The Pharmacist’s Role in Personalized Medicine: A Review of Pharmacogenetics

By Rebecca Tomich, Pharm.D., CGP, consultant director, In Touch Pharmaceuticals; and Joe Brown, B.S. Pharm., senior executive consultant, In Touch Pharmaceuticals, and president, JKB Solutions Inc.

Target Audience
This continuing education activity was designed specifically for pharmacists.

Disclosure Statement
Rebecca Tomich received an honorarium from Boehringer Ingelheim for serving as a speaker; however, she has agreed to present information in an unbiased manner. Joe Brown does not have any conflicts of interest, or financial relationships with a commercial interest, related to the activity.

Learning Objectives
At the end of this activity, participants should be able to:

- explain basic pharmacogenomic and pharmacogenetic concepts.
- explain how genetic variation in proteins, including drug transporters and drug metabolizing enzymes, affect drug metabolism and drug response.
- discuss the availability of evidence-based guidelines and utilize them for the selection of drug therapy.
- review the cost, cost-effectiveness and reimbursement by insurers relevant to pharmacogenomics tests and test interpretation for patients.
- recall the process of acquiring genetic material, completing the necessary paperwork and interpreting the pharmacogenetic testing results.

Background
Medications demonstrate effectiveness in clinical studies, yet they may be less effective in a particular patient, resulting in failure to reach desired treatment goals. Medications can also cause adverse drug events (ADEs), which are unintended effects or injuries to the patient. While most often inconvenient or uncomfortable, ADEs can be extremely dangerous. Adverse drug events contributed to an estimated 13.5 million outpatient visits between 2005 and 2007. The elderly are at an increased risk due to decreased physiologic function, comorbid disease states and an increased number of medications. The decreased physiologic function results in increased drug exposure (decreased renal and hepatic function). There were an estimated 100,000 emergency department visits related to ADEs among Americans 65 and older, resulting in hospital admissions between 2007 and 2009.

Adverse drug events or treatment failure may cause the patient to doubt their physician or pharmacist and prevent future treatment of disease. Reducing the incidence of ADEs may reduce the financial burden on the health care system overall and produce cost savings by preventing a portion of drug-related hospitalizations. One way to achieve this is through personalized medicine (now being called “precision medicine”), which relies, in part, on knowledge of how a patient’s genotype (genetic makeup) influences his or her phenotype (observable trait). By using pharmacogenetics to personalize medication choices, physicians and pharmacists can identify patients susceptible to adverse effects; be aware of dangerous drug-drug, drug-gene, and drug-drug-gene interactions; and provide care in a whole new way that is completely individualized.
Introduction to Personalized Medicine

Research on genetics has provided advances that can be used to more accurately predict the risk of developing certain diseases, personalize screening and surveillance protocols, and, in some cases, prevent the onset of disease. Personalized medicine is the use of patient-specific information and biomarkers to make more informed decisions regarding the optimal therapeutic treatment regimen for that patient. Pharmacogenetics (PGt) is the aspect of personalized medicine whereby patient-specific genomic biomarkers are used to choose the optimal drug and/or dose for the patient. Pharmacogenetics and pharmacogenomics (PGx) are similar terms but PGt is used when discussing specific drug-gene interactions and PGx is used when discussing drug-gene(s) interactions or how the whole genome interacts with drug therapy. The term PGx has been related broadly to pharmacotherapy and the population. The goal of personalized medicine is to achieve efficacy of the drug while avoiding ADEs.

