**review**



**Abstract**

**Potential roles for pharmacists in pharmacogenetics**

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***Objectives:*** To highlight areas of pharmacogenetics in which pharmacists may play a role and to describe those roles in the context of specific examples from a major aca- demic medical center.

***Data sources:*** Literature search (PubMed) and personal interviews for the Univer- sity of California at San Francisco case examples.

***Data synthesis:*** The field of pharmacogenetics presents a wide range of oppor- tunities for pharmacists. Specific roles for pharmacists are likely to fall within three major domains: developing research methodologies and setting research directions, establishing the value of pharmacogenetic testing in clinical practice, and participat- ing in education and infrastructure development that moves pharmacogenetic tech- nologies toward implementation.

***Conclusion:*** As drug therapy experts, pharmacists are in a unique position to push the frontiers of pharmacogenetics in both the research and clinical practice environments.

***Keywords:*** Pharmacogenetics, pharmacists, research.

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**review**

**Learning objectives**

n Define the terms pharmacogenomics, pharmacogenetics, genotype, and phenotype.

n Name at least two roles that pharmacists can play in the field of pharmacogenetics.

n List one drug that has pharmacogenetic information listed in the product package insert approved by FDA.

n Name at least two drugs that are known to have genetic variation in drug response or adverse effect profiles.

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**At a glance**

**Synopsis:** Opportunities in pharmacogenetics— the study of inherited variation in drug-metabolizing enzymes and drug responses—exist for pharmacists in three broad areas: developing research methodologies and setting research directions, establishing the value of pharmacogenetic testing in clinical practice, and par- ticipating in education and infrastructure development that fosters implementation of pharmacogenetic tech- nologies. The current work addresses these three areas by reviewing the literature and highlighting case studies that illustrate the pharmacogenetic roles of pharmacists at the University of California at San Francisco Medical Center. As rapid tests to evaluate metabolic enzymes and guidelines for treatment selection and dosing based on genetic information are developed by FDA, pharmacists in various settings will probably need to evaluate patient genetic information or be involved in testing to ensure appropriate treatment. As practitioners whose training and practice focuses on the clinical monitoring of drug treatment, pharmacists are in a valuable position to help define the eventual role of pharmacogenetics in pharma- cotherapy.

***Analysis:*** *A divide exists between the scope of phar- macogenetic knowledge and its clinical application. Of the advancements foreseen by the Human Genome Project, the concept of personalized medicine received the great- est attention; however, progress in this area has been slow. Pharmacists are well positioned to catalyze the early stages of clinical and translational pharmacogenetic research through their understanding of pharmacokinet- ics, pharmacodynamics, and the relevant clinical and eco- nomic systems that drive health care. They can also help to identify candidate genes that have putative relevance in complex drug response pathways and define and codify drug response phenotypes. A link eventually will be made between genetic variation and drug response, and phar- macists can add value to the trials that evaluate use of new pharmacogenomic applications in clinical settings.*

While the concept of “personalized medicine” (i.e., adjusting therapy on the basis of an individual’s initial response to treat- ment) is not new to research or to clinical practice, pharmaco- genetics is a relatively new field in medical science. It is defined as the study of inherited variation in drug-metabolizing enzymes and drug responses. The term has been used interchangeably with pharmacogenomics, which is defined as the overall study of how genes affect drug behavior and not focused solely on drug- metabolizing enzymes and response.1 New discoveries that link differential drug responses to variability in genes or gene expres-

sion are occurring at a near-bewildering rate. However, just as

success in the clinical application of pharmacogenomic technolo- gies and information will require effective collaboration among the health disciplines, advances in pharmacogenomic research also will benefit from a broad interprofessional and multidis- ciplinary research agenda that includes scientists, physicians, pharmacists, nurses, genetic counselors, payers, and other stakeholders. Pharmacists—as educators, clinical consultants, and providers of health care—will likely influence the way that pharmacogenomic information is used in medical practice and contribute in unique and vital ways.2,3 Currently, pharmacists perform a variety of roles in the health care setting, including educating patients and providers, selecting and monitoring drug therapies for individual patients, ensuring safe and appropri- ate use of medications in populations, and conducting clinical research. The pharmacogenetic revolution will provide unique opportunities for pharmacists to expand these roles as personal- ized medicine evolves.

