

continuing education for pharmacists

Personalized Medicine: Pharmacogenetics as a Method for Improving Patient Outcomes

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Goal. This program is intended to review the fundamentals of pharmacogenetics and genetic testing as a means to improve patient outcomes.

Objectives. At the conclusion of this lesson, successful participants should be able to:

1. compare and contrast pharmacogenetics and pharmacogenomics;
2. demonstrate an understanding of basic DNA terminology and genomic variations;
3. explain “personalized medicine” from the standpoint of drug metabolism, bioactivation, and pharmacologic target screening;
4. describe the limitations to implementing pharmacogenetic screening in health care; and
5. apply knowledge of pharmacogenetics to the initiation of warfarin therapy.

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Introduction

To many pharmacists, it seems like only yesterday that monoclonal antibodies, used to treat various cancers and arthritis, were the new wonder drugs. Advances in drug therapy are changing so rapidly that most health care professionals can hardly keep up. For years, health care professionals have known that different groups of patients can react differently to the same medication. The elderly, children, and even some ethnic groups need dosage adjustments to prevent toxic drug levels or adverse effects. Now, we are beginning to realize that each and every individual may need very specific dosage adjustments based on his/her own genetic make up and DNA. This is the emerging science of *pharmacogenetics* (or *pharmacogenomics*) and pharmacists will play a major role.

Leading the rationale for deploying pharmacogenetics in pharmacy is the finding that 30 to 50 percent of patient variance in warfarin dosing can be attributed to genetic variations in the genes that encode its pharmacological target (VKORC) and its principal route of metabolism (CYP2C9 or P450-2C9)¹. In simple terms, pharmacogenetics involves the screening of patients to identify those who harbor slight changes in their gene sequences that predispose them to adverse drug reactions (ADRs). For example, if a patient harbors a simple change in a spe-

cific gene sequence that results in a decreased ability to metabolize a drug, its clearance rate from the body will be decreased (compared to normal patients), and there will be an increased risk of inadvertent overdosing if the normal dose of that drug is administered.

The most exciting part of pharmacogenetics is the role the community pharmacist can play in its adaptation and use. After all, it is well known that the community pharmacist has the greatest amount of individual patient contact in the health care system. Dr. Alan Guttmacher, MD, member of the government’s Advisory Committee on Genetics, Health, and Society, states that genetic testing for clinical interventions may be applicable to 2 percent of the population now, but that may grow to 60 percent in the future. The primary goal of this program is to introduce pharmacists to pharmacogenetics and the role it will play in patient care in community pharmacies.

The Institute of Medicine estimates that 7,000 deaths occur annually due to ADRs. Other studies have suggested that, in the hospital setting, 6.7 percent or over two million hospitalized patients experience ADRs with over 100,000 of those patients succumbing to these ADRs. ADRs are, therefore, the 4th leading cause of death in the United States and are one of the leading, preventable public health issues today.

ADRs associated with the

Table 1
Pharmacogenetic vs. Pharmacogenomic

	Pharmacogenetic	Pharmacogenomic
Principle Characteristic	Inherited variation in drug effect	Use of genomic technology to identify new drug targets
Target Population	Individual patient/small groups	Large populations
Target Genes	Single or small number of genes	Complex pathways or whole genome
Example	CYP2C9	New drug development for depression
Generalized Goal	Drug Safety	Enhanced Efficacy

therapeutic treatment of disease in many cases are coupled with elevations in plasma drug concentrations. Drug-drug interactions commonly screen for potential CYP drug interactions that can result in elevations in drug levels. However, pharmacogenetic alterations in drug metabolism enzymes can also directly influence drug concentrations in the blood. For example, CYP2D6 and CYP2C9 mutations have been associated with elevations in concentrations in paroxetine³ and warfarin⁴ levels, respectively. Therefore, increasing the accessibility and utility of genetic screening for CYP polymorphisms (drug metabolism enzymes) will reduce ADRs.