Pharmacogenomics more specifically is the study of genetic variations (variations are caused by mutations in the genomic DNA sequence) that influence individual response to drugs. Different forms of genes that are passed on from parent to child are called alleles. The combination of alleles an individual inherits determines his or her genotype, and the expression of these alleles determines his or her phenotype. Some mutations are more common than others in a population and, when this mutation occurs in at least 1 percent of individuals in the population, it is commonly referred to as a polymorphism. The most commonly identified mutations are single nucleotide polymorphisms, also called SNPs (pronounced “snips”). Single nucleotide polymorphisms are when one base replaces another (e.g., G greater than A; A replacing G). Insertions and deletions (indel) are different kinds of genetic variance. A particular SNP may or may not result in changes in protein regulation, expression or activity. Variants are very common; it is estimated that as many as 9-10 million polymorphisms can be found in the human genome (53 million SNPs have been identified).

An identified SNP may affect protein function, by either causing a reduction of activity or an increase in activity. A reduction in activity can be termed a loss-of-function allele (CYP2C19*2 is a loss of function gene). Someone with one (heterozygote) or two (homozygote) loss-of-function alleles will have less overall protein expression and/or activity compared to someone with two normal-function alleles. When an SNP is identified that has an increased protein function, it is termed a gain-of-function allele. Finally, the presence of a gain-of-function allele, or duplication (multiple copies) of a normal function allele, may result in increased protein expression and/or enhanced activity.

Enzymes responsible for drug metabolism and proteins that determine the cellular response to drugs (receptors) are encoded by genes, and can, therefore, be variable in expression, activity level and function when genetic variations are present. There are a large number of medications that can be affected by these genetic variations and represent examples where personalized medicine can play an important role in preventing treatment failures or ADEs. Below is a short list of selected medications influenced by genetic variation that are used in the context of personalized medicine.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Gene(s)</th>
<th>Drug</th>
<th>Gene(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel (Plavix®)</td>
<td>CYP2C19</td>
<td>Atomoxetine (Strattera®)</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Abavavir (Ziagen®)</td>
<td>HLA-B*5701</td>
<td>Codeine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Carbamazepine (Tegretol®)</td>
<td>HLA-B*1502</td>
<td>Tamoxifen (Nolvadex®)</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Warfarin (Coumadin®)</td>
<td>CYP2C9, VKORC1</td>
<td>Azathioprine (Imuran®)</td>
<td>TPMT</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>Her2/neu</td>
<td>Imatinib mesylate (Gleevec®)</td>
<td>C-KIT</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>EGFR</td>
<td>5-Fluorouracil (Efudex®)</td>
<td>DPD</td>
</tr>
</tbody>
</table>

Table 1. Selected Drugs whose Safety and Efficacy are Affected by Gene Variations

4 Research on genetics has provided advances that can be used to more accurately predict the risk of developing certain diseases, personalize screening and surveillance protocols, and, in some cases, prevent the onset of disease. Personalized medicine is the use of patient-specific information and biomarkers to make more informed decisions regarding the optimal therapeutic treatment regimen for that patient. Pharmacogenetics (PGt) is the aspect of personalized medicine whereby patient-specific genomic biomarkers are used to choose the optimal drug and/or dose for the patient. Pharmacogenetics and pharmacogenomics (PGx) are similar terms but PGt is used when discussing specific drug-gene interactions and PGx is used when discussing drug-gene(s) interactions or how the whole genome interacts with drug therapy. The term PGx has been related broadly to pharmacotherapy and the population. The goal of personalized medicine is to achieve efficacy of the drug while avoiding ADEs.

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Cytochrome P450

There are several genes responsible for differences in the drug metabolism and response. Among the most common are the Cytochrome P450 (CYP) genes, encoding enzymes that control the metabolism of more than 90 percent of drugs (the most significant enzymes being CYP3A4 and CYP2D6). A specific gene encodes each CYP450 enzyme. People who carry variations in certain CYP genes often do not metabolize drugs at the same rate or extent as in most people, and this can influence response in many ways. Every person inherits one genetic allele from each parent. Alleles are referred to as “wild type” or “variant,” with wild type occurring most commonly in the general population. A “normal” (extensive) metabolizer has received two copies of normal function genes, most often the wild-type form. Polymorphism occurs when a variant allele replaces one or both wild-type alleles. Variant alleles many times will encode a CYP450 enzyme that has reduced or no activity. A person with two copies of variant alleles is typically a “poor” metabolizer, whereas those with one wild-type and one variant allele have reduced enzyme activity. Finally, some individuals inherit multiple copies of wild-type alleles or make more of a given enzyme, which results in excess enzyme activity. This phenotype is termed an “ultrarapid” metabolizer. A list of some common gene variations and corresponding phenotypes are listed below in Table 2.

