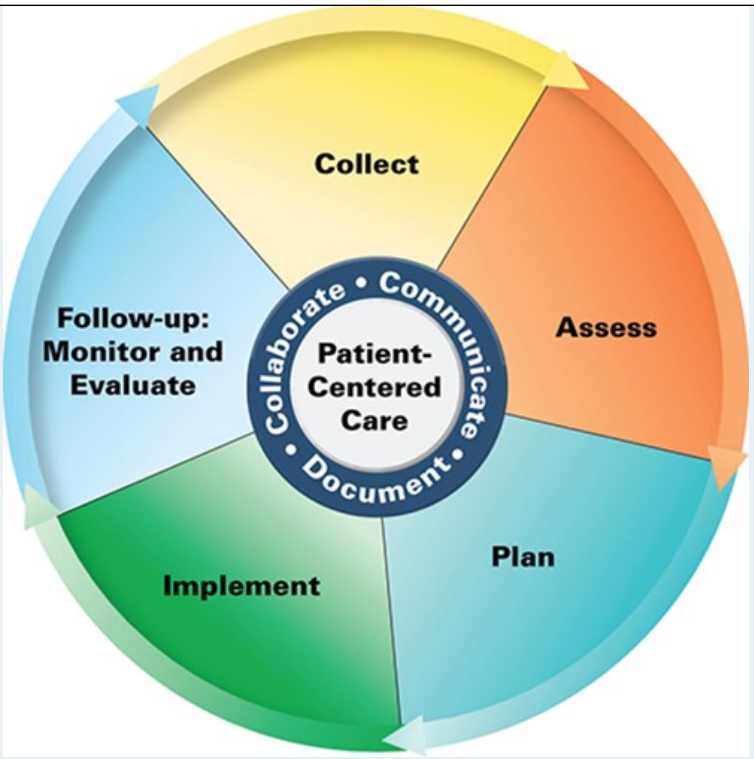
1. Genetic variation contributes to pharmacokinetic and pharmacodynamic properties of medications.
2. Genetic variation affects drug-metabolizing enzymes, transporters, and target proteins, as well as immune-related proteins that may impact medication response.
3. Genetic polymorphisms may influence medication effectiveness and risk for toxicity.
4. Pharmacogenomics is the study of the impact of genetic polymorphisms on medication response.
5. The goals of pharmacogenomics are to optimize medication efficacy and limit toxicity based on an individual's DNA.
6. Single nucleotide polymorphisms are the most common gene variations associated with medication response.
7. Evidence-based resources, such as US Food and Drug Administration medication labels, Clinical Pharmacogenetics Implementation Consortium Guidelines, and the Pharmacogenomics Knowledgebase, are available to help clinicians select and dose medications based on a patient's genetic profile.
8. The pharmacist plays a key role in advancing pharmacogenomics in clinical practice as part of a multidisciplinary healthcare team.

PATIENT CARE PROCESS

Patient Care Process for Application of Pharmacogenomics



Collect

- Patient characteristics (eg, age, sex, pregnancy)
- Patient medical history (personal and family)
- Current medications including OTC use, herbal products, dietary supplements
- Pharmacogenomic test results that are relevant to a patient's care (eg, *CYP2C19* genotype if the patient is being considered for clopidogrel therapy)

Assess

- Pharmacogenomic test results, including translating genotype to phenotype to drug therapy recommendation (see Tables e7-4, e7-6, and e7-7)
- Impact of genetic variation on pharmacokinetics and/or pharmacodynamics (see Fig. e7-3)
- Medication-related problems that may be related to genetic variability, even when a pharmacogenomic test has not been done
- Disease implications of pharmacogenomic test results and refer the patient to a genetics-trained healthcare provider when necessary
- Predisposition to disease and drug response
- Quality and source of existing pharmacogenomic test results
- Actionable versus non-actionable pharmacogenomic test results using high quality, evidence-based pharmacogenomics databases, and clinical guidelines (see Table e7-8)
- Cost, cost-effectiveness, and reimbursement issues relevant to pharmacogenomic tests and services

Plan*

- Integrate pharmacogenomic test results with other clinical variables to optimize medication therapy (see Fig. e7-6)
- Recommend pharmacogenomic testing when appropriate.

Implement*

- Pharmacogenomics-guided care plan
- Document pharmacogenomic test results in the electronic health record

Follow-Up: Monitor and Evaluate

- Presence of medication-related adverse effects
- Pharmacogenomics-guided care plan

****Collaborate with patients, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

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Visit the CPIC Website: https://cpicpgx.org/. Select and review a gene-drug guideline. Briefly describe how these recommendations may be applied to clinical practice. This activity is intended to build your experience with accessing pharmacogenomic guidelines and how they may be integrated into prescribing decisions.

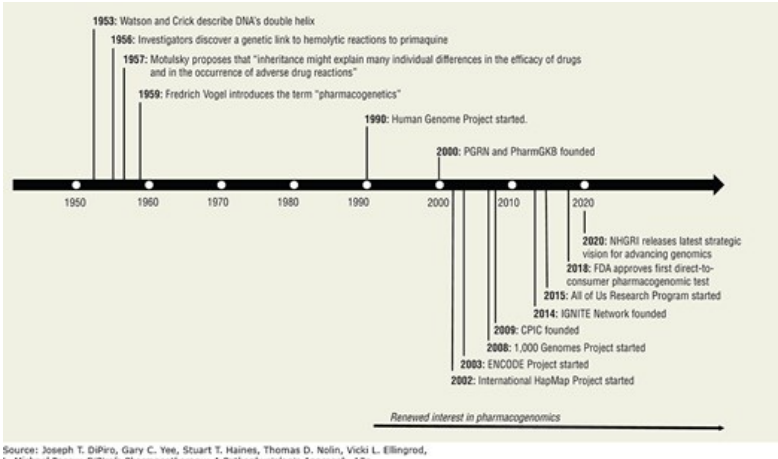
INTRODUCTION

Great variability exists among individuals in response to medication therapy, and it is difficult to predict how effective or safe a medication will be for a particular patient. For example, when treating a patient with depression, it may be necessary to try several agents or a combination of agents before achieving adequate depressive symptom control with acceptable tolerability. Several clinical factors are known to influence medication response, including age, body size, kidney and liver function, and concomitant medication use. However, considering these factors alone is often insufficient in predicting the likelihood of medication efficacy or safety for a given patient. For example, identical antidepressant therapy in two patients of similar age, sex, race, and with similar medical histories and concomitant medication therapy may produce inadequate control of depressive symptoms in one patient and intolerable adverse effects in the other.

[1] [2] The observed interpatient variability in medication response may result largely from genetically determined differences in drug metabolism, distribution, and target proteins. The influence of heredity on medication response was demonstrated as early as 1956 with the discovery that an inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD) was responsible for hemolytic reactions to the antimalarial drug primaquine (Fig. e7-1). Variations in genes encoding cytochrome P450 (CYP) and other drug-metabolizing enzymes are now well-recognized as causes of interindividual differences in plasma concentrations of certain medications. These variations may have serious implications for medications with a narrow therapeutic index such as warfarin, phenytoin, and mercaptopurine. Other variations associated with medication response occur in genes for drug transporters such as the solute carrier organic anion transporter (OAT) family member 1B1 (SLCO1B1) as well as drug targets such as receptors and enzymes. Genetic variations for drug-metabolizing enzymes and transporter proteins may influence drug disposition, thus altering pharmacokinetic properties. Drug target genes may alter pharmacodynamic mechanisms by affecting sensitivity to a medication at its target site. Variation in immune-related genes, such as those that encode human leukocyte antigen (HLA) molecules, may affect a patient's predisposition to severe medication hypersensitivity reactions despite having no direct effect on pharmacokinetic or pharmacodynamic mechanisms.

FIGURE e7-1

Timeline of genomic discoveries and initiatives. (CPIC, Clinical Pharmacogenetics Implementation Consortium; ENCODE, Encyclopedia of DNA Elements; FDA, US Food and Drug Administration; IGNITE, Implementing Genomics in Practice; NHGRI, National Human Genome Research Project; PharmGKB, Pharmacogenomics Knowledgebase; PGRN, Pharmacogenomics Research Network)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

PHARMACOGENOMICS: A DEFINITION

3 4 Pharmacogenomics, the field of study at the intersection of pharmacology and genomics, involves the search for genetic variations that lead to interindividual differences in medication response. The term *pharmacogenetics* often is used interchangeably with the term *pharmacogenomics*. Historically, pharmacogenetics referred to variation in a single gene that affects medication response, whereas pharmacogenomics referred to the entire spectrum of genes that interact to determine medication efficacy and safety. For example, a pharmacogenetic study examines the influence of the *CYP2C9* gene on warfarin dose requirements. Conversely, a pharmacogenomic study might examine the interaction between the *CYP2C9*, vitamin K oxidoreductase complex subunit 1 (*VKORC1*), and *CYP4F2* genes on warfarin dose requirements. Given that multiple proteins are involved in determining the ultimate response to most medications, many investigators are taking a more pharmacogenomic approach to elucidating genetic contributions to medication response. However, most examples of pharmacogenetic testing in clinical practice today involve single genes. Based on the current usage of the terms, this chapter treats pharmacogenetics and pharmacogenomics as synonymous.

5 The goals of clinical pharmacogenomics are to optimize medication therapy and limit toxicity based on an individual's genetic profile. Thus, clinical pharmacogenomics aims to use genetic information to choose a medication and dose that will have the greatest likelihood for achieving therapeutic outcomes with the least potential for harm in a given patient. Pharmacogenomic discoveries have provided opportunities for clinicians to use genetic tests to predict individual responses to medication and specifically select medications for patients based on identified genetic variants. Genotype-guided therapy is already a reality for some diseases, such as cancer and cystic fibrosis, where novel medications have been developed to target specific genetic mutations. Clinical implementation of pharmacogenomics has also emerged in other therapeutic areas, including cardiology, psychiatry, neurology, pain management, and infectious disease.

HUMAN GENOME PROJECT AND SUBSEQUENT EFFORTS IN PRECISION MEDICINE

While the discovery of genetic contributions to medication response dates back to the 1950s, interest in clinical pharmacogenomics began in earnest with the sequencing of the human genome in 2003 (Fig. e7-1). The final version from the Human Genome Project contains 99% of the gene-containing sequence, with 99.9% accuracy. The International HapMap Project followed the Human Genome Project and aimed to identify common patterns of heritability, called haplotypes, in the human genome. This enabled genome-wide association studies that led to discoveries of previously unsuspected variants linked to medication response, including a variant in the *CYP2C18-CYP2C19-CYP2C9-CYP2C8* gene cluster linked to warfarin dose requirement in persons of African ancestry.[1]

The Clinical Pharmacogenetics Implementation Consortium (CPIC), which is funded by the National Institutes of Health, provides evidence-based guidelines describing how to use pharmacogenomic test results to optimize medication therapy (Table e7-1). The US Food and Drug Administration

(FDA) also provides gene-based dosing guidance for certain medications in their labeling. See the "Pharmacogenomic Medication Labeling and Guidelines" section for more information about these and other pharmacogenomics resources. Other major efforts funded by the US government to advance precision medicine are described in Table e7-1.