The roles that pharmacists play in pharmacogenetics have not been clearly defined, and little is known about the future roles of pharmacists in the field. Some publications describing the impact of pharmacogenetics on pharmacists and the profession of pharmacy focus on the roles pharmacists will probably take in the areas of patient and health provider eduction.2,4–7 For exam- ple, in its response to the Human Genetics Commission report on genetic testing, the Royal Pharmaceutical Society emphasized the role that pharmacists may play in performing genetic tests (perhaps in collaboration with local physician practitioners) and in counseling patients about the results of tests that are either ordered by their physician or purchased from other sources (e.g., the Internet).4 Others have emphasized the role that pharma- cists will likely play in the selection of drug therapies.7 Brock et al.2 characterized the pharmacogenetic “revolution” as more of a “renaissance,” with genetic advances causing a “rebirth” in the way patient-specific information guides future drug therapy. They also characterized future roles for pharmacists in research, education, and clinical practice. Pharmacy education has been mentioned slightly more in the literature, suggesting needed changes in the pharmacy and health care professional curricula to accommodate the future roles of pharmacists in pharmaco- genetics.3,4,8–11 In particular, the Academic Affairs Committee of the American Association of Colleges of Pharmacy drafted rec- ommendations for pharmacy education in light of the emerging field of pharmacogenomics in 2002.3 The report includes goals for knowledge, skills, and attitudes that pharmacists and student pharmacists should aim to achieve in preparation for potential pharmacist roles in pharmacogenetics.2 Our own exploration of pharmacist roles at the University of California at San Francisco (UCSF) supports a broad vision of the ways in which pharmacy professionals will advance the field of pharmacogenetics. In dis- cussions with pharmacy practitioners, educators, policy mak- ers, and professional leaders, we identified three major roles for

pharmacists in research and clinical settings.

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**Objectives**

The aim of this article is to highlight areas of pharmacogenet- ics in which pharmacists may play a role. We focus on three broad areas in which pharmacists can contribute to advancing pharmacogenetics in clinical settings: (1) developing research methodologies and projects, (2) establishing the value of phar- macogenetic testing in clinical practice, and (3) moving toward implementation in the clinical setting. We address these three areas by reviewing the literature and highlighting case studies that illustrate the pharmacogenetic roles of pharmacists at the UCSF Medical Center.

**Developing research methodologies: Evaluating the link between genetics and drug response**

Of the various scientific advancements anticipated from the Human Genome Project, the concept of personalized medicine received the greatest emphasis in both the lay and scientific press.12–14 However, progress in this area has been slower than many would have preferred. Thus, research in this area is at a crucial stage if funding agencies and the general public are to continue supporting investigations at the juncture of genetics and disease. Pharmacists can, and in some cases currently do, serve important roles in pharmacogenetic research. The phar- macogenetic roles that pharmacists can play in this regard will likely be patient centered and focused on optimizing disease and health-related quality-of-life outcomes.2 However, pharmacists are also in a unique position to drive the early stages of clini- cal and translational pharmacogenetic research through their understanding of pharmacokinetics, pharmacodynamics, and the relevant clinical and economic systems that drive health care delivery as either principal investigators or key members of a research team.8 Within both academia and the pharmaceutical industry, pharmacists have been involved in the early stages of pharmacogenomic research for specific diseases in which drug therapy is an important management component. As might be expected, this has begun with a focus on drug therapies that are inconsistently effective (i.e., large heterogeneity in clinical response) and prone to adverse effects.

In any pharmacogenomic study (i.e., whether focused on drug efficacy or toxicity), careful consideration must be given to the specific criteria used to codify the drug response phenotype. Phe- notype is defined as the observed features that result from one’s genetic makeup, whereas genotype is the actual genetic makeup that may or may not result in an observable feature. (For example, a person may have a recessive trait for blue eyes and a dominant one for brown eyes [genotype], but the observable eye color is brown [phenotype].) Unfortunately, advances in drug response “phenomics” have lagged behind those related to genomics. And, as Freimer and Sabatti13 emphasized, current approaches for defining phenotypes are largely inadequate to permit the opti-

mal use of advances in high-throughput genetics. For example,

phenotypes for drug response are difficult to quantify or specify. A variety of drug outcomes could be considered a success, including resolution of a medical condition or minimal adverse effects. The difficulty is determining what defines a successful drug response outcome (e.g., number of hospitalizations in 1 year, length of time a patient is disease free). No consistent method exists for mea- suring phenotypes. A comprehensive approach to drug response phenomics likely will entail the collection of data at the molecu- lar, cellular, tissue, and whole-organism levels.13 As practitioners whose training and practice focuses on the clinical monitoring of drug treatment success (and failure), pharmacists are in a valuable position to help define the criteria used to standardize clinical drug responses. For example, most any pharmacist who routinely monitors or manages patients on oral warfarin therapy could cite a number of clinical outcomes that might be of poten- tial value in a pharmacogenetic study assessing the association between genetic variation (e.g., related to *CYP2C9* or *VKORC1*) and the adequacy of anticoagulation therapy, as evaluated by, for example, major/minor bleeding events, time to first therapeutic international normalized ratio (INR) value, and time to stable warfarin dosage.