Response to drug therapy varies markedly across therapeutic areas. For example, the estimated response rate to the selective serotonin reuptake inhibitors (SSRIs) used in the treatment of depression is 60 percent⁵. The resistance to the antiplatelet drug clopidogrel has been estimated to be up to 30 percent⁶. Clopidogrel is a prodrug that requires CYP3A4 bioactivation⁶, and changes in the gene that regulate CYP3A4 enzyme synthesis will result in clopidogrel not being effective in some patients. Therefore, pharmacogenetic screening can both reduce the rate of ADRs and also enhance overall therapeutic response to drug therapy by identifying patients deficient in prodrug bioactivation processes.

Fundamentally, pharmacogenetics is aimed at increasing drug safety and drug efficacy assurance based on genetic screening of patients.

The patient concerns with genotyping in the clinic, which are also applicable to electronic health records (EHR) in general, are privacy and security. The benefits of incorporating genotyping (genetic information) in therapeutics and medicine are questioned when the risk of 'information abuse' is considered. For example, a patient may be unwilling to utilize the benefits of genotyping if they fear that their employer and/or insurance provider can utilize the same information to (accurately or inaccurately) predict the patient's future health status. This dilemma involves both societal and genetic components. At the genetic level, the validity of extrapolative health assessment based solely on genotypic data has not been broadly established and is limited to a few known genetic diseases. Yet, it should be noted that the risk of ADRs based on known genetic anomalies in drug metabolism enzymes has been established and represents a short-term benefit in clinical genotyping.

Pharmacogenetic vs. Pharmacogenomic

Although most pharmacists use the terms *pharmacogenetics* and *pharmacogenomics* interchangeably, the two terms actually have

different meaning. Pharmacogenetics is an inherited variation in drug effects based on a single gene interaction with drugs. These single gene interactions can alter drug disposition, safety, tolerability and efficacy.

Pharmacogenomics represents the effect of a drug on gene expression OR the use of genomic technologies to identify new drug targets. In the latter case, identifying a gene that is expressed very highly in a diseased tissue, yet very low expression is seen in the normal state, could be used to identify that gene as a drug target or a biomarker of the disease state. Therefore, finding a single change in a CYP gene would represent a pharmacogenetic and not a pharmacogenomic trait (Table 1). Single gene changes will be referred to as *pharmacogenetic* from this point forward.

Human Genome Overview

Every human cell, with the exception of reproductive cells, contains 23 chromosomes. A *genome* is a patient's complete set of chromosomes. These chromosomes carry the genetic coding for all proteins in every cell. Chromosomes consist of DNA tightly wound around special protein structures called histones. DNA is comprised of a string of four nucleotide bases: adenine, guanine, thymine, cytosine (more commonly referred to as A, G, T and C, respectively). They are linked together in a double helix. A segment of DNA containing all the information needed to encode for one protein is called a gene. For example, the P450 (CYP) enzymes are proteins. Thus, a gene found on a chromosome codes for the synthesis of each specific CYP enzyme.

Single Nucleotide Polymorphisms (SNPs)

Within the nucleus of the cell, DNA is transcribed into messenger RNA (mRNA). In the cytoplasm of the cell, every three nucleotide bases on the mRNA codes for a single amino acid in the resulting protein. Within the ribosome, transfer

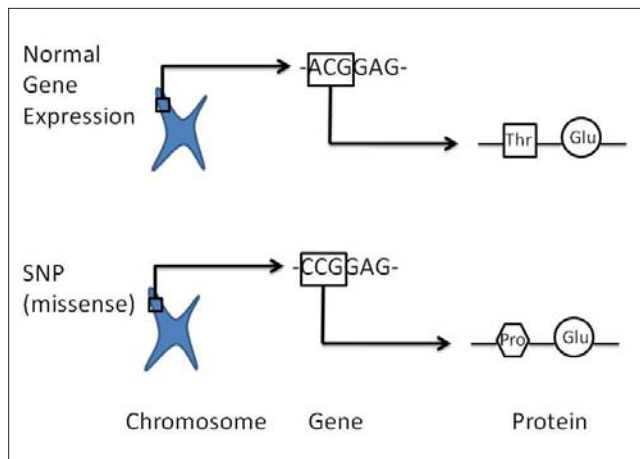


Figure 1. Normally, ACG codes for the amino acid threonine (Thr). With the SNP example above, the ACG code is switched to CCG which codes the amino acid proline (Pro). This change in amino acid results in the synthesis of a non-functional protein.