TABLE e7-1

Federally Funded Efforts to Advance Precision Medicine

Year Started	Project Name	Goal
2000	Pharmacogenomics Research Network (PGRN) (www.pgrn.org)[a]	Discover genetic associations with drug response across a number of diseases.
2000	Pharmacogenomics Knowledgebase (PharmGKB) (www.pharmgkb.org)	Collect, curate, and disseminate information about a human genetic variation on drug response.
2002	International HapMap Project (https://www.genome.gov/10001688/international-hapmap-project)	Determine the common patterns of DNA sequence variation in the human genome and make this information freely available in the public domain.
2003	Encyclopedia of DNA Elements (ENCODE) Project (www.encodeproject.org)	Create a catalog of functional elements in the human genome.
2008	1,000 Genomes Project (www.internationalgenomes.org)	Develop a comprehensive catalog of less common genetic variation in the human genome through a DNA sequencing approach.
2009	Clinical Pharmacogenetics Implementation Consortium (CPIC) (cpicpgx.org)	Create consensus-based clinical guidelines on how to use genetic test results to optimize pharmacotherapy.
2014	Implementing Genomics in Practice (IGNITE) Network (https://ignite-genomics.org)	Enhance the use of genomic medicine, including pharmacogenomics, in clinical care.
2015	*All of Us* Research Program (www.allofus.nih.gov)	Build a national research resource of longitudinal data, including genetic data, from at least one million persons in the United StatesU.S. to facilitate novel approaches to prevent and treat disease based on genetic, environmental, and social factors.

[a]Renamed in 2021 as the "Pharmacogenomics Global Research Network."

GENETIC CONCEPTS

The human genome contains more than 3 billion nucleotide base pairs, which include approximately 20,000 protein-coding genes. Two purine nucleotide bases, adenine (A) and guanine (G), and two pyrimidine nucleotide bases, cytosine (C) and thymidine (T), are present in deoxyribonucleic acid (DNA), with purines and pyrimidines always pairing together as A-T and C-G in the two strands that make up the DNA double-helix. Most nucleotide base pairs are identical from person to person, with only 0.1% contributing to individual differences.

According to the central dogma of biology, when one strand of DNA is transcribed into RNA and translated to make a protein, three consecutive nucleotides form a codon. Each codon specifies an amino acid or amino acid chain termination. For example, the nucleotide sequence, or codon, GGA specifies the amino acid glycine. The genetic code has substantial redundancy, in which two or more codons code for the same amino acid. For

example, GGC, GGG, and GGT also code for glycine. Amino acids are the basic constituents of proteins, which mediate all cellular functions. Only 20 different amino acids, in various arrangements, form the basic units of all the proteins in the human body.

A gene is a series of codons that specifies a particular protein. Genes contain several regions: *exons* that encode for the final protein, *introns* that consist of intervening noncoding regions, and *regulatory regions* that control gene transcription. Introns may also contain regulatory sequences. In most cases, an individual carries two alleles, one from each parent, at each gene locus. An *allele* is defined as the sequence of nucleic acid bases at a given gene chromosomal locus. Two identical alleles make up a *homozygous* genotype, and two different alleles make up a *heterozygous* genotype. A *phenotype* refers to the outward expression of the genotype. Common genetic terms and their definitions are provided in Table e7-2.

TABLE e7-2

Common Genetic Terms and Their Definitions

Term	Definition
Allele	A version of a gene. An individual inherits two alleles for each gene, one from each parent.
Diplotype	A haplotype pair (eg, two alleles inherited for a particular gene).
Gene	Basic physical unit of inheritance.
Genotype	An individual's collection of genes. Can also refer to the two alleles inherited for a particular gene.
Haplotype	A set of DNA variations that tend to be inherited together.
Heterozygous	Two different alleles inherited for a given gene.
Homozygous	Two identical alleles inherited for a given gene.
Nucleotide	Basic building block of nucleic acids (RNA and DNA). Consists of a sugar molecule (ribose in RNA or deoxyribose in DNA) attached to a phosphate group and a nitrogen-containing base. The bases in DNA are adenine (A), cytosine (C), guanine (G), and thymine (T). In RNA, the base uracil (U) takes the place of thymine.
Phenotype	An individual's observable traits
Polymorphism	One of two or more variants of a particular DNA sequence. The most common type of polymorphism involves variation at a single base pair (ie, single nucleotide polymorphism or SNP).

TYPES OF GENETIC VARIATIONS

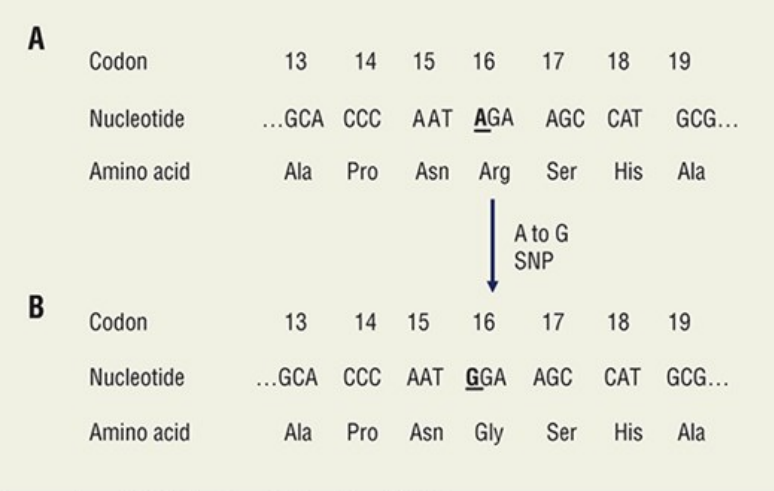
Genetic variations occur as either rare defects or polymorphisms. *Polymorphisms* are defined as variations in the genome that occur at a frequency of at least 1% in the human population. For example, the genes encoding the CYP enzymes 2B6, 2C9, 2C19, 2D6, and 3A5 are polymorphic, with functional gene variants of greater than 1% occurring in different biogeographical ancestry groups. In contrast, some variants occur in less than 1% of the population and cause inherited diseases such as cystic fibrosis, hemophilia, and Huntington's disease. Common diseases, such as essential hypertension and Type 2 diabetes mellitus, are polygenic in which multiple genetic polymorphisms in conjunction with environmental factors contribute to the disease susceptibility.

6 Single-nucleotide polymorphisms, abbreviated as SNPs and pronounced "snips," are the most common genetic variations in human DNA, occurring once approximately every 300 base pairs. More than 20 million SNPs have been mapped in the human genome. SNPs occur when one nucleotide base pair replaces another, as illustrated in Fig. e7-2. Thus, SNPs are single-base differences that exist between individuals. Nucleotide

substitution results in two possible alleles. One allele, typically either the most commonly occurring allele or the allele originally sequenced, is considered the *normal* or *wild type*, and the alternative allele is considered the *variant allele*.

FIGURE e7-2

Nucleotide sequence of the β_2-adrenergic receptor gene from codons 13 to 19. (*A*) Nucleotide sequence of the wild-type allele with adenine (A) at nucleotide position 46 (*underlined*) located in codon 16 of the β_2-adrenergic receptor gene. The AGA codon designates the amino acid arginine (Arg), with an average frequency of 39% in the human population. (*B*) Nucleotide sequence of the variant allele with guanine (G) at nucleotide position 46 (*underlined*), located in codon 16. The GGA codon designates the amino acid glycine (Gly), which occurs at an average frequency of 61%. Although the Arg16 polymorphism occurs less commonly than the Gly16 polymorphism, it is referred to as the wild type because it was identified first.



An SNP may result in amino acid substitution, which may or may not alter the function of the encoded protein. For example, in Fig. e7-2, guanine (G) is substituted for adenine (A) at nucleotide 46 in the β_2-adrenergic receptor gene.[2] This results in the substitution of glycine for arginine at amino acid position (codon) 16 and alterations in receptor downregulation on prolonged exposure to β_2-receptor agonists. SNPs that result in amino acid substitution are referred to as *nonsynonymous*. SNPs that do not result in amino acid substitution are called *synonymous*, which often are silent (ie, have no effect on the resultant protein product). Referring to a previous example of redundancy in the genetic code, replacement of thymine (T) with cytosine (C) in the codon CGT is an example of a synonymous SNP because both CGT and CGC code for arginine. Synonymous SNPs and variants occurring in regulatory regions of the gene are usually abbreviated based on the nucleotides involved and the nucleotide base position. For example, c.3608C > T indicates that either cytosine or thymine may occur, with cytosine occurring most often at position 3608 of a given gene region. Nonsynonymous SNPs usually are designated by the amino acids and codons involved. For example, p.Arg144Cys (or p.R144C using amino acid symbols) indicates that cysteine may be substituted for arginine at codon 144. Alternatively, SNPs may be referred to by their reference SNP number (or rs number, eg, rs12777823), as designated by the National Center for Biotechnology Information SNP database (dbSNP; https://www.ncbi.nlm.nih.gov/snp/). If an SNP changes the amount or function of a protein that contributes to medication response, it may alter pharmacokinetic properties or a patient's sensitivity to a medication or otherwise predispose a patient to adverse medication reactions.

The following are other examples of genetic variants:

1. *Insertion-deletion polymorphisms*, in which a nucleotide or nucleotide sequence is either added to or deleted from a DNA sequence.
2. *Tandem repeats*, in which a nucleotide sequence repeats in tandem (eg, if "AG" is the nucleotide repeat unit, "AGAGAGAGAG" is a five-tandem repeat).
3. *Frameshift mutation*, in which there is an insertion/deletion polymorphism, and the number of nucleotides added or lost is not a multiple of three, resulting in disruption of the gene's reading frame.

4. *Defective splicing*, in which an internal polypeptide segment is abnormally removed, and the ends of the remaining polypeptide chain are joined.
5. *Aberrant splice site*, in which processing of the protein occurs at an alternate site.
6. *Premature stop codon polymorphisms*, in which there is the premature termination of the polypeptide chain by a stop codon (a specific sequence of three nucleotides that do not code for an amino acid but rather specify polypeptide chain termination).
7. *Copy number variants*, in which entire copies of genes or gene segments more than 1 kb in size are duplicated, deleted, or rearranged.

Single nucleotide polymorphisms may occur in exon, intron, or regulatory regions of a gene. Those occurring in exons may alter protein function, whereas those in regulatory regions (eg, the promoter region) may alter gene expression and the amount of protein that is produced. For example, the variant c.-1639 G>A in the promoter region of the *VKORC1* gene alters a transcription factor binding site and results in decreased gene expression and decreased VKORC1 enzyme produced, which is clinically relevant for warfarin dosing.[3] Variations in the intron region may be silent unless they affect intron splicing or otherwise alter gene expression. Multiple SNPs may be in *linkage disequilibrium* with each other. This means that two or more SNPs are inherited together more frequently than would be expected based on chance alone. For example, if there are two possible SNPs, c.-1639 G>A and c-1173 C>T, in a given gene (eg, *VKORC1* in this example), and an A at position -1639 always occurs with a T at position -1173 and vice versa, the two SNPs are said to be in *complete linkage disequilibrium*.[3] A set of SNPs that are inherited together is called a *haplotype*.

Within the field of clinical pharmacogenomics, the "star (*) allele" nomenclature is used. The wild-type allele is denoted as **1* ("star one"). Every other allele is given another number as its name (eg, **2*, **3*, **4*, **5*) to easily distinguish one from the other. Each star allele (ie, haplotype) may be defined by one or more SNPs or other types of genetic variants. Two star alleles together (eg, **1*/**2*), representing one maternal allele and one paternal allele, are referred to as a diplotype or a genotype. In clinical practice, pharmacogenomic testing is often conducted using genotyping rather than sequencing. In other words, laboratories have a prespecified set of SNPs they are looking for rather than identifying each nucleotide in the gene, which would be a more costly approach and lead to the identification of variants of unknown significance.