Although variation in a single gene can have a profound influ- ence on drug response (e.g., effect of thiopurine methyltrans- ferase polymorphisms on azathioprine-induced myelosuppres- sion), most drug responses are thought to be complex, involving multiple genes that interact as part of a drug response “pathway.” As such, delineating drug response pathways by representing the various genes involved in drug responses has been a useful tool in the early phases of pharmacogenomic research for selected drugs and diseases ([www.pharmgkb.org /search /browse.](http://www.pharmgkb.org/search/browse) action?browseKey=pathways). An example of a drug pathway for phenytoin is shown in Figure 1. Polymorphisms in any of the genes shown in this pathway could have an influence on clinical response to phenytoin. One limitation to this approach is that our understanding of all the relevant components (genes and proteins) of a drug pathway is limited. However, because phar- macists are highly knowledgeable regarding the various phar- macokinetic and pharmacodynamic components that are likely involved in clinical drug response (e.g., metabolizing enzymes, transporters, drug targets), they should be viewed as valued allies in the construction of comprehensive pathways. For example, Fig- ure 1 is a pharmacist-developed schematic that originated as part of an interdisciplinary effort to evaluate the pharmacogenetics of antiseizure drug resistance.

**Case example: Research methodology development**

The following case example demonstrates how pharmacists can play an integral role in the development of research methodolo- gies in early pharmacogenomic studies.

At UCSF, a pharmacist faculty member has been active in

the clinical care of epilepsy patients for more than 10 years. This

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Renal excretion

(<5%)

Phenytoin

*MAJOR METABOLIC PATHWAY*

Cell membrane

Phenytoin

CYP2C9

CYP2C19

PHT arene oxide

(unstable intermediate)

*p*-HPPH

(inactive)

UDPGT

LIVER CELL

Minor metabolic pathways

(inactive)

UDPGT

Glucuronide conjugates

ABCC1

Phenytoin

Phenytoin

ABCB1

RLIP76

Idiosyncratic toxicity / Teratogenicity

BLOOD

BLOOD-BRAIN BARRIER

ABCB1

Voltage-gated

Na+ channel

Voltage-gated

Ca++ channel

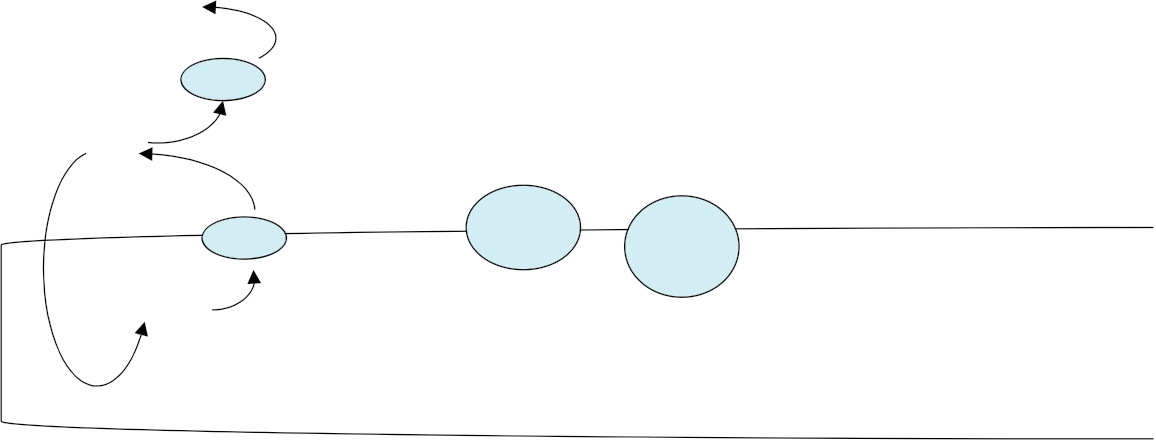
Cell membrane

Phenytoin

*SPECIFIC DRUG TARGET GENES IDENTIFIED IN EPGP TARGET GENE LIST (ION CHANNELS, NEUROTRANSMISSION, NEUROMODULATION)*

NEURON

**Figure 1.** Example drug pathway for phenytoin: Candidate genes involved in metabolism, distribution, and mechanism of action



Abbreviations used: ABCB1, ATP-binding cassette, subfamily B (MDR/TAP), member 1; ABCC1, ATP-binding cassette, subfamily C (CFTR/MRP), member 1;

*p*-HPPH, 5- (4-hydroxyphenyl) -5-phenylhydantoin; PHT, phenytoin; RLIP76, RalA-binding protein 1 (also known as RALBP1); UDPGT, uridine diphosphate glucuronyltransferase.

Red lines indicate repression.

pharmacist has worked as part of an interprofessional team affili- ated with a comprehensive epilepsy management program (the UCSF Epilepsy Center) that includes active clinical and research activities in outpatient care, investigational drug studies, inpatient neurophysiologic evaluation of epilepsy phenotype (video–elec- troencephalography telemetry monitoring unit), and surgical management of patients with medically refractory epilepsy. The role of the pharmacist developed in large part as a result of the pharmacokinetic complexity of standard antiepileptic drugs, the inconsistent effectiveness of these agents, the perceived need for educating patients regarding the desired and undesired effects of antiepileptic drug therapy, and the need for frequent medication revisions in the predominantly pharmacoresistant patient popula- tion that was referred to this specialty center.