RNA (tRNA) brings the amino acid coded for by three nucleotide bases on the mRNA (see Figure 1). For example, ACG codes for the amino acid threonine. As the amino acid chain grows, the protein is formed. SNPs occur when there is a single nucleotide base change in the genome, and are of concern when the SNP occurs in the three nucleotide base sequence coding for an amino acid (i.e., codon). Thus, there is a mistake in the “coding” region of the DNA that encodes a specific protein, enzyme or receptor. Coding polymorphisms (mistakes in the DNA) are thus classified based on the effects this single nucleotide base change makes in the amino acid delivered to the ribosome (see below).

It is important to note that SNPs are very common in the human genome, and it is estimated that a SNP can occur about every 1,000 base pairs, which totals well over a possible one million SNPs per individual. Technically speaking, a genetic variation at specific base-pair must occur in at least 1 percent of the population to be termed a SNP⁷. Most of these are benign changes in the genome that have no impact on our health, yet SNPs that occur in genes involved in drug metabolism and drug-target pharmacology are of interest in pharmacogenetics. These otherwise harmless SNPs become a concern

since drug dosing represents the introduction of an otherwise foreign compound or chemical to the body.

SNP

Classifications.

1. *Non-synonymous (missense)* results in translation of a different amino acid. For example, ACG codes for the amino acid threonine. If a SNP occurs converting the ACG to CCG, the amino acid coded for is proline. Now the final product protein is incorrect and unable to function in a normal fashion.

2. *Synonymous (sense)* results in the translation of the same amino acid. Many amino acids are coded for by several different three nucleotide base sequences. Using the threonine example, if ACG is converted to ACA then threonine is still added during protein synthesis and the overall function of the protein is maintained.

3. *Nonsense* results in the insertion of a stop codon which terminates protein synthesis early. These SNPs are used to characterize genetic differences between individuals. Thus, patients can then be differentiated based on SNPs specific to a protein. For example, a SNP(*) in CYP2C9 may occur on the 2nd gene (or allele). Thus, this specific SNP would be presented as CYP2C9*2. Because humans inherit one copy of a gene from each parent, SNPs may also be represented as CYP2C9*2/*2. The *2/*2 is simply rendering an identity to each of the two potentially variable genes (e.g., gene from mom/gene from dad).

Many other known SNPs are under investigation within disease research groups to identify those that are genetically linked to disease risk, ultimately to identify patients who are genetically predisposed to a specific disease or disorder, thereby allowing more effective diagnostics and prophylactic

treatments.

Types of ADRs based on SNPs

There are three types of ADRs that can be associated with SNPs:

1. decreased drug clearance due to decreased metabolism, which results in higher blood levels of the drug;

2. increased drug clearance due to an increase in metabolism, which results in lower blood levels of the drug; and

3. decreased prodrug bioactivation, which results in lower blood levels of active drug in the body. These are described in Table 2. In this case, prodrug bioactivation is defined as the activation of a prodrug by a P450 enzyme to the pharmacologically-active drug in the patient's body for the drug to be effective. For example, clopidogrel is a prodrug that is bioactivated by CYP3A4. Clopidogrel resistance may result from a patient having a SNP in CYP3A4 (resulting in decreased levels of CYP3A4). Other selected drugs requiring bioactivation before drug initiation, and thus potential targets for SNP screening, are listed in Table 3.

SNP and ADRs associated with Antidepressant Therapy

One potential area of concern with SNP-mediated metabolism is the antidepressants, namely the tricyclic antidepressants (TCAs). TCAs have a narrow therapeutic window and are, therefore, more susceptible to ADRs. Because TCAs are metabolized by CYP2D6, a SNP in 2D6 can result in higher drug concentrations and subsequently toxicity. CYP2D6*4 is the most common variant gene in Caucasians with a population frequency of ~20 percent⁸. Poor metabolizers (PM), those with CYP2D6 polymorphisms, have higher concentrations of antidepressants than their extensive metabolizer (EM) comparison group⁹. Indeed, patients with CYP2D6 polymorphisms have been demonstrated to have an increased risk of ADRs¹⁰ and to not respond