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Gene Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid Metabolizer</td>
<td>CYP2C19*17/*17</td>
</tr>
<tr>
<td>Normal Metabolizer</td>
<td>CYP2C19*1/*1</td>
</tr>
<tr>
<td>Poor Metabolizer</td>
<td>CYP2C19*3/*5</td>
</tr>
<tr>
<td>Intermediate Metabolizer</td>
<td>CYP2D6*1/*5</td>
</tr>
<tr>
<td>Normal Metabolizer</td>
<td>CYP3A4*1/*1</td>
</tr>
<tr>
<td>Ultrarapid Metabolizer</td>
<td>CYP2D6*2xN (multiple copies)</td>
</tr>
</tbody>
</table>

Pharmacists are familiar with the CYP450 enzymes, as they are the most important system affecting drug metabolism. It is useful to understand the naming of CYP450 alleles, and how the activity of the protein products of the variant genes (i.e., CYP enzymes) influence drug metabolism. These genes are frequently tested in the context of PGx. The human cytochrome (CYP) P450 genes are defined by a well-accepted nomenclature.

The Naming of CYP Example: CYP2C9*2

CYP-Super Family
2- Family
C9-Subfamily
*2- Individual Member

Pharmacogenetics Effect on Drug Metabolism

The metabolizer phenotype describes the patient’s ability to metabolize certain drugs and is based on the number and type of functional alleles of certain genes that a patient carries. Depending on the type of CYP variation present, the patient’s metabolizer phenotype and the type of drug (active pharmacologic agent or inactive prodrug precursor), the therapeutic drug response is often suboptimal (see Table 3). For example, poor metabolizers are unable to metabolize certain drugs efficiently, resulting in a potentially toxic build-up of an active drug or the lack of conversion of a prodrug into an active metabolite. In contrast, in ultra-rapid metabolizers, an active drug is inactivated quickly, leading to a subtherapeutic response, while a prodrug is quickly metabolized, leading to rapid onset of therapeutic effect with the potential of increased exposure to the active compound.
Table 3. Effects of CYP Variants on Therapeutic Efficacy

<table>
<thead>
<tr>
<th>Metabolizer Phenotype</th>
<th>Active Drug (inactivated by metabolism)</th>
<th>Prodrug (needs metabolism to produce active metabolite)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (PM)</td>
<td>Increased efficacy; active drug may accumulate; may require lower dose to avoid toxicity.</td>
<td>Decreased efficacy; may require higher dose or alternative drug. Prodrug may accumulate, which can increase toxicity.</td>
</tr>
<tr>
<td>Intermediate Metabolizer (IM)</td>
<td>Increased efficacy; active drug may accumulate; may require lower dose to avoid toxicity (not as much as PM).</td>
<td>Decreased efficacy; may require higher dose or alternative drug. Prodrug may accumulate, which can increase toxicity.</td>
</tr>
<tr>
<td>Normal Metabolizer (NM) (extensive)</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Ultrarapid Metabolizer (UM)</td>
<td>Decreased efficacy; active drug rapidly inactivated; may require higher doses.</td>
<td>Increased efficacy; rapid onset of effect; greater exposure; may require lower doses.</td>
</tr>
</tbody>
</table>

CYP2C19 enzyme contributes to the metabolism of many clinically relevant drugs such as clopidogrel (Plavix). Clopidogrel is a platelet inhibitor used in the treatment of a number of cardiovascular diseases. It is often prescribed for secondary prevention following acute coronary syndromes and for patients undergoing percutaneous coronary intervention. Almost 25 percent of patients experience subtherapeutic antiplatelet response. Clopidogrel is a prodrug that requires hepatic biotransformation to form an active metabolite that selectively and irreversibly inhibits the purinergic P2RY12 receptor and, thereby, platelet aggregation. Conversion of clopidogrel to its active metabolites requires activation by several CYP450 enzymes including prominently CYP2C19.