In 2002, a multidisciplinary group of researchers with inter- ests in epilepsy began to conceptualize a large-scale study to evaluate the contribution of genetic variation to epilepsy suscep- tibility and to pharmacoresistance. Preliminary evidence sug- gested associations between genetic variance and epilepsy sus-

ceptibility (particularly for rare Mendelian types of epilepsy) and

antiepileptic drug metabolism, but the contribution of genetics to common epilepsy types and clinically relevant drug response phe- notypes had not been adequately studied. The group of investiga- tors included several UCSF faculty members, including the clinical pharmacist affiliated with UCSF Epilepsy Center, and faculty from

15 collaborating academic medical centers with strong epilepsy research and clinical care programs. In collaboration with two epileptologists and a pharmacogenetic scientist, the pharmacist developed the rationale for including pharmacogenetics as an important component of this large study, for which grant support was requested from the National Institute for Neurological Disor- ders and Stroke (NINDS). This group of four, comprising the phar- macogenetic core of the project, collaboratively developed drug response pathways for relevant antiseizure drugs (e.g., Figure 1) and a detailed phenotyping instrument for pharmacoresponse. Patient exposure to each antiseizure medication is coded for effi- cacy (i.e., as success, failure, or noninformative) using clinical parameters such as minimum effective dose, blood levels attained, duration of drug exposure, pretreatment seizure frequency, and

posttreatment seizure frequency. Each patient–drug exposure is

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also coded for toxicity based on the organ system involved and relevant drug exposure data similar to that mentioned above. Standard genetic association and analytic techniques are used to evaluate the link between genotype and phenotype. The collaborative effort to define a pharmacogenomic research agenda for the project has been quite successful. This project has received funding from the NINDS, and participant enrollment began in mid-2007 (www.epgp.org).

As the example above illustrates, pharmacists have expertise in areas that are highly relevant to the early stages of pharma- cogenomic research. They have an appreciation for many of the factors that drive the expansion of pharmacogenetics into new areas of disease management, such as knowledge of

n Drug treatments for which efficacy responses are unpredict-

able (e.g., anticancer and antiseizure drugs)

n Drugs that cause serious adverse events resulting in patient harm (e.g., antipsychotic medications and hepatotoxins)

n Serious and nonserious adverse drug events or complications that cause drug failure or substantially delay successful treat- ment of disease (e.g., need for frequent dosing adjustments of warfarin resulting in delays to therapeutic anticoagulation)

n Drug treatments that have marked efficacy in small subpopu-

lations but dramatically less efficacy in the larger population of patients with a given disease (e.g., gefitinib response in patients with non–small-cell lung cancer)15,16

As practitioners with a broad appreciation for these drug–dis- ease response challenges, pharmacists can help to identify new areas in which pharmacogenetic research might be of clinical value. They can also help to define and codify drug response phe- notypes and identify candidate genes that have putative relevance in complex drug response pathways. Armed with these skills and knowledge, pharmacists are in a position to lead and develop research, assuming the roles of principal investigators on proj- ects. When a link between genetic variation and drug response is ultimately made, pharmacists can also add value to trials that evaluate the practical use of new pharmacogenomic applications in clinical settings.

**Establishing the value of pharmacogenetic testing in clinical practice**

Translation of research is an important step in the implementa- tion of early research findings in patient care. Pharmacists have a role in the early steps of pharmacogenetic research and in testing the application of early research results in patient care settings. Once a relationship between drug response and genetic varia- tion has been established, subsequent research should establish the use of pharmacogenomic testing as measured by specific therapeutic outcomes. Pharmacists can help develop ways to evaluate the application of testing in patients, with the goal of proving or disproving that pharmacogenomic testing adds ben- efit to clinical practice. Pharmacogenomic models would be most

useful in complex drug therapies that require individualized dose

management, such as epileptic, lipid, anticoagulation cardiovas- cular, and hypertensive management. Consequently, because of the complex drug therapy and management of these conditions, pharmacists already tend to be involved in these areas and, in some cases, are managing medication therapies under collab- orative agreements.17–23 As such, pharmacists are in a unique position to collaborate in these areas.

A link between specific genetic variants and drug disposition has been established for some drugs. Warfarin, for example, is an anticoagulation medication that has a narrow therapeutic window. Bleeding, the most common adverse effect of warfarin, occurs in

6% to 39% of treated patients each year and is most common at initiation of therapy.24,25 Early studies showed that warfarin was metabolized by cytochrome P450 (CYP) enzymes, particularly CYP2C9. Subsequently, the gene encoding *CYP2C9* was found to have many variant alleles that were differentially expressed in various populations. Expression of these variant alleles, par- ticularly *CYP2C9\*2* and *CYP2C9\*3*, were shown to affect the metabolism rate of various drugs such as warfarin. Approxi- mately 8% to 20% of whites are carriers of the *CYP2C9\*2* allele, and 6% to 10% are carriers of the *CYP2C9\*3* allele.26 Asians and blacks have lower frequencies of these variant alleles.26,27 When compared with patients who were homozygous for the wild-type (*CYP2C9\*1*) allele, patients with one copy of the *CYP2C9\*2* allele required warfarin maintenance doses that were 20% lower and patients with one copy of the *CYP2C9\*3* allele required warfarin doses that were 34% lower.26,28 An even more dramatic decrease in dose was required for those who were homozygous or heterozy- gous for the *CYP2C9\*2* and/or *CYP2C9\*3* alleles, which would require a 60% to 75% dose reduction.26,29 Furthermore, those with variant alleles were found to have a significantly increased risk of developing serious bleeding events.29 Based on some of this information, FDA recently approved updated warfarin prescribing information based on outcomes related to genetic variations. The new information may help improve the initial dosing regimens to improve treatment and decrease adverse effects.30