A limitation of genotyping is that a **1* designation is assigned if none of the prespecified variants was detected for a particular gene. In clinical practice, we would assume the patient to have the "normal" allele, but in reality, the patient could harbor a clinically important genetic variant that was not tested by the lab. Allele frequencies vary across biogeographical ancestry groups; therefore, it is important to assess the variants tested by a clinical laboratory to ensure that they are adequately representative across populations. For example, many labs have traditionally only tested the **2* and **3* alleles for *CYP2C9*, which are the most common alleles associated with a loss of enzyme activity in patients of European ancestry, but not in those of African ancestry in whom the reduced function **5*, **6*, **8*, and **11* occur. Genotyping for *CYP2C9*2* and **3* only in African ancestry populations can lead to misclassifying a large percentage of individuals as normal metabolizers when in fact they have a reduced function allele for which the lab did not test. The Association for Molecular Pathology now publishes guidelines on what alleles should be tested for certain pharmacogenes to ensure appropriate coverage of clinically relevant variants for diverse populations.[4–6]

POLYMORPHISMS IN GENES FOR DRUG-METABOLIZING ENZYMES

Polymorphisms in the drug-metabolizing enzymes represent the first recognized and, so far, the most documented examples of genetic variants with consequences in medication response and toxicity. The major phase-I enzymes are the CYP superfamily of isoenzymes. *N*-acetyltransferase, uridine diphosphate glucuronosyltransferase (UGT), and glutathione *S*-transferase are examples of phase II metabolizing enzymes that exhibit genetic polymorphisms. Thiopurine *S*-methyltransferase (TPMT) and dihydropyrimidine dehydrogenase (DPD) are examples of nucleotide base-metabolizing enzymes. Genetic variation can lead to a spectrum of drug-metabolizing enzyme activity (ie, phenotypes): poor metabolizer (PM), intermediate metabolizer (IM), normal metabolizer (NM), rapid metabolizer (RM), and ultrarapid metabolizer (UM).[7]

When assessing the effects of genetic variation on drug metabolism, it is important to consider whether the parent drug is active or inactive (ie, a prodrug) and whether it is metabolized into an active or an inactive metabolite (Fig. e7-3). For example, if an active drug is metabolized into an inactive metabolite by a specific enzyme, genetic variation leading to ultrarapid metabolism could yield subtherapeutic plasma concentrations and treatment failure with normal doses. In contrast, decreased metabolism could yield supratherapeutic concentrations and toxicity with normal doses. In the case of a prodrug, the opposite is true (Fig. e7-3). The clinical significance of genetic variation in plasma concentrations of drugs and their metabolites depends on the drug's therapeutic index and number of enzymatic pathways involved.

FIGURE e7-3

The clinical impact of genetic variation on drug metabolism depends on whether the parent drug is active or inactive, and whether its metabolite is active or inactive. (*A*) Active drug converted into an inactive metabolite and (*B*) prodrug (inactive) converted into an active metabolite.

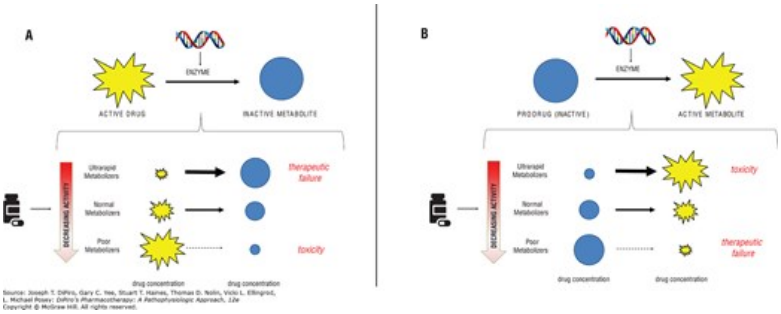


Table e7-3 lists examples of polymorphic metabolizing enzymes and corresponding drug substrates whose plasma concentrations and pharmacologic effects may be altered as a consequence of genetic variation. Examples of such effects are discussed in the following sections.

TABLE e7-3

Examples of Substrates for Drug-Metabolizing Enzymes Exhibiting Genetic Variability

Enzyme	Drug Substrate
CYP2D6	Atomoxetine
	Antipsychotics (aripiprazole, brexpiprazole, iloperidone, pimozide)
	Metoclopramide
	Ondansetron
	Opioid analgesics (codeine, tramadol)
	Selective serotonin reuptake inhibitors (paroxetine, fluvoxamine)
	Tamoxifen
	Tricyclic antidepressants (desipramine, nortriptyline, amitriptyline, imipramine)
	Venlafaxine
	Vortioxetine
CYP2C9	Nonsteroidal anti-inflammatory drugs (celecoxib, flurbiprofen, ibuprofen, meloxicam, piroxicam)
	Phenytoin
	Warfarin
CYP2C19	Clobazam
	Clopidogrel

	Proton pump inhibitors (dexlansoprazole, lansoprazole, omeprazole, pantoprazole)
	Selective serotonin reuptake inhibitors (citalopram, escitalopram, sertraline)
	Tricyclic antidepressants (amitriptyline, imipramine)
	Voriconazole
CYP2B6	Efavirenz
	Methadone
Thiopurine *S*-methyltransferase	Thiopurines (azathioprine, mercaptopurine, thioguanine)
N-acetyltransferase	Hydralazine
	Isoniazid
Uridine diphosphate glucuronosyltransferase	Irinotecan

Cytochrome P450 Enzymes

About 57 different CYP isoenzymes have been documented to be present in humans, with 42 involved in the metabolism of exogenous xenobiotics and endogenous substances such as steroids and prostaglandins.[8] Isoenzymes within CYP families 1, 2, and 3 are known to be involved in the metabolism of medications, and significant interindividual variabilities in enzyme activity exist as a result of induction, inhibition, and genetic inheritance. The Pharmacogene Variation (PharmVar) Consortium (www.pharmvar.org) maintains a list of important pharmacogenes and their known alleles. Functional genetic polymorphism has been discovered for *CYP2D6*, *CYP2C19*, *CYP2C9*, *CYP2B6,* and *CYP3A4/5*, and their impacts on medication therapy are described hereunder.

CYP2D6

CYP2D6 is involved in the metabolism of numerous medications spanning a variety of therapeutic areas, including analgesics, antidepressants, antipsychotics, antiarrhythmics, antihypertensives, and anticancer agents, among others.[9] *CYP2D6* genetic variants are the best characterized among all of the *CYP* variants. The *CYP2D6* gene is one of the most polymorphic human genes; over 140 alleles have been identified. Each allele is assigned a function—normal function, decreased function, or no-function—depending on the effect of that allele on the resultant protein (see www.pharmvar.org for a complete list of alleles and their functions). In some individuals, the *CYP2D6* gene is deleted (as denoted by *CYP2D6*5*) or duplicated. This type of structural genetic variation, called copy number variation, can have a significant impact on CYP2D6 enzyme activity.

Translating *CYP2D6* genotype into phenotype uses an "activity score" system (Table e7-4)[10]. An "activity value" is assigned to each allele, based on its assigned function: 0 for no-function, 0.25 or 0.5 for decreased function, or 1 for normal function. If an allele is duplicated, then the activity value is multiplied by the number of copies present. An individual's CYP2D6 activity score is the sum of the activity values for each of their alleles. For example, an individual with the *CYP2D6*1/*4* diplotype has one normal function allele (**1*, activity value = 1) and one no-function allele (**4*, activity value = 0) and thus would have an activity score of 1 + 0 = 1. An activity score of 1 corresponds to the IM phenotype.

TABLE e7-4

Phenotype Definitions Based on *CYP2D6*, *CYP2C19*, and *CYP2C9* Genotypes

Gene	Phenotype	Definition Based on Genotype
CYP2D6	Poor metabolizer	Activity score[a] = 0 (eg, two no-function alleles, such as **4/*5*)
	Intermediate metabolizer	Activity score[a]= 0 < x ≤ 1 (eg, one normal function allele and one no-function allele, such as **1/*4*)
	Normal metabolizer	Activity Score[a] = 1 < x ≤ 2.25 (eg, two normal function alleles, such as **1/*1*)
	Ultrarapid metabolizer	Activity score[a] > 2.25 (eg, more than two normal function alleles, such as **1/*2xN*)
CYP2C19	Poor metabolizer	Two no-function alleles (eg, **2/*2*)
	Likely poor metabolizer	One decreased function allele and one no-function allele (eg, **2/*9*)
	Intermediate metabolizer	One normal function allele and one no-function allele (eg, **1/*2*) or one increased function allele and one no-function allele (eg. **2/*17*)
	Likely intermediate metabolizer	One normal function allele and one decreased function allele (eg, **1/*9*) or one increased function allele and one decreased function allele (eg, **9/*17*) or two decreased function alleles (eg, **9/*9*)
	Normal metabolizer	Two normal function alleles (eg, **1/*1*)
	Rapid metabolizer	One normal function allele and one increased function allele *(*1/*17*)
	Ultrarapid metabolizer	Two increased function alleles (**17/*17*)
CYP2C9	Poor metabolizer	Activity score[a] = 0 (eg, two no-function alleles, such as **3/*3*)
	Intermediate metabolizer	Activity score[a] = 1 (eg, one normal function allele and one no-function allele, such as **1/*3* or two decreased function alleles, such as **2/*2*) or Activity Score[a] = 1.5 (eg, one normal function allele and one decreased function allele, such as **1/*2*)
	Normal metabolizer	Activity score[a] = 2 (two normal function alleles, such as **1/*1*)

[a]The activity score is the sum of the activity values for each allele in a diplotype.

The no-function variants, *CYP2D6*4* (c.1847G>A, defective splicing) and *CYP2D6*5* (gene deletion), are predominantly found in patients of European ancestry (5%-10% of the population are PMs) and result in an inactive enzyme and absence of enzyme, respectively. The predominant variants in

people of Asian and African ancestry are *CYP2D6*10* (c.100C>T, Pro34Ser) and *CYP2D6*17* (c.1022C>T, Thr107Ile), respectively, both resulting in single-amino-acid substitution and consequent reduction in enzyme activity. The presence of two no-function alleles (eg, *CYP2D6*3, CYP2D6*4*, *CYP2D6*5*, or *CYP2D6*6*) results in the PM phenotype and the inability to metabolize CYP2D6-dependent substrates. Depending on the importance of the affected CYP2D6 pathway to overall drug metabolism and the drug's therapeutic index, clinically significant side effects may occur. A medication administered in its active form to a PM may result in elevated concentrations (Fig. e7-3, panel *A*). For example, the selective serotonin reuptake inhibitor paroxetine is primarily metabolized by CYP2D6 into inactive metabolites. A CYP2D6 PM who receives a normal dose of paroxetine will likely experience supratherapeutic plasma concentrations and be at higher risk for adverse effects. Per CPIC guidelines, these patients should receive 50% of the normal paroxetine dose or avoid the medication altogether.[11]

The therapeutic implication of *CYP2D6* polymorphism is different if the substrate is a prodrug (Fig. e7-3, panel *B*). In this case, PMs would not be able to convert the drug into the therapeutically active metabolite. Two examples of prodrugs dependent on CYP2D6-mediated conversion to active forms are codeine and tramadol. Codeine and tramadol are converted by CYP2D6 to morphine and *O*-desmethyltramadol, respectively, and CYP2D6 PMs experience little to no analgesic relief after taking these medications.[12] Similarly, lower efficacy of tamoxifen may be observed in PMs. Tamoxifen is converted by CYP2D6 to the more potent antiestrogen metabolite, endoxifen, and PMs have shortened time to recurrence of breast cancer and worse relapse-free survival.[13]