Patients who are considered a CYP2C19 Poor Metabolizer (PM) show reduced ability to convert clopidogrel into its active metabolite, resulting in a diminished antiplatelet effect. As you would expect, these individuals are more likely to have an ischemic event while taking clopidogrel therapy. It is estimated that 2-20 percent of patients are likely to carry the CYP2C19*2 variant. An Intermediate Metabolizer (IM) may also have reduced platelet inhibition and an increased risk for cardiovascular events. A boxed warning is included in the product labeling to alert health care providers about this genetic variation, related to the PM individual.

Table 4. Clopidogrel Therapy Based on CYP2C19 Phenotype for ACS/PCI Patients Initiating Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Implications for Clopidogrel</th>
<th>Therapeutic Recommendations</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid and Normal (UM, NM)</td>
<td>Normal (NM) or increased (UM) platelet inhibition; normal (NM) or decreased (UM) residual platelet aggregation.</td>
<td>Clopidogrel label-recommended dosage and administration</td>
<td>STRONG</td>
</tr>
<tr>
<td>Intermediate (IM)</td>
<td>Reduced platelet inhibition; increased residual platelet aggregation; increased</td>
<td>Prasugrel or other alternative therapy</td>
<td>MODERATE</td>
</tr>
</tbody>
</table>
Another prodrug is the analgesic codeine. Codeine is converted to morphine by the Cytochrome 450 enzyme CYP2D6. The same principles apply as they did with clopidogrel in regard to PM and IM metabolizers. Poor Metabolizers will receive little therapeutic benefit from codeine; it cannot be converted to active form. Physicians not realizing the patient is a CYP2D6 PM may try to increase the dose and may find the patient still not getting pain relief.

| Poor (PM) | Significantly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse CV events. | Prasugrel or other alternative therapy | STRONG |

STOP AND REFLECT

JS is a 35-year-old woman who was given a prescription for APAP 300 mg/codeine after the recent birth of her child. Despite taking no more than the prescribed dose, JS experienced nausea and dizziness while she was taking the APAP/codeine. She also noticed that her breastfed infant was lethargic and feeding poorly. She mentions this to her physician and the physician suggests discontinuation of the drug. Within a few days, both JS and her infant are no longer experiencing adverse drug events. How would genetic testing help JS?

There are other genes known to affect drug response, which encode the receptors for regulatory molecules such as neurotransmitters, hormones, cytokines and growth factors, and cellular proteins such as enzymes, transporters, carriers, ion channels, structural proteins and transcription factors. These are referred to as either pharmacokinetic or pharmacodynamics biomarkers. Variations in these genes can lead to poor response or ADEs by disabling, inactivating, interfering with, or inaccurately inducing the signaling mechanisms or cellular machinery that must function for the body to respond properly to the drug; or by causing ADEs that prevent continued use of the drug.

Abacavir (Ziagen®) is a nucleoside reverse transcriptase inhibitor used in combination with other antiretrovirals to treat HIV infection. Abacavir can cause severe life-threatening reactions in patients with variations in genes that encode a specific pharmacodynamic biomarker. Human leukocyte antigen B (HLA-B) is responsible for presenting peptides to immune cells and plays a critical role in normal immune recognition and pathogens. Patients who carry the HLA-B*5701 allele have an increased risk for developing a hypersensitivity reaction. Symptoms include a combination of fever, rash, gastrointestinal tract symptoms and respiratory symptoms that can become more severe with continued use. HLA-B*5701 screening before abacavir treatment results in a significantly reduced number of hypersensitivity cases. Abacavir product labeling recommends genetic testing to detect the presence of HLA-B*5701.