Additional research shows that *CYP2C9* polymorphisms are not the only determinants of variation in warfarin response, but genetic variability in the target protein also influences warfa- rin response. Warfarin inhibits the enzyme vitamin K epoxide reductase (VKOR). Inhibiting this enzyme results in decreased amounts of vitamin K, which in turn decreases blood clotting. The gene that encodes for VKOR, VKOR complex subunit 1 gene (VKORC1), has been found to be polymorphic in various popula- tions. Individuals with the *VKORC1* 1173CC genotype have been found to require higher daily doses of warfarin than those with the CT or TT genotypes (6.2, 4.8, and 3.5 mg/day, respectively).31

Despite adequate literature to support the influence of *CYP2C9* and *VKORC1* genotype on warfarin dosage, no published clinical trials have evaluated the clinical use and efficiency of genetic tests in warfarin therapy.32 Knowing the genetic makeup

of an individual and *CYP2C9* activity can potentially help predict

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warfarin response to a particular dose and avoid unnecessary adverse effects or subtherapeutic treatment that occurs with the current trial-and-error approach. At this time, warfarin dos- ing requires frequent changes and regular monitoring of INR to avoid subtherapeutic and supratherapeutic levels that could lead to undesired outcomes such as stroke or internal bleeding. Phar- macists often are integral to warfarin therapy management and have been successful in showing benefits in health and economic outcomes.17–19,33,34 By teaming with interdisciplinary health care professionals, a pharmacist could play a large role in collaborat- ing and designing pilot studies to evaluate knowledge already produced in the literature.

**Case example: Pharmacist collaborative role** As an example, the following case illustrates the role of a clinical pharmacist collaborating with others in a clinical study to help establish the value of pharmacogenetic testing in warfarin-naive patients.

At UCSF and San Francisco General Hospital (SFGH), phar- macist-managed anticoagulation clinics have been in practice for more than 30 years. The anticoagulation service involves a multidisciplinary approach to managing patients on warfarin in both the inpatient and outpatient setting and may treat up to 40 patients (20 patients per pharmacist) in 1 day.

In 2006, working with the known data about warfarin, phar- macists involved in anticoagulation clinics at UCSF and SFGH teamed with physicians from laboratory medicine, cardiology, and pharmacology to test hypotheses based on the current knowledge of *CYP2C9* and *VKORC1* polymorphisms. The team developed a prospective, randomized, clinical trial to determine the clinical benefit of using the *CYP2C9* and *VKORC1* genotypes for warfa- rin dosing. The group is piloting the study in 30 patients newly started on warfarin. Participants will be tested for the *CYP2C9* and *VKORC1* genotypes, and those with variant alleles will be randomly assigned to receive empiric warfarin doses of 5 mg or a genotype-guided warfarin dose according to Sconce et al.35

Those with normal alleles will receive empiric warfarin induction

therapy. Outcomes for a 3-month follow-up include the number of dose adjustments, INR levels at the first three anticoagula- tion follow-up visits, percentage of INR values that fall out of the therapeutic range, and number of mild to serious adverse effects related to bleeding.

Currently, only pharmacists involved in the study enroll patients and follow them in clinic. Difficulties, however, have arisen in identifying patients who are candidates for the study before initiating warfarin. Steps to alleviate the problem have involved inpatient staffing pharmacists notifying investigators when a new order for warfarin is written, which may help to cap- ture participants before they receive their first dose of warfarin.

With the future of pharmacogenetic tests expanding, pharma- cogenetic testing may be an added responsibility for pharmacists

already involved in managing warfarin patients. The routine use

of pharmacogenetic tests and warfarin therapy, however, has not materialized, and pharmacist roles in this area are currently undefined. At this juncture, pharmacists must take the initiative and get involved by developing projects and collaborating with others in the field to ensure pharmacist involvement as current research moves to implementation in patient care and pharmaco- genetic models begin to have a place in clinical practice.

**Toward implementation of pharmacogenetics in the clinical setting**

Once prospective studies have been established, the clinical rele- vance of genetic testing and the regulatory, ethical, and economic aspects of such testing need to be considered. From a regula- tory standpoint, FDA has partnered with industry to establish workshops and advisory groups that discuss and develop policies related to pharmacogenetics.16 FDA encourages voluntary sub- mission of genomic data during the drug development process. In addition, the agency recommends including pharmacogenetic information in the package insert if the data affect the safety and efficacy of a particular drug.36

Several drugs have been investigated in detail for associa- tions between enzyme polymorphisms and drug toxicities and/or therapeutic benefit. For some, the evidence for genotype-associ- ated toxicity or efficacy is substantial enough that information on pharmacogenetic testing appears in the drug label. To this end, pharmacists should be aware of the regulatory issues surround- ing these medications and the implications of the label informa- tion for clinical practice.