Table 2
Genetic basis for adverse drug reactions (ADRs) in drug metabolism

ADR Type	Effect of SNP on Metabolic Enzyme	Effect on Peak Drug Plasma Concentration	ADR	Remediation of ADR Risk
Decreased Clearance	(1) Decreased enzyme activity (2) Altered enzyme activity	Upon normal dosing, peak plasma concentrations will exceed normal levels due to decreased metabolic capability of the patient	Risk of drug-induced toxicity due to inadvertent overdosing of patient	Decrease the drug dose or choose an alternate drug therapy
Increased Clearance	Increased enzyme activity and/or inducibility	Upon normal dosing, peak plasma concentrations will not reach efficacious levels due to increased metabolic capability of the patient	Risk of under-medicating due to increased drug metabolism	Increase the drug dose or choose an alternate drug therapy
Decreased Bioactivation	(1) Decreased enzyme activity (2) altered enzyme activity	Drug will not be activated. Therefore, efficacious levels will not be reached.	Risk of under-medicating due to the absence of bioactivation of the prodrug	Choose an alternate drug therapy

Table 3
Selected drugs that require cytochrome P450 activation

Parent Drug	Active Metabolite
<i>CYP2D6 Activation</i>	
amitriptyline	nortriptyline
codeine	morphine
morphine	morphine-6-glucuronide
tramadol	o-desmethyltramadol
<i>CYP3A4 Activation</i>	
carbamazepine	carbamazepine-10,11-epoxide
clopidogrel	unidentified
citalopram	desmethylcitalopram
diazepam	desmethyldiazepam
fluoxetine	norfluoxetine
isosorbide dinitrate	isosorbide 5-mononitrate
primidone	phenobarbital
venlafaxine	o-desmethylvenlafaxine
verapamil	norverapamil
zidovudine	zidovudine triphosphate

to TCA therapy¹¹. By comparison, SSRIs have a much broader therapeutic window than the TCAs. However, CYP2D6 polymorphisms have been associated with higher plasma drug concentrations^{3,12} and potential ADRs¹³ with SSRIs. Thus, the narrow therapeutic window associated with TCA therapy makes them a logical candidate for CYP2D6 SNP screening.

S-warfarin forms of the drug. S-warfarin is approximately three times more potent than R-warfarin¹⁵. S-warfarin is predominantly metabolized by CYP2C9⁴. In order to induce its anticoagulant effects, warfarin pharmacologically inhibits vitamin K epoxide reductase complex 1 (VKORC)¹⁶. The FDA guidelines, therefore, recommend CYP2C9 and VKORC screening for patients upon initiation of

Warfarin and CYP2C9 Polymorphisms

In August of 2007, the U.S. Food and Drug Administration (FDA) updated the warfarin prescribing guidelines to include genetic testing¹⁴. Warfarin is a racemic mixture of the R- and

warfarin therapy. Maintenance therapy should still be guided by the patient's International Normalized Ratio (INR) measurement of prothrombin time in coagulation. These new guidelines are the first steps made to "personalized medicine" through the use of pharmacogenetic data. Table 4 presents an example dosing regimen for warfarin based on specific SNPs in CYP2C9.

SNP Testing Methods and Privacy Concerns

There are numerous methods for genetically screening patients prior to, or coinciding with, the initiation of drug therapy. Under ideal conditions, the results from a genetic screen for a patient are available immediately upon receipt of a prescription, and the pharmacist on-site can utilize this information as part of a decision support process during drug dispensing. Historically speaking, most genetic information has been derived from straight-forward gene sequencing, which involves a basic research laboratory environment (i.e., not a clinical testing environment) and expensive instrumentation. Although the utilization of DNA se-

quencing methods as a SNP screening technique is possible, other methods have been (and continue to be) developed that are designed to test for known SNPs that are much more feasible within the paradigm of clinical genotyping.

In all cases, the adoption of clinical genotyping testing methods requires that the testing be carried out quickly, provide rigorous results, and be relatively inexpensive. This can be achieved by limiting the test to specific genetic variations (SNPs) in the patient's sample that are relevant to drug safety and efficacy. By limiting the SNPs that are screened for each patient, the test can be carried out much more quickly and cost-effectively, and can alleviate many of the privacy concerns inherent to genetic testing in the clinic.