Two important biomarkers involved in drug transport include the SLCO1B1 gene, which codes for the OAT1B1 transporter, and the ABCB1 gene, which codes for p-glycoprotein. OAT1B1 is an influx transporter, meaning it moves drugs into cells, and p-glycoprotein is an efflux transporter, meaning it moves drugs out of cells and into the intestinal tract, bile, blood and urine. This can result in altering how a drug will be absorbed, distributed, metabolized and excreted.
The Pharmacist’s Role

Personalized (“precision”) medicine information changes are constant. There are a number of resources for health care providers to locate evidence-based guidelines for drug therapy based on pharmacogenomic advances. The Clinical Pharmacogenetic Implementation Consortium (CPIC) is one resource.\textsuperscript{10} The CPIC provides guidelines to help clinicians understand how available genetic test results should be used to optimize drug therapy, rather than whether tests should be ordered. With the idea that genetic testing will be more widely performed and clinicians will have the patient’s genetic results and be asked to recommend therapy, CPIC provides guidelines that enable the translation of genetic lab test results into actionable prescribing decisions for specific drugs.

Pharmacists are already familiar with manufacturer package inserts to provide necessary information about the medication they are dispensing. Pharmacogenetic testing recommendations are also listed in the prescribing information for many drugs. Warfarin (Coumadin\textsuperscript{®}) is a widely prescribed anticoagulant used to treat and prevent thromboembolic diseases.\textsuperscript{4,11} It is metabolized by the CYP2C9 enzyme, and its anticoagulant effect is mediated by the enzyme vitamin K epoxide reductase subunit 1 (VKORC1). Patients carrying certain CYP2C9 and VKORC1 variations are likely to require altered doses and may require prolonged time to reach a stable maintenance dose. Warfarin product labeling states “The patient’s CYP2C9 and VKORC1 genotype information, when available, can assist in selection of the starting dose” and includes the following table (Table 5) of expected therapeutic doses in mg/day for patients with different combinations of CYP2C9 and VKORC1 allele variations. Using the personalized medicine approach can assist the clinician in getting the right medication to the right patient at the right dose.

### Table 5. Ranges of Expected Therapeutic Warfarin Doses (mg/day) for CYP2C9 and VKORC1 Genotypes\textsuperscript{11}

<table>
<thead>
<tr>
<th>VKORC1 Genotype</th>
<th>CYP2C9 Genotype</th>
<th>*1/*1</th>
<th>*1/*2</th>
<th>*1/*3</th>
<th>*2/*2</th>
<th>*2/*3</th>
<th>*3/*3</th>
</tr>
</thead>
<tbody>
<tr>
<td>GG</td>
<td></td>
<td>5-7</td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AG</td>
<td></td>
<td>5-7</td>
<td>3-4</td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td>3-4</td>
<td>3-4</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
<td>0.5-2</td>
</tr>
</tbody>
</table>

STOP AND REFLECT

JB is a 66-year-old woman who was recently diagnosed with atrial fibrillation. To reduce the risk of stroke, JB’s physician recommends warfarin therapy and refers her to your pharmacist-managed warfarin clinic. How would genetic testing help with JB’s initial warfarin dosing?

You recommend genetic testing to JB’s physician and the results reveal the following genotype: VKORC1 AA and CYP2C9 *1/*3. What would be the recommended starting dose of warfarin for JB?