UMs possess higher than normal enzyme activity as a result of having more than two fully functional gene alleles. This phenotype has clinical implications in terms of dosage adjustment for some CYP2D6 substrates and risk for toxicity with other substrates. For the CYP2D6 substrate nortriptyline, which is inactivated by CYP2D6, patients with multiple copies of *CYP2D6*2* may require doses threefold to fivefold higher than normally recommended to achieve therapeutic plasma concentrations (50-150 ng/mL [mcg/L; 190-570 nmol/L]).[14] Similarly, lower efficacy may be observed in UMs with antiemetics such as ondansetron.[15] Conversely, UMs administered the usual therapeutic dose of codeine or tramadol might exhibit symptoms of narcotic overdose associated with high morphine or *O*-desmethyltramadol concentration, respectively. This toxicity potential had been observed in children who receive codeine or tramadol post-tonsillectomy and who are CYP2D6 UMs.[16,17] The FDA required a labeling change for codeine or tramadol contraindicating use of these medications to manage pain in children post-tonsillectomy because of the increased risk for respiratory depression in UMs. The American Academy of Pediatrics also cautioned against codeine use in children.[18] In April 2017, FDA contraindicated codeine use in all children younger than 12 years without regard to CYP2D6 status. FDA is considering amending this contraindication to include an exception for children who are known to be CYP2D6 NMs or IMs if they are not post-tonsillectomy as a result of a Citizen Petition submitted by an interdisciplinary group of pharmacogenomics experts.[19]

In general, drug interactions involving inhibition of CYP2D6 are relevant for UMs, NMs, and IMs, but not for PMs, who have no enzyme activity. For example, in NMs, but not PMs, hemodynamic responses to metoprolol (a CYP2D6 substrate) are pronounced and prolonged during concomitant diphenhydramine administration.[20] Strong CYP2D6 inhibitors, such as paroxetine, fluoxetine, and bupropion may substantially reduce the metabolic capacity of NMs so that they appear phenotypically as PMs.[21] This phenomenon is called *phenoconversion*. Moderate CYP2D6 inhibitors, such as duloxetine, may phenoconvert patients who are NMs based on genotype to IMs. Given the abundance and greater antiestrogenic activity of endoxifen,[13] the use of paroxetine, fluoxetine, or duloxetine in tamoxifen-treated patients should best be avoided. When there is a need for concurrent antidepressant administration with tamoxifen, those with a lesser extent of CYP2D6 inhibition, such as citalopram and venlafaxine,[21] would be better alternatives.

CYP2C19

Of over 35 alleles for the *CYP2C19* gene, the principal no-function alleles are *CYP2C19*2* (c.681G > A, aberrant splice site) in exon 5 and *CYP2C19*3* (c.636G > A, premature stop codon) in exon 4 of *CYP2C19*.[22] Individuals with two no-function alleles have no enzyme activity and are assigned the PM phenotype. IMs have a single no-function allele and reduced enzyme activity compared to NMs with two fully functional alleles (Table e7-4). The clinical relevance of *CYP2C19* genetic variation has been demonstrated for certain proton pump inhibitors (omeprazole, lansoprazole, pantoprazole, and dexlansoprazole), selective serotonin reuptake inhibitors (citalopram, escitalopram, and sertraline), tertiary amine tricyclic antidepressants (eg, amitriptyline), voriconazole, and clopidogrel.

CYP2C19 PMs exhibit up to a 10-fold increase in the area under the curve (AUC) of omeprazole compared with NMs.[23] The presence of a no-function

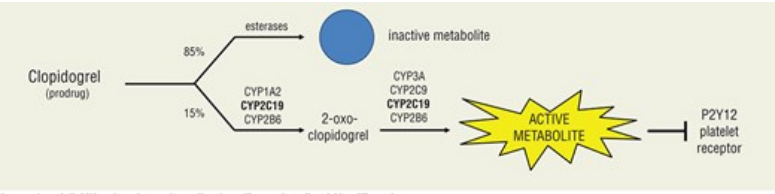
CYP2C19 allele has been associated with improved *Helicobacter pylori* cure rates after dual therapy including omeprazole,[24] and triple therapy including omeprazole, lansoprazole, or pantoprazole.[25,26] The cure rate achieved with dual therapy was 100% in PMs compared with 60% and 29% in IMs and NMs, respectively.[24]

These differences likely reflect the higher achievable intragastric pH in the PMs.[23] NMs who failed initial triple therapy (lansoprazole, clarithromycin, and amoxicillin) were retreated with high-dose lansoprazole (30 mg four times daily) and amoxicillin achieved a 97% *H. pylori* eradication.[23] A gene–dose effect in attainment of desirable intragastric pH ranges and *H. pylori* eradication rate, as well as the cost-effectiveness of pharmacogenomic-guided dosing is known for lansoprazole.[23,27] CPIC provides *CYP2C19* genotype-guided recommendations for proton pump inhibitors.[28]

Conversely, CYP2C19 IMs and PMs may have reduced response to the antiplatelet agent clopidogrel. This is because clopidogrel is a prodrug that requires conversion via CYP2C19 to its active form, as shown in Fig. e7-4. In IMs and PMs, clopidogrel may be less effective at inhibiting platelet aggregation and preventing cardiovascular events than in NMs, particularly in patients who suffer an acute coronary syndrome and undergo percutaneous coronary intervention (PCI).[29] In these patients, guidelines by CPIC recommend alternative therapy with prasugrel or ticagrelor for IMs and PMs in the absence of contraindications.[29] Patients who are genotyped as part of clinical care at the time of PCI exhibit a significantly lower risk of major adverse cardiovascular events in IMs and PMs treated with alternative therapy versus clopidogrel.[30] A large randomized controlled trial, the POPular Genetics trial (ClinicalTrials.gov Identifier NCT01761786), and a meta-analyses further support the value of *CYP2C19* genotyping to guide antiplatelet therapy.[31–33]

FIGURE e7-4

Clopidogrel bioactivation pathway. Approximately 85% of the drug is inactivated by esterases, and the remaining 15% is bioactivated to the active thiol metabolite that inhibits platelet activation via a two-step process. Cytochrome P450 (CYP) 2C19 is involved in both steps of the process.



The allelic variant *CYP2C19*17* is a promoter variant that leads to increased gene expression and increased overall CYP2C19 enzyme activity. Individuals with one normal function allele and one **17* allele are considered RMs (ie, *CYP2C19*1/*17*), whereas individuals with two **17* alleles are considered UMs (ie, *CYP2C19*17/*17*) (Table e7-4). CPIC guidelines recommend that CYP2C19 UMs receive higher doses of certain proton pump inhibitors and alternative therapy for other CYP2C19 substrates such as voriconazole, citalopram, and escitalopram.[11,28,34]

CYP2C9

Another polymorphic isoenzyme of CYP2C is CYP2C9, which metabolizes narrow therapeutic index drugs such as warfarin and phenytoin into inactive metabolites. Like *CYP2D6*, there is an activity score system to translate *CYP2C9* genotype into phenotype (Table e7-4). Warfarin is a racemic mixture, and the more potent *S*-isomer is metabolized by CYP2C9. *CYP2C9*2* (p.Arg144Cys; a decreased function allele) and *CYP2C9*3* (p. Ile359Leu; a no-function allele) are the two most common *CYP2C9* variants in patients of European ancestry, and both exhibit single-amino-acid substitutions at positions critical for enzyme activity.[35] This could have clinically important consequences in warfarin-treated patients. For example, a 90% reduction in *S*-warfarin clearance occurs in *CYP2C9*3* homozygotes compared with subjects homozygous for the wild-type (**1*) variant,[36] requiring dose reduction to 0.5 mg/day in a patient expressing the *CYP2C9*3* homozygote initially given usual doses of warfarin.[37] Patients requiring low doses of warfarin (less than or equal to 1.5 mg/day) have an overrepresentation of *CYP2C9* variant alleles and more difficulty with warfarin induction, requiring longer hospital stays to stabilize the warfarin regimen and experiencing a higher incidence of bleeding complications.[38] Similar to CYP2D6, concurrent medication therapy that affects CYP2C9 enzyme activity would influence the association between warfarin dose requirement and *CYP2C9* genotypes.[39]

Both *CYP2C9*2* and *CYP2C9*3* are more common in people of European ancestry than in those with Asian or African ancestry. The *CYP2C9*2* allele is

rare to absent in people of Asian ancestry. The *CYP2C9*5*, **6*, **8*, and **11* alleles are decreased or no-function alleles occurring predominately in African ancestry populations and leading to lower warfarin dose requirements.[35] The *CYP2C9*8* allele is most common among these, occurring in approximately 12% of people of African ancestry, and may have important implications for the metabolism of *CYP2C9* substrates in this population.

CYP2C9 polymorphisms, in conjunction with a polymorphism in the *VKORC1* gene (which encodes warfarin's target enzyme), influence warfarin dose requirements and form the basis for a consensus-based guideline from CPIC.[35] The use of *CYP2C9* and *VKORC1* genotypes in dosing warfarin is discussed in the "Polymorphisms in Drug Target Genes" section

CYP2B6

Although the role of CYP2B6 in the metabolism of anticancer medications such as cyclophosphamide and ifosfamide, the smoking cessation agent bupropion, and methadone has been studied, it is with the antiretroviral agents that its clinical relevance is most apparent.[40] The nonnucleoside reverse transcriptase inhibitor efavirenz is metabolized by CYP2B6 into inactive metabolites. Many patients receiving efavirenz experience central nervous system (CNS) adverse effects that are related to variable systemic exposure to the medication, which could be related to the lower metabolizing efficiency of the *CYP2B6*6*, **16*, or **18* alleles.[41] As such, dose reduction in patients with decreased CYP2B6 activity is recommended to minimize the risk of CNS adverse effects without compromising efficacy.[42]

CYP3A4/5

Within the *CYP3A* subfamily, at least three isoenzymes, namely, CYP3A4, CYP3A5, and CYP3A7, have been characterized. Despite as much as 40-fold interindividual variability in its expression, functional CYP3A4 is expressed in most adults, with intestinal expression playing a significant role in the first-pass metabolism of numerous medications. Although several *CYP3A4* variants (eg, **6*, **17*, and **20*) have been associated with decreased activity, their low frequency suggests limited clinical relevance.

CYP3A5 is polymorphically expressed in up to 60% of people of African ancestry and 33% of people of European ancestry, with *CYP3A5*3* (c.6986A>G, aberrant splice site) in intron 3 as the primary allele variant (no-function allele). In contrast to individuals with the *CYP3A5*1* allele, those with *CYP3A5*3* have no-functional CYP3A5 enzyme.[43] CYP3A4 and CYP3A5 mediate the metabolism of more than 50% of all clinically useful medications. However, with overlapping substrate specificities, it remains unknown whether some medications are substrates for *CYP3A5* but not *CYP3A4* and vice versa. Although variability exists between dose-adjusted concentration and *CYP3A5* genotypes, a correlation exists between trough concentrations of tacrolimus and *CYP3A5* genetic constitution. "Standard" dosing of tacrolimus is appropriate for CYP3A5 PMs (also known as "CYP3A5 nonexpressers"), common in patients of European ancestry. In contrast, patients of African ancestry who are likely to express the wild type (ie, **1*) *CYP3A5* allele (also known as "CYP3A5 expressers"), metabolize tacrolimus into inactive metabolites more quickly and thus may require higher starting doses to achieve therapeutic plasma concentrations. Genotyping for both *CYP3A5*3* and *CYP3A4*22,* a decreased function allele, is associated with improved dose prediction for tacrolimus.[44] CPIC guidelines providing pharmacogenomic-based dosing recommendations for tacrolimus are available.[43]

Phase II and Nucleotide-Base Metabolizing Enzymes

The clinical relevance of genetic polymorphisms pertaining to the thiopurine methyltransferase (TPMT), dihydropyrimidine dehydrogenase (DPD), and uridine diphosphate glucuronosyltransferase (UGT) enzymes has been demonstrated in the treatment of cancer. The *TPMT* gene has four primary no-function alleles: *TPMT*3A* (the most common), *TPMT*2*, *TPMT*3B*, and *TPMT*3C*. Thiopurine medications, such as 6-thioguanine, 6-mercaptopurine, and its precursor, azathioprine, are inactivated by TPMT, and patients who are homozygous or heterozygous for the *TPMT* variant alleles are at higher risk for developing serious hematological toxicities during treatment with the thiopurines.[45] TPMT represents one of the most successful examples of pharmacogenomic application of genotyping and phenotyping (eg, measuring enzyme activity). The most recent guideline is available through the CPIC.[45]

DPD mediates the metabolism of 5-fluorouracil and its precursor capecitabine. Patients with a no-function or decreased function allele of the *DPYD* gene encoding for the DPD enzyme cannot effectively metabolize 5-fluorouracil and thus may experience enhanced medication-related toxicities, including neutropenia, nausea, vomiting, severe diarrhea, stomatitis, mucositis, and hand-foot syndrome.[46] However, the usefulness and sensitivity of genotyping are related to which *DPYD* variants are included in individual test panels.