The management of privacy concerns to the patient is paramount to the adoption and implementation of personalized medicine. There are minimal privacy concerns associated with SNPs in genes associated with drug targets and drug metabolism processes. In contrast, most patients will be much more concerned about genetic variations that indicate the patient is at an elevated risk of developing a serious disease, and any deleterious effects that this knowledge may have on their employment or insurance prospects if the testing results were made available to these entities. Therefore, a critical component of patient counseling in personalized medicine will be the fact that the testing methods are limited to drug safety and efficacy assessments, which arguably can only benefit the patient, health insurer and employer.

DNA samples can be obtained from a wide variety of sources. Most common sources include samples obtained from buccal swabs or hair. It is important to note that red blood cells (RBCs) and platelets do NOT have chromosomal DNA, since these "cells" are derived from progenitor cells in the bone marrow. Even though RBCs and platelets lack chromo-

Mutation	Increased Clearance	Decreased Clearance	Dosage Adjustment
CYP2C9*1/*1	27%		dose x 1.27
CYP2C9*1/*2		20%	dose x 0.8
CYP2C9*1/*3		40%	dose x 0.6
CYP2C9*2/*2		50%	dose x 0.5
CYP2C9*2/*3		60%	dose x 0.4
CYP2C9*3/*3		85%	dose x 0.15

Developed from Caraco *et al.*, (2008)¹⁹
Because humans inherit one copy of a gene from each parent, SNPs may be represented as CYP2C9*2/*2. The *2/*2 is simply rendering an identity to each of the two potentially variable genes (e.g., gene from mom/gene from dad).

somal DNA, a "DNA sample" can still be derived from a blood sample due to the presence of other DNA-containing white blood cells in the blood (i.e., neutrophils, eosinophils, lymphocytes, monocytes, etc.).

Case Application of Pharmacogenetic Data to Patient Care

QQ is a 69-year-old female who has arrived at the emergency department after traveling for six hours non-stop from central Pennsylvania. She states that she fell getting out of the car and that her calf hurt really badly afterwards. Doppler studies reveal that she has deep vein thrombosis. She is now at the pharmacy to get a prescription filled for warfarin as part of her treatment plan. Her physician has written for warfarin 5 mg daily. Because the pharmacy is progressive and utilizes cutting edge technology, the pharmacist follows the current FDA guidelines and conducts a genetic screen for CYP2C9 and VKORC. This testing takes several hours to complete, but reveals a SNP in CYP2C9*1/*3. As a result of this SNP, CYP2C9 activity will be reduced. This reduction in CYP2C9 activity increases the patient's warfarin levels and INR, and enhances the likelihood of bleeding. In order to prevent these toxicities, the pharmacist uses the dosing information in Table 4 to calculate a new initial dose of 3 mg

(5 mg initially prescribed x 0.6). In order to implement this dosage change, the pharmacist needs to educate both the physician and patient about pharmacogenetics to varying degrees. This educational component will be initially difficult, but will become easier as the level of understanding about the health care benefits derived from pharmacogenetic testing grows.

Conclusions

The problem with ADRs in the community setting is that research available regarding incidence and prevalence of ADRs is lacking. The rate of ADRs in the community (outpatient) setting is unknown². It is known that community pharmacists with a greater workload are more likely to dispense medications to patients with drug-drug interactions¹⁷. Furthermore, the relative risk for dispensing a medication with a drug-drug interaction increases by over 3 percent for each prescription processed per pharmacist hour, and by 10 percent for each additional prescription per pharmacy staff hour. Finally, another study found that when physicians prescribe medications with drug interactions, they typically do not document this in the patient chart. In fact, 16 to 37 percent of patients had no documentation in the patient chart of drugs with potential drug-drug interactions¹⁸. The researchers

suggested that the physicians may not have even known the patient was on medications with the potential for drug-drug interactions. Thus, preventing ADRs associated with drug-drug interactions represents an area requiring some focused attention by pharmacists. Expanding the pharmacists' role in the area of drug-gene interaction screening is the next logical step in preventing ADRs.