Chemotherapeutic agents have been researched extensively. These agents are especially challenging to administer because of their narrow therapeutic windows and interpatient variability in how the agents are metabolized and cleared from the body. Cur- rently, initial doses of chemotherapeutic agents are based on body weight or surface area, with dose adjustments made after signs of toxicity appear. Pharmacogenetic testing aims to associate specific genetic polymorphisms with clinical outcomes in patients treated with commonly prescribed chemotherapy drugs, thereby predicting the toxicity and/or efficacy of a particular dose of a particular agent for an individual.37,38

The toxicities of some medications have long been known to be associated with genetic variations. One such example is the enzyme uridine 5′-diphosphate-glucuronosyltransferase 1A1 (UGT1A1) and the topoisomerase inhibitor irinotecan (Camp- tosar—Pfizer).39

Irinotecan is often used in the treatment of metastatic col- orectal cancers, usually in combination with 5-fluorouracil.39

*UGT1A1* is responsible for metabolizing the active metabolite of irinotecan, SN-38. Multiple studies have shown that a certain *UGT1A1* variant, known as *UGT1A1\*28 (TA) TAA*, results in the accumulation of SN-38 and is directly correlated with an increased incidence of myelosuppression, neutropenia, and severe diarrhea

*7*

compared with the wild-type *UGT1A1* alleles.40–42 An estimated

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10% of the North American population is homozygous for the vari- ant *UGT1A1\*28* allele, and these individuals are at higher risk for experiencing toxicities with irinotecan therapy.39 A pharmacoge- netic test for *UGT1A1* activity would potentially predict the risk of serious adverse effects from irinotecan treatment and allow clini- cians to individualize the irinotecan dose to optimize therapeutic benefit while minimizing serious toxicities. Based on a patient’s genotype, the clinician would be able to decide to give irinotecan at reduced doses or use an alternative chemotherapeutic regimen that does not include irinotecan.

Another example is thiopurine S-methyltransferase (TPMT) and the antimetabolite mercaptopurine (Purinethol—DSM Pharmaceuticals). Similar to irinotecan, mercaptopurine is a chemotherapeutic agent that has been rigorously studied for associations between genotype and toxicities and/or efficacy.43–45

Mercaptopurine is used in the treatment of acute lymphoblastic leukemia.46 TPMT is a polymorphic enzyme that converts mercap- topurine to its inactive metabolite. Thus, patients who are TPMT- deficient are at high risk for myelosuppression and secondary tumors with administration of mercaptopurine or other thiopu- rines (e.g., azathioprine) that are converted to mercaptopurine. Conversely, patients with high TPMT activity may experience a decreased therapeutic effect from treatment with these agents. Approximately 0.3% of whites and blacks have two nonfunctional alleles of the *TPMT* gene leading to little or no detectable enzyme activity. Approximately 10% of patients have one *TPMT* nonfunc- tional allele and have low or intermediate TPMT activity.46

The most current version of the manufacturer’s prescribing information for irinotecan (June 2006) refers to the increased risk of neutropenia associated with a homozygous *UGT1A1\*28* allele in patients receiving one dose of irinotecan every 3 weeks. Guidelines for initiating irinotecan at a lower starting dose for these patients are provided in the prescribing information; how- ever, the precise dose reduction needed in these patients is not known, and subsequent dose modifications should be made based on the patient’s tolerance to treatment.39 To date, based on our lit- erature search and observations, no clear recommendation exists to perform genetic testing for all patients before administering the drug, so the decision to perform genetic testing is based on the discretion of the clinician.

As for the irinotecan label, the prescribing information for mercaptopurine informs clinicians about the availability of geno- typic and phenotypic *TPMT* testing and recommends “substantial dose reductions” in patients homozygous for *TMPT* variants (i.e., *TMPT\*2, TMPT\*3A,* or *TMPT\*3C* ).46 However, specific guidelines for these dose reductions are not provided. In fact, the prescribing information suggests considering *TPMT* testing when a patient experiences severe myelosuppression after receiving mercap- topurine. Currently, *TMPT* testing is not routinely performed before mercaptopurine or other thiopurines are administered because of the absence of clear guidelines on using the test

results and lack of adequate information regarding the benefits

of genotype-guided dosing compared with traditional monitoring for adverse effects.47

As illustrated by these examples, a divide exists between the extent of pharmacogenetic knowledge and its clinical application. The ambiguities of the labeling for irinotecan and mercaptopurine highlight the need for research proving that pharmacogenetic testing prior to therapy improves patient outcomes and reduces health care costs.48 Such research is currently underway for *UGT1A1* and *TPMT* genotyping, and we can expect to see data from these studies during the next several years.49,50 Socioeco- nomic aspects of testing, including economic, ethical, and legal factors, also need to be clarified before pharmacogenetics can be integrated into daily clinical practice. Currently, the pharmacoge- netic labeling for irinotecan and mercaptopurine are for informa- tional purposes only. However, requiring the use of pharmacoge- netic information to guide dosing of certain drugs may occur in the not-too-distant future, particularly as cost-effectiveness and clinical use data begin to emerge.51

**Case example: Implementation of pharmacogenetic testing**

The following case example demonstrates the challenges of implementing established pharmacogenetic testing and steps pharmacists have taken to move toward implementation of these tests in a clinical setting.