The camptothecin derivative irinotecan (CPT-11) is activated by carboxylesterase to SN-38, a potent topoisomerase I inhibitor. SN-38 is inactivated by glucuronidation via the polymorphic UGT1A1 enzyme, which may play a role in CPT-11-related toxicity. An extra thymine-adenine (TA) repeat within the TATA section of the *UGT1A1* promoter results in the *(TA)7TAA* allele (also known as *UGT1A1*28*), which possesses lower enzyme activity than the wild-type *(TA)6TAA* allele (ie, *UGT1A1*1*). Impaired SN-38 glucuronidation secondary to the *(TA)7TAA* allele may result in abnormally high SN-38 concentrations. More severe diarrhea and neutropenia are observed in irinotecan-treated patients who are homozygous or heterozygous carriers of the *(TA)7TAA* allele.[47] Moreover, a dose-related increase in the risk for severe neutropenia with irinotecan with the *UGT1A1 (TA)7TAA* allele is likely.[48] In 2005, the FDA approved the Invader® UGT1A1 Molecular Assay (Third Wave Technologies) to genotype for *UGT1A1* alleles, and the labeling for irinotecan was revised to recommend dose adjustment for individuals who are homozygous for the *(TA)7TAA* allele. Although the predictive value of *UGT1A1*28* polymorphism is confirmed in a meta-analysis, genetic testing is not a requirement by the regulatory agency.[49] The antiretroviral protease inhibitor atazanavir is an inhibitor of UGT1A1. Atazanavir can inhibit UGT1A1-mediated glucuronidation and elimination of bilirubin, which can lead to hyperbilirubinemia and jaundice. This effect is more pronounced in individuals with the *UGT1A1*28* allele, and CPIC guidelines recommend using alternative agents in homozygotes for the **28* allele.[50]

POLYMORPHISMS IN DRUG TRANSPORTER GENES

An example of a polymorphic drug transporter protein is OAT, a member of the solute carrier (SLC) transporter family. The *SLCO1B1* gene encodes for OAT polypeptide B1, which mediates the uptake of β-hydroxy-β-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) into the liver. Although statins effectively lower total and low-density lipoprotein cholesterol and reduce the risk for cardiovascular events in coronary heart disease, their use is associated with an increased risk for myopathy (muscle pain or weakness with elevated creatine kinase levels), particularly with higher statin doses or concomitant medications that increase statin bioavailability. Myopathy may rarely cause rhabdomyolysis, characterized by muscle breakdown and potentially leading to acute kidney injury. The reduced function *SLCO1B1* c.521T > C SNP, resulting in the p.Val174Ala substitution and contained within the *SLCO1B1*5* haplotype, has been associated with higher statin concentrations.[51] Each copy of the *C* allele increased the risk for myopathy with simvastatin 40 mg/day by ~2.5-fold in a genome-wide association study (GWAS).[52] The association between the 521C allele and statin-induced myopathy is now well established.

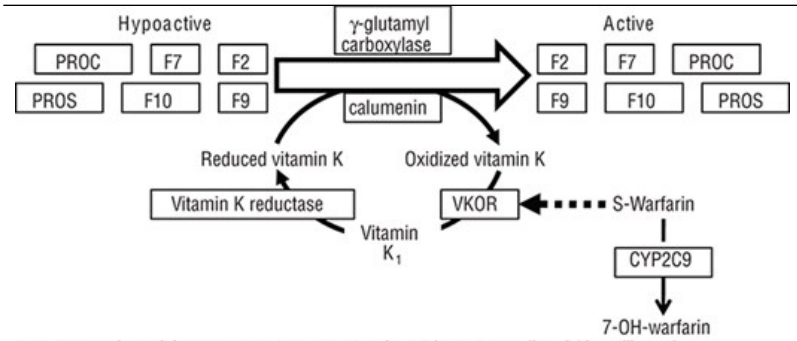
Similarly, the 521C allele is associated with an increased incidence of less severe yet troubling adverse effects that lead to statin discontinuation, including myalgias without significant creatine kinase elevation.[53] For example, there is a known risk for myopathy in patients expressing the 521T>C allele and receiving simvastatin. Hence, lower simvastatin doses or alternative statin drugs should be used in 521C carriers. CPIC guidelines support this strategy.[51]

POLYMORPHISMS IN DRUG TARGET GENES

2 Genetic polymorphisms occur commonly for drug target proteins, including receptors, enzymes, and ion channels. Drug target genes may work in concert with genes that affect pharmacokinetic properties (ie, genes for drug-metabolizing enzymes and transporters) to contribute to overall medication response. For example, the genes for *CYP2C9*, the major metabolizing enzyme for *S*-warfarin, and vitamin K oxidoreductase (VKOR), the target enzyme for warfarin, together influence warfarin dose response, as shown in Fig. e7-5. The following section highlights some of the drug target protein genes known to influence the efficacy, safety, or optimal dosage of various pharmacologic agents.

FIGURE e7-5

Proteins involved in warfarin pharmacokinetics and pharmacodynamics. Warfarin inhibits VKOR, thus preventing the formation of reduced vitamin K_1, which is a necessary cofactor for γ-carboxylation and activation of clotting factors II, VII, IX, X, and proteins C and S. (CYP2C9, cytochrome P450 2C9; F, clotting factor; PROC, protein C; PROS, protein S; VKOR, vitamin K oxidoreductase.)



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

Receptor Genotypes and Medication Response

The β_1-adrenergic receptor gene (*ADRB1*) has been a major focus of research into genetic determinants of responses to β-adrenergic receptor antagonists in cardiovascular disease and heart failure. β_1-Receptors are located in the heart and kidney, where they are involved in the regulation of heart rate, cardiac contractility, and blood pressure. There are two common nonsynonymous SNPs in the *ADRB1* at codons 49 (p.Ser49Gly) and 389 (p.Arg389Gly). The Ser49Gly and Arg389Gly SNPs are in strong linkage disequilibrium. The Ser49-Arg389 haplotype is associated with an increased risk for death among patients with coronary heart disease. The *ADRB1* Ser49Gly and Arg389Gly SNPs also appear to modulate blood pressure and clinical responses to β_1-receptor blockade. Specifically, hypertensive patients who were homozygous for the Ser49-Arg389 haplotype were found to have greater blood pressure reductions with metoprolol, compared with carriers of the Gly49 and/or Gly389 alleles.[54] In patients with coronary heart disease, atenolol treatment abolishes the increased risk for mortality associated with the Ser49-Arg389 haplotype. Among patients with heart failure, the Arg/Arg389 genotype was associated with greater improvements in left ventricular ejection fraction with carvedilol and metoprolol treatment and greater survival benefits with bucindolol, an agent not approved for use in the United States. CPIC guidelines addressing the use of *ADRB1* genotype in β-blocker prescribing are forthcoming.

The mu-opioid receptor gene (*OPRM1*) codes for the target protein of opioid analgesics, including codeine and tramadol. Although a common polymorphism, A118G, results in lower protein expression, its contribution to individual differences in opioid response is unclear.[12,55] As such, the evidence associated with the *OPRM1* gene is ranked as CPIC level C, meaning that no prescribing action is recommended based on genotype results. Nonetheless, the A118G polymorphism is included on some commercial pharmacogenomic testing panels.

Enzyme Genes and Medication Response

Vitamin K oxidoreductase (VKOR) is an example of an enzyme with genetic contributions to medication response. Warfarin exerts its anticoagulant effects by inhibiting VKOR and thus preventing carboxylation of the vitamin K-dependent clotting factors II, VII, IX, and X, as shown in Fig. e7-5. *VKORC1* encodes for the warfarin-sensitive component of VKOR. Variants in the *VKORC1* coding region cause rare cases of warfarin resistance, with carriers of these mutations requiring either exceptionally high warfarin doses (more than 100 mg/week) to achieve effective anticoagulation or failing to respond to warfarin at any dose.[35]

Aside from rare cases of warfarin resistance, there is substantial variability among patients in the dose of warfarin necessary to produce optimal anticoagulation, defined as an international normalized ratio of 2 to 3 for most indications. A common SNP in the *VKORC1* regulatory region, c.-1639G>A, significantly contributes to the interpatient variability in warfarin response, as it modulates *VKORC1* gene expression. Specifically, the –1639 AA, AG, and GG genotypes lead to high, intermediate, and low sensitivity to warfarin, respectively. Corresponding warfarin dose requirements are approximately 3 mg/day with the AA genotype, 5 mg/day with the AG genotype, and 6 to 7 mg/day with the GG genotype. *VKORC1* genotype, together with *CYP2C9* genotype, explains approximately 30% of the interpatient variability in warfarin dose requirements.[35] Clinical characteristics (eg, age, body size) and vitamin K intake contribute to additional dose variability.

Warfarin dose requirements vary by ancestry, with higher dose requirements among individuals of African ancestry and lower requirements among patients of Asian ancestry compared with patients of European ancestry. This variability is largely explained by differences in *VKORC1* genotype frequency. Specifically, the low-dose AA genotype is most common in patients of Asian ancestry, and the high-dose GG genotype is most common in

patients of African ancestry, whereas the intermediate-dose AG genotype is most common in persons of European ancestry.

Warfarin-dosing algorithms that incorporate *CYP2C9* and *VKORC1* genotypes and clinical (eg, age, weight, interacting medications) factors are publicly available to assist with warfarin dosing (eg, www.warfarindosing.org). In addition, the FDA-approved labeling for warfarin contains a dosing table based on *CYP2C9* and *VKORC1* genotypes (Table e7-5). Among people of predominately European ancestry, greater time in the therapeutic INR range and a reduction in the composite endpoint of major bleeding, venous thromboembolism, INR ≥4, and death following hip or knee arthroplasty were observed with genotype-guided compared to standard warfarin dosing.[56,57] Importantly, when limiting *CYP2C9* genotyping to the **2* and **3* alleles, dosing using a pharmacogenomic algorithm may lead to overestimation of warfarin dose requirements in individuals of African ancestry.[58] Thus, it is important to genotype for *CYP2C9* variants that occur commonly in people of African ancestry (eg, **5, *6, *8*, and **11*), as highlighted in CPIC guidelines.[35]

TABLE e7-5

Initial Warfarin Dose Recommendations (in mg/day) Provided in the FDA-Approved Warfarin Labeling According to *CYP2C9* and *VKORC1* Genotypes

	CYP2C9					
VKORC1	**1/*1*	**1/*2*	**1/*3*	**2/*2*	**2/*3*	**3/*3*
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2
AG	5-7	3-4	3-4	3-4	0.5-2	0.5-2
GG	5-7	5-7	3-4	3-4	3-4	0.5-2

IMMMUNE-RELATED GENES

The human leukocyte antigen (*HLA*) genes are among the most polymorphic in the human genome. These genes encode for proteins that recognize “self” from “non-self” and play a key role in the function of the immune system. The presence of certain *HLA* alleles has been linked to serious, potentially life-threatening adverse skin reactions with carbamazepine and phenytoin, commonly prescribed antiepileptic agents.[59,60] Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are hypersensitivity reactions characterized by blistering, mucosal erosions, and epidermal detachment. TEN is associated with more extensive skin involvement and a mortality rate approaching 25%.