Many factors have contributed to obstacles that limit the utilization of genomic data to routine use in patient care. Concerns over privacy, security and ethical issues are just a few of the issues that have limited this translation from "bench to bedside." We suggest that targeting known SNPs in P450 metabolizing enzymes will avoid these issues and will place pharmacists at the forefront in the management of genomic data in health care. With the pharmacist as the key player, patients will only be screened for metabolizing enzyme and drug target SNPs, and only these data will be stored. No other genomic anomalies will be screened or collected by the pharmacist.

In the future, patients should be able to enter any hospital or community pharmacy practice setting and obtain a buccal swab sample of DNA that will be immediately screened for clinically-relevant P450 polymorphisms. This information will then be seamlessly integrated into prescription filling systems. During the prescription filling process, the pharmacist will be "alerted" if there is a drug-genomic interaction. The pharmacist will then be provided therapeutic and genomic data that will assist the consultation with the physician to tailor the patient's drug therapy. This future will only happen if pharmacists are willing to embrace pharmacogenetics as an opportunity to prevent ADRs and improve overall health care.

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continuing education quiz

Personalized Medicine: Pharmacogenetics as a Method for Improving Patient Outcomes

1. Where do ADRs rank as the leading cause of death in the United States?
 - a. 1st
 - b. 2nd
 - c. 3rd
 - d. 4th
2. Pharmacogenetics is defined as:
 - a. the effects of a drug on gene expression.
 - b. inherited variation in drug effects based on a single gene interaction with drugs.
 - c. use of genomic technologies to identify new drug targets.
 - d. drugs developed and derived from genes.
3. SNPs result in a synonymous (sense) translation if the single nucleotide mistake in the coding sequence results in the:
 - a. amino acid substitution being the *same* as the normal protein amino acid.
 - b. amino acid substitution being *different* from the normal protein amino acid.
 - c. termination of protein synthesis.
4. A SNP in CYP2C9 resulting in decreased enzyme activity may result in:
 - a. decreased drug clearance.
 - b. increased risk of drug-induced toxicity.
 - c. potentially choosing an alternative drug.
 - d. all of the above.
5. CYP2D6 has potential for SNP screening with tricyclic antidepressants (TCAs) dosing because:
 - a. CYP2D6 is the pharmacological target for TCAs.
 - b. TCAs are rarely associated with ADRs.
 - c. CYP2D6 is rarely associated with genetic polymorphisms.
 - d. TCAs have a narrow therapeutic window.
6. In August 2007, FDA updated the warfarin prescribing guidelines to include genetic testing for:
 - a. CYP2D6.
 - b. CYP3A4.
 - c. VKORC.
 - d. all CYP isoforms.

*For questions 7-10, use this mini case. JS is a 70 YOM with a 7-year history of atrial fibrillation. His physician places him on warfarin 5 mg a day for stroke prevention. Genetic testing reveals a CYP2C9*1/*1 SNP which would result in an increased clearance of warfarin.*

7. Because of this SNP, JS would be predicted to have warfarin plasma concentrations that:
 - a. are higher than expected for the prescribed dose.
 - b. are lower than expected for the prescribed dose.
 - c. would be as expected for the prescribed dose.
8. In discussing JS' pharmacogenetic results, the pharmacist should explain that the genetic information obtained:
 - a. helps determine a safe and effective warfarin dosage.
 - b. will determine a warfarin dosage to cure his atrial fibrillation.
 - c. tells all about his susceptibility to disease.
9. Which of the following statements about the risk of ADRs pertain to the initially prescribed dose?
 - a. There is risk for drug-induced toxicity due to inadvertent overdosing.
 - b. There is risk of under-medicating JS due to increased drug metabolism.
 - c. There is risk of under-medicating JS due to the absence of bioactivation of the prodrug.
 - d. There is risk for drug-induced toxicity due to enhanced bioactivation of the prodrug.
10. Based on the genetic information obtained, what would be your suggested starting dose (rounded)?
 - a. 2 mg
 - b. 4 mg
 - c. 5 mg
 - d. 6 mg



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