At the UCSF Comprehensive Cancer Center, *UGT1A1* testing for all patients planning to undergo treatment with irinotecan is under discussion because of the pharmacogenetic information in the drug label. However, several obstacles to the clinical applica- tion of this test exist, including the lack of a protocol by which dose adjustments should be made, the optimal timing of testing, and whether all patients or only a select few (e.g., those receiving particularly high doses of irinotecan) should be tested. Whether patients who are receiving off-label doses of irinotecan (e.g., once weekly) should be tested is also unknown.

To address these and other concerns, a pharmacogenetic working group led by a pharmacist has convened to (1) iden- tify opportunities for pharmacogenetic research at UCSF, (2) determine when and how to apply genotype/phenotype testing of well-studied enzyme polymorphisms and their drug targets (e.g., *UGT1A1* and irinotecan) to clinical practice, and (3) support research activities in various ways, including solicitation of grant support. The working group consists of university representatives from various disciplines, including clinical laboratory, medicine, pharmacy, pharmacology, and genetics, many of whom are lead- ing contributors to the field of pharmacogenetics. Industry rep- resentatives are also invited to participate.

To be actively involved in planning and implementing phar- macogenetic testing, as demonstrated in the case example above, pharmacists should be aware of some of the key fac- tors that will drive the integration of pharmacogenetics into

pharmacy practice. These include mechanisms for pharmacist

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education on pharmacogenetics (e.g., as continuing educa- tion programs sponsored by professional organizations or industry), establishing a means of keeping abreast of emerg- ing guidelines and regulations regarding pharmacogenetics and drugs, gauging the cost of testing and determining when testing should be done and under what circumstances health plans will cover such testing, determining how test results should be stored and shared with other providers, and creating protocols that define the role of the pharmacist in the pharma- cogenetic arena, particularly when FDA incorporates genetic testing information into the warnings or dosing sections of a drug’s prescribing information. The following are examples of resources available for such information:52

n FDA information regarding pharmacogenomic information

printed on drug labels: [www.fda.gov/cder/genomics](http://www.fda.gov/cder/genomics)

n National Human Genome Research Institute policy and legis- lative information regarding ethical and legal ramifications of genetic testing: [www.genome.gov/10002077](http://www.genome.gov/10002077)

n National Academy of Clinical Biochemistry practice guidelines for the application of pharmacogenetic testing in health care: [www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/](http://www.aacc.org/AACC/members/nacb/LMPG/OnlineGuide/) DraftGuidelines/Pharmacogenetics

**Conclusion**

Pharmacogenetics may not be a part of routine clinical and community practice for some time; therefore, the field pres- ents opportunities for a wide range of pharmacists, from the basic scientist to the clinician to the administrator, to collabo- rate with other health professionals in pharmacogenetic dis- covery and application. Pharmacists are already engaging in some of these roles and paving the way for future pharmacist involvement in personalized medicine and pharmacogenomic research. The case examples reported here offer insight into future roles for pharmacists in pharmacogenetics. At some point, all pharmacists, not just those involved in a clinical or research setting, will probably need to understand pharma- cogenetic information to better aid in drug selection. As rapid tests to evaluate metabolic enzymes and guidelines for treat- ment selection and dosing based on genetic information are developed by FDA, pharmacists in various settings, whether community, institutional, or academic, will probably need to evaluate a patient’s genetic information or be involved in test- ing to ensure the most appropriate treatment for a patient. As drug experts, pharmacists offer unique perspectives on the appropriate use and disposition of medications in the body and therefore are a natural fit for helping to define the eventual role of pharmacogenetics in pharmacotherapy.

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**1. Pharmacogenetics is defined as**

a. The overall study of how genes affect drug behavior

b. The study of economics related to pharmacotherapeutic outcomes and genetic diseases

c. The study of how drugs interfere with and alter the genetic code within certain populations

d. The study of inherited variation in drug metabolizing- enzymes and drug responses

**2. A genotype is defined as**

a. The observable features of genetic expression b. The specific genetic expression of one’s traits

c. The specific genetic expression of one’s traits and observable features

d. None of the above is correct.

**3. Which of the following is true regarding the field of phenomics?**

a. Phenomics is a difficult way to predict drug responses because many outcomes can be classified as a pheno- typic success.

b. Phenomics is well studied and does not require geno- typic association to help predict drug response.

c. Phenomic study probably will not require data collec- tion of molecular, cellular, tissue, and whole-organism levels.

d. Phenomics is a clear way to predict drug responses in different patient populations.