Individuals with southeastern Asian ancestry (ie, southern China, Thailand, Malaysia, Indonesia, Taiwan, and Philippines) have a twofold to threefold higher prevalence of carbamazepine- or phenytoin-induced SJS and TEN than individuals of Japanese, Korean, or European ancestry. The human leukocyte antigen type B (*HLA-B*) **15:02* allele also occurs at a higher prevalence in individuals of southeastern Asian ancestry and has been highly correlated with risk for medication-induced SJS and TEN. Individuals of South Asian descent, including India, have an intermediate prevalence of this allele (2%-4%). It occurs in less than 1% of those with Japanese and Korean ancestry and is largely absent in others.

While the mechanism by which the *HLA-B*15:02* allele increases the risk for these toxic cutaneous reactions is unclear, it may involve activation and proliferation of T lymphocytes on carbamazepine exposure. The FDA-approved carbamazepine labeling recommends *HLA-B*15:02* screening in individuals with ancestry from southern Asia prior to carbamazepine use (see Table e7-6). Carbamazepine should be avoided in patients testing positive for the *HLA-B*15:02* allele.[59] Moreover, because of potential for phenytoin-induced SJS in the presence of the *HLA-B*1502* allele, phenytoin should also be avoided in individuals with the *HLA-B*15:02* allele.[60] In addition, the *HLA-B*31:01* allele is associated with risk of serious cutaneous reactions during carbamazepine treatment and is addressed in updated CPIC guidelines.[59] Allopurinol, a commonly-used treatment for hyperuricemia and gout, is also associated with severe cutaneous adverse reactions in the presence of a specific *HLA* allele, namely *HLA-B*58:01*. Allopurinol is contraindicated in patients who carry the *HLA-B*58:01* allele.[61]

TABLE e7-6

Examples of Drugs and Corresponding Pharmacogenomic Information in Their FDA-Approved Labels

Drug(s)	Gene(s)	Content
Abacavir	*HLA-B*	The *HLA-B*57:01* allele increases the risk for abacavir hypersensitivity. Genotype screening is recommended prior to abacavir use. Abacavir should be avoided in patients with the *HLA-B*57:01* allele, unless the potential benefit of abacavir clearly outweighs the risk.
Atomoxetine	*CYP2D6*	*CYP2D6* PMs may have 10-fold increased atomoxetine exposure compared with extensive metabolizers. In CYP2D6 PMs, a starting dose of 0.5 mg/kg/day is recommended in children and adolescents < 70 kg and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.
Azathioprine, 6-mercaptopurine, thioguanine	*TPMT*	Patients with a no-function *TPMT* allele are at increased risk for serious, potentially life-threatening myelosuppression if given conventional doses of thiopurine. Consideration of either *TPMT* genotyping or phenotyping recommended, with dose reduction in patients with a reduced activity genotype or phenotype.
5-Fluorouracil, capecitabine	*DPYD*	Dihydropyrimidine dehydrogenase (DPD) deficiency may rarely lead to severe toxicity (eg, diarrhea, neutropenia, neurotoxicity) with 5-fluorouracil and capecitabine. 5-fluorouracil and capecitabine should be avoided in patients with DPD deficiency.
Carbamazepine	*HLA-B*	The *HLA-B*15:02* allele increases the risk for serious and potentially fatal dermatologic reactions (eg, Stevens–Johnson syndrome and toxic epidermal necrolysis) with carbamazepine. At-risk populations include those from southeast Asia who should be screened for the *HLA-B*15:02* allele prior to starting carbamazepine. Carbamazepine should be avoided in *HLA-B*15:02* positive patients unless the potential benefit clearly outweighs the risks.
Celecoxib	*CYP2C9*	Celecoxib clearance is reduced in carriers of the *CYP2C9*3* allele. Celecoxib should be administered with caution and at lower doses in patients with the *CYP2C9*3* allele.
Cetuximab, panitumumab	*EGFR*	Cetuximab and panitumumab inhibit the epidermal growth factor receptor (EGFR). Candidates for these agents should have immunohistochemical evidence of EGFR expression.
	KRAS mutations	KRAS is a G protein in the EGFR pathway. Patients with a *KRAS* mutation in codon 12 or 13 may not derive any benefit from cetuximab or panitumumab, and use of these drugs is not recommended.
Clopidogrel	*CYP2C19*	*CYP2C19* is involved in the biotransformation of clopidogrel to its active form. Individuals with the *CYP2C19* PM phenotype secondary to genetic polymorphism may fail to derive sufficient protection against adverse cardiovascular events with clopidogrel. These risks are particularly high in patients who undergo coronary artery stent placement.
Codeine	*CYP2D6*	CYP2D6 metabolizes codeine into morphine. Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being CYP2D6 ultrarapid metabolizers. Codeine is contraindicated in children younger than 12 years and in children younger than 18 years following tonsillectomy and/or adenoidectomy.
Irinotecan	*UGT1A1*	The *UGT1A1*28* allele is associated with increased risk for irinotecan-induced neutropenia, with homozygotes having the highest risk. Lower irinotecan starting doses are indicated in patients known to be homozygous for the *UGT1A1*28* allele.

Lenalidomide	Chromosome *5q* deletion	Myelodysplastic syndromes with the chromosome 5q deletion are associated with an increased risk of hematologic toxicity with lenalidomide. More frequent monitoring of complete blood counts is recommended during lenalidomide initiation in patients with the chromosome 5q deletion. Consider lenalidomide dose reduction or interruption and use of blood products and/or growth factors if CBC alterations are detected.
Primaquine	*G6PD*	Genetic variation leading to *G6PD* deficiency increases the risk for primaquine-induced hemolytic anemia. Obtaining a *G6PD* enzyme activity level prior to primaquine use is recommended for patients of African or Mediterranean ancestry, who are at higher risk of *G6PD* deficiency, with the use of lower doses in patients who have a deficient level.
Rasburicase	*G6PD*	Genetic variation leading to *G6PD* deficiency increases the risk for rasburicase-induced hemolytic anemia. Obtaining a *G6PD* enzyme activity level prior to rasburicase use is recommended in patients of African or Mediterranean ancestry, who are at higher risk of *G6PD* deficiency. Rasburicase should be avoided in individuals with a *G6PD* deficiency.
Tramadol	*CYP2D6*	CYP2D6 metabolizes tramadol into its more potent active metabolite, O-desmethyltramadol. Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases followed tonsillectomy and/or adenoidectomy; in at least one case, the child was a CYP2D6 ultrarapid metabolizer. Tramadol is contraindicated in children younger than 12 years and in children younger than 18 years following tonsillectomy and/or adenoidectomy.
Trastuzumab	*HER2*	Decreased tumor progression in breast cancer with trastuzumab has only been demonstrated when *HER2* is overexpressed. Overexpression of *HER2* should be confirmed by protein overexpression or gene amplification prior to trastuzumab initiation.
Voriconazole	*CYP2C19*	Patients with the IM or PM phenotype have twofold to fourfold higher voriconazole exposure, respectively. However, no recommendations are made in the FDA label for genetic screening or dose adjustment.
Warfarin	*CYP2C9, VKORC1*	The *CYP2C9*2* and **3* alleles are associated with reduced warfarin metabolism and increased bleeding risk, while the *VKORC1-1639A* allele is associated with increased warfarin sensitivity. Lower doses of warfarin should be started in patients known to have decreased or no-function *CYP2C9* or *VKORC1* alleles. However, genetic testing is not mandated.

CBC, complete blood count; CXCR4, chemokine-related receptor; EGFR, epidermal growth factor receptor; G6PD, glucose-6-phosphate dehydrogenase; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IM, intermediate metabolizer; PM, poor metabolizer

Data from https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. Accessed January 12, 2022.

The use of abacavir, a nucleoside reverse transcriptase inhibitor of HIV-1, causes a severe, and occasionally fatal, hypersensitivity reaction in some patients. The abacavir hypersensitivity reaction (AHR) is strongly associated with the presence of another allelic variant of the *HLA* gene, *HLA B*57:01*. Screening for *HLA B*57:01* with avoidance of abacavir in patients testing positive for the allele reduces AHR incidence.[62] The screening recommendation has been incorporated into abacavir product labeling as well as treatment guidelines.[62]

NEW GENETIC TARGETS AND THERAPEUTIC INTERVENTIONS

The discovery of genes that confer disease has led to an improved understanding of the molecular mechanisms involved in disease pathophysiology. Once associations between genes and diseases are discovered, scientists can elucidate the functions of the encoded proteins and more clearly define the consequences of genetic mutations. Insight into the genetic control of cellular functions may reveal new strategies for disease treatment and prevention.

Targeted Therapies for Cancer. Cancer is a disease of the genome, with genetic mutations driving uncontrolled cell growth and division. Knowledge of the molecular mechanisms behind cancer growth can lead to the development of targeted therapies. For example, overexpression of the human epidermal growth factor receptor 2 (HER2, also known as Her2/neu and ErbB2), secondary to *HER2* gene amplification occurs in 20% of metastatic breast cancers and is associated with more aggressive cancer and decreased survival.[63] The discovery of *HER2* overexpression and its effects on cancer prognosis led to the development of trastuzumab, a recombinant monoclonal antibody that targets HER2 and blocks HER2-stimulated growth and survival of cancer cells. The addition of trastuzumab to breast cancer chemotherapy slows the progression of cancer and improves tumor response rates in women with HER2-positive tumors.[63] Testing for *HER2* overexpression is necessary to determine which patients may benefit from trastuzumab. The FDA has approved several tests that detect *HER2* overexpression either directly by measuring the amount of protein or indirectly by measuring gene amplification.

Similarly, overexpression of the epidermal growth factor receptor (EGFR, also known as HER1 or ErbB1) in head and neck, colon, and rectal cancer is associated with cancer growth and a poor clinical prognosis. Cetuximab and panitumumab are recombinant monoclonal antibodies that block activation of the EGFR. Both improve survival in metastatic colorectal cancer that overexpresses EGFR and are thus indicated in this setting.[64,65] Erlotinib and gefitinib inhibit the intracellular phosphorylation of tyrosine kinase associated with the EGFR and are indicated in non-small cell lung cancer. Other examples of targeted chemotherapy developed based on genetic abnormalities include rituximab, a monoclonal antibody used to treat CD20-positive, B-cell non-Hodgkin's lymphoma and chronic lymphocytic leukemia; imatinib, dasatinib, and nilotinib, kinase inhibitors that block the product of a reciprocal translocation between chromosomes 9 and 22 in chronic myeloid leukemia (CML); and crizotinib, an anaplastic lymphoma kinase (ALK) and c-ros oncogene 1, receptor tyrosine kinase (ROS-1) inhibitor that targets the *EML4-ALK* gene fusion product in non-small cell lung cancer.

Targeted Therapy for Cystic Fibrosis. Cystic fibrosis is caused by genetic mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which is expressed in the airways, intestines, pancreas, bile duct, and sweat glands. In these locations, the CFTR protein serves a critical role in the regulation of fluid and ion transport. The CFTR is composed of two nucleotide-binding domains and two transmembrane domains. The transmembrane domain forms a chloride channel, while the nucleotide-binding domain acts as a gate to regulate chloride transport across the cell membrane. Mutations in the *CFTR* gene lead to altered fluid and ion transport and disrupt mucus clearance in the airways and intestinal tract resulting in airway obstruction and digestive problems.

Mutations in the *CFTR* gene affect protein synthesis, processing, regulation, or ion conductance. Ivacaftor was approved by the FDA in 2012 as the first medication to target defects in the CFTR.[66] Ivacaftor was initially approved for the treatment of cystic fibrosis in children who have the Gly551Asp mutation, which occurs in about 4% of patients with cystic fibrosis and causes defects in chloride transport through the ion channel. Ivacaftor potentiates chloride ion flow and results in rapid and sustained improvement in lung function in patients with cystic fibrosis. The labeling for ivacaftor has been updated to include additional variants that are also responsive to ivacaftor potentiation. Additional targeted therapies for cystic fibrosis have come to market that collectively impact 90% of the cystic fibrosis patient population. These agents, including lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor, have the potential to improve the quality and length of life of these patients, as they all target the underlying cause of cystic fibrosis. In particular, they are relevant for patients who have at least one (elexacaftor/tezacaftor/ivacaftor) or two copies (lumacaftor/ivacaftor, tezacaftor/ivacaftor) of the F508del mutation, the most common mutation implicated in cystic fibrosis. Presence of this mutation prevents the proper folding and trafficking of the CFTR protein to the cell membrane, and lumacaftor, tezacaftor, and elexacaftor work to correct this issue.

PHARMACOGENOMIC MEDICATION LABELING AND GUIDELINES

7 More than 250 medications now contain pharmacogenomic information in their FDA-approved labeling.[67] Examples of these are shown in Table e7-6. Note that not all of the pharmacogenomic information in FDA labels is considered clinically actionable (ie, associated with a specific medication or dosage recommendation). Pharmacogenomic information appears in various sections of the label. For example, the information appears as a Boxed Warning for clopidogrel and carbamazepine because of the serious consequences of genetic variation on medication response. However, for warfarin, mercaptopurine, and irinotecan, the pharmacogenomic information appears in the medication dosing section. The FDA maintains a table of pharmacogenomic biomarkers in medication labels (https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling) as well as tables of pharmacogenetic associations supporting therapeutic management recommendations, potential impact on safety or response, and potential impact on pharmacokinetic properties only (https://www.fda.gov/medical-devices/precision-medicine/table-

pharmacogenetic-associations).[67,68] Other regulatory agencies worldwide (eg, the European Medicines Agency) also include pharmacogenomic information on medication labeling. This information is curated through the Pharmacogenomics Knowledgebase (PharmGKB; www.pharmgkb.org), which is a searchable database of pharmacogenomics literature and guidelines.

Guidelines are available to assist with translating genotype results into actionable prescribing decisions for many medications. Among these are guidelines from CPIC (https://cpicpgx.org/) and the Dutch Pharmacogenetics Working Group (DPWG).[69,70] These consortia do not recommend whether genetic tests should be ordered, but rather, how to use existing genetic information.

Genes and drugs/drug classes with CPIC guidelines published as of 2021 are listed in Table e7-7. The CPIC guidelines, DPWG guidelines, in addition to other pharmacogenomic information, are freely available through PharmGKB and/or CPIC websites. A list of these and other key pharmacogenomics resources are listed in Table e7-8.

TABLE e7-7

Examples of Drugs/Drug Classes and Genes with Available Guidelines from the Clinical Pharmacogenetics Implementation Consortium

Drugs/Drug Classes	Genes
Abacavir	*HLA-B*
Allopurinol	*HLA-B*
Aminoglycosides	*MT-RNR1*
Atazanavir	*UGT1A1*
Atomoxetine	*CYP2D6*
Carbamazepine	*HLA-A, HLA-B*
Clopidogrel	*CYP2C19*
Efavirenz	*CYP2B6*
Fluoropyrimidines	*DPYD*
Ivacaftor	*CFTR*
Non-steroidal anti-inflammatory drugs	*CYP2C9*
Ondansetron	*CYP2D6*
Opioids	*CYP2D6, OPRM1, COMT*
Oxcarbazepine	*HLA-B*
Peginterferon-alpha-based regimens	*IFNL3*
Phenytoin	*CYP2C9, HLA-B*
Proton pump inhibitors	*CYP2C19*

Rasburicase	*G6PD*
Selective serotonin reuptake inhibitors	*CYP2D6, CYP2C19*
Simvastatin	*SLCO1B1*
Succinylcholine	*RYR1, CACNA1S*
Tacrolimus	*CYP3A5*
Tamoxifen	*CYP2D6*
Thiopurines	*TPMT, NUDT15*
Tricyclic antidepressants	*CYP2D6, CYP2C19*
Volatile anesthetic agents	*RYR1, CACNA1S*
Voriconazole	*CYP2C19*
Warfarin	*CYP2C9, CYP4F2, VKORC1*

Data from https://cpicpgx.org/guidelines/. Accessed January 12, 2022.

TABLE e7-8

Pharmacogenomics Resources

Resource	Description	Website
Clinical Pharmacogenetics Implementation Consortium (CPIC)	Creates gene/drug pair guidelines that provide guidance on how to use existing pharmacogenomic test results to optimize medication therapy	www.cpicpgx.org
Dutch Pharmacogenetics Working Group (DPWG)	Creates gene/drug pair guidelines that provide guidance on how to use existing pharmacogenomic test results to optimize medication therapy	Available through www.pharmgkb.org
FDA Table of Pharmacogenetic Associations	List of gene/drug associations that the FDA has evaluated and believes there is sufficient scientific evidence to support. List is continually being evaluated and updated with input from the pharmacogenomics community.	www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations
FDA Table of Pharmacogenomic Biomarkers	Contains a list of drugs with pharmacogenomic information in their FDA-approved labeling	www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling
Genetic Testing Registry (GTR)	Centralized database of genetic testing labs worldwide and their test offerings created via voluntary submissions	www.ncbi.nlm.nih.gov/gtr/
Pharmacogenomics Knowledgebase (PharmGKB)	Searchable database of curated pharmacogenomic literature and information, including clinical guidelines and drug labeling from around the world. Also includes important pharmacogene summaries and pharmacogenomic pathway diagrams	www.pharmgkb.org
Pharmacogene Variation Consortium (PharmVar)	Online repository for pharmacogene nomenclature. Publishes “GeneFocus” papers that summarize key information about important pharmacogenes.	www.pharmvar.org

ETHICAL CONSIDERATIONS

Traditionally, *genetic testing* refers to screening human genetic material to identify genotypes associated with disease susceptibility or carrier status for heritable diseases, such as Huntington’s disease or breast cancer. This kind of testing can have serious ethical and social implications. For example, knowledge that a patient is at risk for developing a genetic disorder could result in emotional distress for the individual at risk and his or her family members and the fear of discrimination by employers or insurance companies.

Within the context of pharmacogenomics, however, testing involves searching for genetic variations linked to medication efficacy or toxicity rather than to disease susceptibility. In many instances, this form of testing will carry little risk for ethical, legal, and social concerns. For example, knowledge that a person has a genotype associated with a poor response to clopidogrel may be of little consequence because there are alternative therapies available. However, more serious implications may arise if a person is predicted to respond poorly to a medication based on genotype, and treatment options are limited. The federal Genetic Information Nondiscrimination Act (GINA) of 2008 prohibits health insurance providers and employers from discriminating against an individual based on genetic information. However, GINA does not protect against discrimination related to disability, life, and

long-term care insurance. In addition, it does not apply to employers with fewer than 15 employees.

ROLE OF CLINICIANS

8 Pharmacogenomics provides opportunities to improve medication outcomes but requires that clinicians be knowledgeable about genetic determinants of medication response and how to translate genetic information into prescribing decisions. Importantly, genetic information needs to be considered in the context of important clinical factors, such as age, body size, organ function, and concomitant medication therapy.

Pharmacists are broadly trained in a number of medication-related areas, including pharmacology, pharmacokinetics, and pharmacodynamics. This places pharmacists in a unique position in dealing with the complexities of pharmacotherapy in the era of pharmacogenomics. Pharmacists can take a leadership role on multidisciplinary teams charged with interpreting genetic test results and choosing the most appropriate medication for a given patient based on genotype, and in counseling patients about the clinical implications of their results.[71,72] Furthermore, it is becoming more common for patients to obtain their pharmacogenomic test results, either from clinical services, large-scale research projects (eg, *All of Us* Research Program), or direct-to-consumer testing.[73,74] Thus, it will be essential for clinicians to stay abreast of important pharmacogenomic discoveries and guideline updates. Genomics competencies for healthcare professionals are available via the Genetics/Genomics Competency Center (https://genomicseducation.net/).

In addition, pharmacists can form partnerships with other healthcare professionals in the provision of clinical pharmacogenomics services. For example, some pharmacists are working together with genetic counselors in pharmacogenomics. Genetic counselors have specific training in communicating complex health-related genetic information to patients and can explain secondary (ie, disease-associated) findings from pharmacogenomic testing (eg, *UGT1A1*28/*28* and Gilbert syndrome), whereas the pharmacist can provide genotype-guided medication recommendations to maximize medication efficacy and safety. Others who may be involved with pharmacogenomics implementation include informatics personnel for integrating results into electronic health records with clinical decision support (eg, drug-gene interaction alerts), and clinical pathologists who can establish genotyping methodology when performed in-house. Some clinicians pursue post-graduate residency or fellowship training in pharmacogenomics. These individuals often lead the implementation of pharmacogenomics in health systems, develop new clinical pharmacogenomics services, and/or engage in pharmacogenomics research and educational efforts.

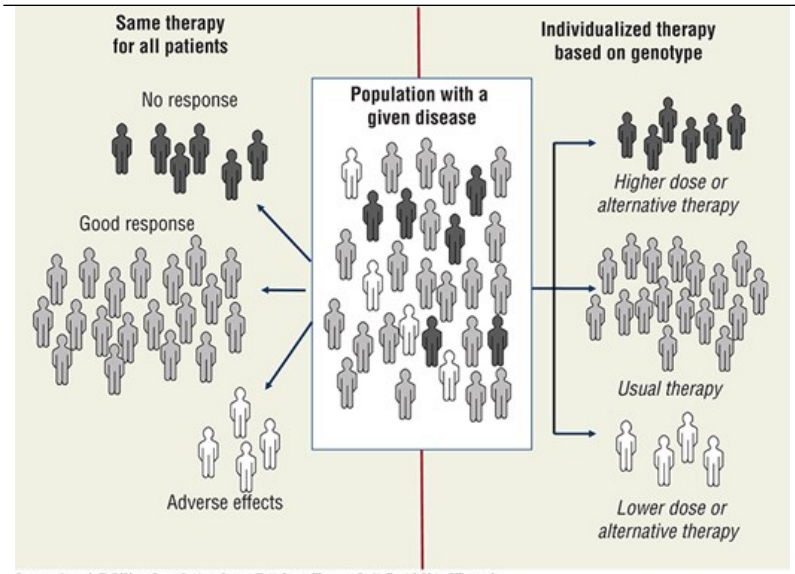
APPLICATION OF PHARMACOGENOMICS TO MEDICATION MANAGEMENT

Pharmacogenomics has the potential to greatly improve medication use and therapy outcomes when applied across the Patient Care Process.[75] Clinicians may be able to predict the likelihood that an individual will respond to a particular medication based on the patient's genotype. Medications may be avoided or prescribed in lower doses with careful monitoring in patients genetically predisposed to their adverse effects. This would be of particular benefit for narrow therapeutic index drugs. For example, warfarin may be initiated at lower doses with closer monitoring in patients with a *VKORC1* genotype associated with increased warfarin sensitivity or a *CYP2C9* allele associated with reduced warfarin metabolism.

With pharmacogenomics, it also may be possible to eliminate the trial-and-error approach to medication prescribing for many diseases. Instead, clinicians may be able to use genetic information to match the right medication to the right patient at the right dose while minimizing adverse effects. For example, the current approach to depression management involves the trial of various antidepressants until symptom remission is achieved with acceptable medication tolerability. Commonly, the initial agent(s) fails to control depressive symptoms or produces intolerable adverse effects (Fig. e7-6). Trials of additional or alternative antidepressants must be undertaken until treatment is deemed successful. In the interim, the patient remains depressed, which has significant implications for the patient's quality of life, work productivity, and potentially, risk for suicide. With pharmacogenomics, clinicians may be able to choose the antidepressant medication expected to provide the greatest response with the best tolerability for a particular patient based on his or her DNA.