**4. Genetic variation of *VKORC1* affects the metabolism of which of the following drugs?**

a. Phenytoin

b. Azathioprine c. Warfarin

d. Mercaptopurine

**5. Based on the studies of *CYP2C9* variant alleles and warfarin doses, which of the following combinations would likely require the greatest dose reduction?**

a. Homozygous: *CYP2C9\*1*

b. Heterozygous: *CYP2C9\*1* and *CYP2C9\*2* c. Heterozygous: *CYP2C9\*1* and *CYP2C9\*3* d. Homozygous: *CYP2C9\*3*

**6. Which of the following is not a common cause for slow advances in the field of pharmacogenomics research?** a. Limited understanding of the full range of gene-

encoded proteins that modulate drug response (e.g., metabolizing enzymes, transporters, and drug targets)

b. The well-known fact that variability in drug response is more likely to result from environmental factors than genetic factors

c. Difficulty in assigning clear, unambiguous drug response phenotypes based on clinical data from patient care databases for selected diseases

d. Lack of a clear mechanism for evaluating the cost- effectiveness and clinical use of pharmacogenomic tests (e.g., genotyping tests) once an association between genotype and drug response has been identified

**7. Pharmacists are uniquely qualified to participate in interdisciplinary efforts to study the genetic contribu- tions to drug response because of all of the following except**

a. Knowledge of interpatient variability in patient responses (both toxic and therapeutic)

b. An appreciation for unusual patient responses to drug therapy (e.g., idiosyncratic reactions)

c. Access to Health Insurance Portability and Account- ability Act (HIPAA)–protected databases that include patient information

d. Knowledge of gene-encoded proteins (e.g., metabolizing

enzymes, drug targets) that influence drug response

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**8. Which of the following hypothetical drugs would appear to be the best candidate for further study from a pharmacogenomic perspective?**

a. A new antihypertensive metabolized by the CYP2D6 enzyme that is expensive and not covered by most pri- vate insurers; no information exists currently regarding its mechanism of action

b. A new combination product that includes two mood- stabilizing drugs that have been proven effective, neither of which seem to be influenced by genetic vari- ability

c. A new cognitive-enhancing agent metabolized by the CYP2C9 enzyme that is effective in 100% of patients and causes no toxicity

d. A new antiarrhythmic agent that is metabolized by the CYP2D6 enzyme and absorbed by a genetically poly- morphic gut transporter and that effectively eliminates arrhythmias in 50% of patients but is completely inef- fective in the other 50% of patients

**9. For pharmacogenetic data to be included in the pack- age insert of a drug product, the information must be** a. Easy to apply in clinical settings and cost-effective

b. Derived from randomized, controlled, clinical trials exclusively

c. Helpful for predicting which patients are likely to have life-threatening idiosyncratic reactions

d. None of the above is correct.

**10. Which of the following is not true regarding phar- macist involvement in clinical pharmacogenomic research to date?**

a. Most pharmacists involved in this research have been employed in academic or pharmaceutical industry settings.

b. Pharmacists are useful allies in deciding which drugs are amenable to pharmacogenomic study.

c. Pharmacists cannot participate in defining drug response phenotypes (i.e., responders versus nonre- sponders) because that activity is considered beyond the scope of a pharmacist’s professional responsibility.

d. Pharmacists often contribute to pharmacogenomic research as part of interprofessional/interdisciplinary teams that include scientists and other health

professionals.

**11. The enzyme uridine 5′diphosphate-glucuronosyl- transferase 1A1 (UGT1A1) is responsible for which of the following?**

a. Metabolizing irinotecan b. Metabolizing SN-38

c. Metabolizing warfarin

d. Metabolizing mercaptopurine

**12. Individuals who are homozygous for the *UGT1A1\*28***

**allele who receive irinotecan would require**

a. Increased dosage because the irinotecan would be metabolized faster

b. Increased dosage because irinotecan would be metabo- lized slower

c. Decreased dosage because the active metabolite would be metabolized faster

d. Decreased dosage because the active metabolite would be metabolized slower

**13. Which of the following is true regarding individuals who have low thiopurine S-methyltransferase (TPMT) activity?**

a. They are at higher risk for myelosuppression. b. They are at lower risk for myelosuppression.

c. They would require higher doses of thiopurines.

d. They would require higher doses of anticonvulsants.

**14. The consequences of drug-metabolizing enzyme poly- morphisms appear in the prescribing information for all of the following drugs except**

a. Coumadin b. Purinethol c. Dilantin

d. Camptosar

**15. Strategies to address barriers to implementing pharmacogenomic testing include**

a. Lack of convincing evidence supporting the link between genotype and toxicity

b. Lack of cost-effectiveness and clinical use data

c. Lack of mechanisms by which pharmacists and other health providers can stay informed about advances in pharmacogenomics

d. Unavailability of pharmacogenomic tests

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