FIGURE e7-6

Traditional and individualized approaches to pharmacologic management of disease.



New medications may be developed based on knowledge about genetic control of cellular functions. For example, the discovery that CML was caused by chromosome translocation and consequent production of an enzyme capable of producing life-threatening lymphocyte levels led to accelerated FDA approval of imatinib, an inhibitor of the translocation-created enzyme, for treatment of CML. In addition, future medication development may focus on treating specific genetic subgroups instead of broadly treating all individuals with a particular disease. Along these lines, the FDA is encouraging pharmaceutical companies to submit pharmacogenomic data during the medication development process. Ultimately, pharmacogenomics may improve the quality and reduce the costs of healthcare by decreasing treatment failures and adverse medication reactions, and by leading to the discovery of new genetic targets and therapeutic interventions for disease management.

ABBREVIATIONS

A	adenine
ADRB1	β_1-adrenergic receptor gene
AHR	abacavir hypersensitivity reaction
ALK	anaplastic lymphoma kinase
AUC	area under the curve
C	cytosine
CFTR	cystic fibrosis transmembrane conductance regulator
CML	chronic myeloid leukemia
CNS	central nervous system
CPIC	Clinical Pharmacogenetics Implementation Consortium
CYP	cytochrome P450

dbSNP	National Center for Biotechnology Information SNP database
DPD	dihydropyrimidine dehydrogenase
EGFR	epidermal growth factor receptor
ENCODE	ENCyclopedia of DNA Elements
FDA	Food and Drug Administration
G	guanine
G6PD	glucose-6-phosphate dehydrogenase
GINA	Genetic Information Nondiscrimination Act
GWAS	genome-wide association study
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMG-CoA	β-hydroxy-β-methylglutaryl-coenzyme A
IM	intermediate metabolizer
NIH	National Institutes of Health
NM	normal metabolizer
OAT	organic anion transporter
PGRN	Pharmacogenomics Research Network
PharmGKB	Pharmacogenomics Knowledgebase
PM	poor metabolizer
RM	rapid metabolizer
SJS	Stevens–Johnson syndrome
SLC	solute carrier
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitor
T	thymine

TA	thymine-adenine
TEN	toxic epidermal necrolysis
TPMT	thiopurine *S*-methyltransferase
UGT	uridine diphosphate glucuronosyltransferase
UM	ultrarapid metabolizer
VKOR	vitamin K oxidoreductase

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SELF-ASSESSMENT QUESTIONS

1. The site(s) for genetic variations that may affect drug pharmacodynamics include:
   A. Drug-metabolizing enzymes
   B. Drug target proteins
   C. Drug transporter proteins
   D. A and B
2. The most commonly occurring variant in the human genome is:
   A. Single nucleotide polymorphism
   B. Tandem repeat polymorphism

C. Nucleotide base deletion

D. Nucleotide base insertion

3. *CYP2D6* polymorphism can affect:

A. Drug toxicity

B. Drug interaction potential

C. Drug delivery

D. A and B

4. Which CYP2D6 phenotype is associated with the least analgesic response to codeine?

A. Ultrarapid metabolizer

B. Normal metabolizer

C. Intermediate metabolizer

D. Poor metabolizer

5. Which of the following is an example of a drug target gene?

A. *TPMT*

B. *SLCO1B1*

C. *CYP2C19*

D. *VKORC1*

6. Which gene is predictive of clopidogrel effectiveness?

A. *CYP2C9*

B. *CYP2C19*

C. *CYP2D6*

D. *CYP3A5*

7. A patient with newly diagnosed atrial fibrillation will be starting warfarin. A SNP test is performed and reveals the *CYP2C9*2/*3* and *VKORC1* c.-1639 AA genotypes. Which of the following responses to warfarin would be predicted based on this genotype?

A. Increased metabolism and usual sensitivity; use lower dose

B. Decreased metabolism and decreased sensitivity; use higher dose

C. Decreased metabolism and increased sensitivity; use lower dose

D. Increased metabolism and decreased sensitivity; use higher dose

8. Screening for which of the following polymorphisms is indicated prior to carbamazepine use in a person of Southeast Asian descent?

A. *CYP2D6*2*

B. *HLA-B*15:02*

C. *CYP2C9*2*

D. *TPMT*2*

9. Which gene predicts risk for muscle toxicity with simvastatin use?

A. *SLCO1B1*

B. *HLA-B*

C. *HMG-CoA*

D. *LDLR*

10. Which drug is recommended to reduce tumor progression in a patient with breast cancer who overexpresses the HER2 gene?

A. Mercaptopurine

B. Tamoxifen

C. Trastuzumab

D. Voriconazole

11. What is the CYP2D6 activity score and phenotype for a patient whose genotype is *CYP2D6*1/*4*?

A. 0 / poor metabolizer

B. 1 / intermediate metabolizer

C. 2 / normal metabolizer

D. 3 / ultrarapid metabolizer

12. What is the CYP2C19 phenotype for a patient whose genotype is *CYP2C19*17/*17*?

A. Ultrarapid metabolizer

B. Rapid metabolizer

C. Normal metabolizer

D. Poor metabolizer

13. If Drug X requires metabolism by a specific CYP enzyme into an active metabolite to produce its therapeutic effect, which phenotype of that enzyme is most likely to result in treatment failure?

A. Ultrarapid metabolizer

B. Normal metabolizer

C. Intermediate metabolizer

D. Poor metabolizer

14. Which of the following information is provided by the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines?

A. When clinicians should order pharmacogenomic tests

B. How clinicians should use pharmacogenomic test results to guide prescribing

C. A searchable database of pharmacogenomics literature and guidelines

D. A table of pharmacogenomic biomarkers on FDA drug labels

15. Which of the following is true regarding the clinical implementation of pharmacogenomics?

A. Pharmacists can take a lead role in the clinical implementation of pharmacogenomics

B. Pharmacogenomics must be implemented as part of a research protocol

C. Opportunities for patients to obtain pharmacogenomic testing are decreasing

D. Pharmacogenomic information is more important that other clinical factors when making medication recommendations

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Genetic variation in drug-metabolizing enzymes and drug transporters may affect drug pharmacokinetics, whereas genetic variation in drug targets may affect drug pharmacodynamics.

2. **A.** A single nucleotide polymorphism (SNP) is the most commonly occurring variant in the human genome, occurring once approximately every 300 base pairs. SNPs occur when one nucleotide base pair replaces another, as illustrated in Fig. e7-2.

3. **D.** *CYP2D6* polymorphism can influence a patient's risk of drug toxicity. For example, if a drug is primarily metabolized by CYP2D6 into inactive metabolites (eg, paroxetine), a CYP2D6 poor metabolizer can experience supratherapeutic plasma concentrations of drug at standard doses and may experience toxic effects as a result (see Fig. e7-3). In addition, CYP2D6 polymorphism can affect drug interaction potential. A patient who is a CYP2D6 poor metabolizer will not experience a drug-drug interaction with a strong CYP2D6 inhibitor, because there no enzyme activity to inhibit. In contrast, a CYP2D6 normal metabolizer who is exposed to a strong CYP2D6 inhibitor will act like a CYP2D6 poor metabolizer. This phenomenon is called phenoconversion.

4. **D.** Codeine is a prodrug that requires bioactivation via the CYP2D6 enzyme to morphine for analgesic effect. CYP2D6 poor metabolizers are unable to transform codeine into morphine and thus will not experience adequate analgesia with codeine. CYP2D6 intermediate metabolizers may also have reduced analgesia, but not to the extent of poor metabolizers.

5. **D.** *VKORC1* encodes for vitamin K epoxide reductase, which warfarin inhibits to exert its therapeutic effect. *TPMT* and *CYP2C19* are genes that encode for drug-metabolizing enzymes, and *SLCO1B1* is a gene that encodes for a drug transporter.

6. **B.** Clopidogrel is a prodrug that requires bioactivation via the CYP2C19 enzyme into active metabolites that exert its antiplatelet effects, as illustrated in Fig. e7-4.

7. **C.** Warfarin is metabolized into inactive metabolites via the CYP2C9 enzyme. Patients who carry the *CYP2C9*2* and/or *CYP2C9*3* alleles have decreased CYP2C9 enzyme activity and thus will have decreased warfarin metabolism. In addition, a common SNP in the *VKORC1* regulatory region, c.-1639G>A, significantly contributes to the interpatient variability in warfarin response, as it modulates *VKORC1* gene expression. Specifically, the –1639 AA, AG, and GG genotypes lead to high, intermediate, and low sensitivity to warfarin, respectively. The patient's results, therefore, both indicate a need for a lower warfarin dose. Other clinical factors, such as age, body size, and vitamin K intake, may also influence warfarin dose.

8. **B.** The FDA label for carbamazepine has a boxed warning to screen patients of Southeast Asian descent for the presence of the *HLA-B*15:02* allele. Having this allele puts patients at risk for severe cutaneous adverse reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis.

9. **A.** The gene *SLCO1B1* predicts risk for muscle toxicity with simvastatin use. This gene encodes for an organic anion transporter that mediates the

uptake of statins from the bloodstream into the liver. Patients who have reduced SLCO1B1 transporter function experience decreased simvastatin clearance and may be at increased risk of myopathy.

10. **C.** The discovery of *HER2* overexpression and its effects on cancer prognosis led to the development of trastuzumab, a recombinant monoclonal antibody that targets HER2 and blocks HER2-stimulated growth and survival of cancer cells. The addition of trastuzumab to breast cancer chemotherapy significantly slows the progression of cancer and improves tumor response rates in women with HER2-positive tumors. Testing for HER2-overexpression is necessary to determine which patients may benefit from trastuzumab.

11. **B.** A genotype's activity score is the sum of the activity values for each allele. In this case, the activity score is the sum of 1 (activity value for **1*, a normal function allele) and 0 (activity value for **4*, a no-function allele), giving a total score of 1. A CYP2D6 activity score of 1 corresponds to an intermediate metabolizer. Refer to Table e7-4 for phenotype definitions based on genotype data for *CYP2D6*, *CYP2C19*, and *CYP2C9*.

12. **A.** Patients who inherit two copies of the *CYP2C19* increased function allele, **17*, are considered ultrarapid metabolizers. These individuals have increased *CYP2C19* gene expression, and thus, have increased CYP2C19 enzyme activity. Refer to Table e7-4 for phenotype definitions based on genotype data for *CYP2D6*, *CYP2C19*, and *CYP2C9*.

13. **D.** If the patient is a poor metabolizer of the enzyme, they will not be able to effectively metabolized the drug into its active form, which could result in subtherapeutic plasma concentrations of the active metabolite and treatment failure. Refer to Fig. e7-3, panel *B*, for a visual representation of this concept.

14. **B.** CPIC guidelines do not recommend whether genetic tests should be ordered, but rather, how to use existing genetic information to guide prescribing. The Pharmacogenomics Knowledgebase (PharmGKB) is a searchable database of pharmacogenomics literature and guidelines. The FDA maintains its own tables of pharmacogenomic biomarkers and pharmacogenetic associations on its Website.

15. **A.** As the medication experts, pharmacists are leading the clinical implementation of pharmacogenomics across healthcare settings as part of multidisciplinary teams. Pharmacogenomics is implemented both clinically and as part of research programs. Opportunities for patients to obtain pharmacogenomic testing are increasing, especially with increasing clinical and research programs as well as direct-to-consumer genetic testing. Genetic information needs to be considered in the context of other important clinical factors, such as age, body size, organ function, and concomitant drug therapy, when making medication recommendations.