Starting Pharmacogenetic (PGt) Testing

There are numerous PGt testing labs to choose from. When selecting a laboratory to use, consider the following services:

- Does the lab offer payment plans for patients?
- Are a variety of insurance providers accepted?
- Is there an ease of paperwork for both the patient and pharmacist?
- How much time does it take to get results?
• What is the ease of reading results?
• How secure and available are the results (physician and patient access)?
• Is there training for health care staff, including pharmacists?
• Can the results easily be interpreted?
• Is there hands-on assistance from the lab representative?

Most laboratories have similar insurance coverage, but costs and patient payment plans may differ. Patients will often want to know the cost before agreeing to perform the test especially if it is not covered by their insurance plan. Most laboratories will have a secure link or portal for you to get results and sometimes they can even e-mail results directly to the provider and patient utilizing encryption software. Most results can be obtained in a week or less. It is important that you search for a laboratory that meets the needs of your specific pharmacy site.

Selection of patients and type of genetic test should be considered. In your practice site, consider patients who are taking medications or have disease states that may require medications that have known tests available. The physician may want to start clopidogrel for a patient that received stents and you may want to test them for CYP2C19 activity. You could consider a patient who started clopidogrel, but it may be more helpful if the patient had their genetic information before they started medications to improve efficacy and prevent ADEs. The genetic test will only need to be done once in a lifetime. Pharmacogenetic laboratories may offer one test at a time (patient taking clopidogrel) or multiple “panels” of tests or a comprehensive test (all available genetic tests available). A comprehensive test would be beneficial for someone on a medication that may have several genes that can effect activity. For instance, numerous biomarkers can play a role in predicting the function of “statins” and a comprehensive test may be more appropriate for this patient. Most importantly, cost will need to be determined. The insurance company may not pay until the patient has an order for the drug or special documentation may be required to get payment for specific tests.

Many may be surprised how easy it is to obtain a PGt test. DNA collection can be completed by supplying saliva, urine or buccal swab. Typically, for ease for the patient and the clinician, the buccal swab test is the most convenient option; testing typically requires two cotton swabs for each cheek. The swab is rubbed against the cheek for 20-30 seconds, and then air dried and placed in provided envelopes to be mailed to the lab with appropriate paperwork. This is a test that can be done easily in all pharmacy settings. Often in the long-term care setting and in hospitals, the nursing staff works with pharmacists to help obtain the cheek swabs and paperwork. In the community setting, the pharmacist can help the patient perform the test in the pharmacy.

Pharmacists can have an important role in interpreting the PGt results. Each laboratory will display the results differently, but the interpretation of these results is similar. Typically they are color coded or symbol coded for ease of interpretation by the pharmacist or health care provider. For instance, a medication that should be avoided may have a stop sign or be coded in red. A medication that is recommended may be colored coded in green or have a symbol of a check mark. See the example below in “Stop and Reflect.”
STOP and REFLECT

TP is a patient in a local nursing facility. You have been asked for consultation on her behavior medications because she continues to experience depression symptoms. She has tried citalopram (Celexa®) and venlafaxine (Effexor®). She was also started on Risperidone (Risperdal®) to help stabilize her mood. You recommend a PGt test. Here is a sample of her test. What recommendations would you make?

PERSONALIZED PRESCRIBING REPORT

Patient: TP DOB: 5/16/43

SULT4A1-1 POSITIVE

Consider olanzapine. SULT4A-1 positive patients have been shown to demonstrate enhanced treatment efficacy and reduced hospitalization risk when treated with olanzapine compared to both SULT4A1-1 negative patients treated with olanzapine and SULT4A1-1 positive patients treated with risperidone.

CYP2D6 INTERMEDIATE METABOLIZER (IM)

Avoid: Alternative Considerations:
Risperidone Quetiapine, olanzapine, clozapine
Venlafaxine Citalopram, sertraline

A IM may require lower than average drug dosages for medications inactivated by CYP2D6 or higher than average dosages for medications that are converted to active metabolites by CYP2D6.

SLC6A4 POOR RESPONDER

Decreased serotonin transporter expression expected. Risk of decreased response to SSRI-based therapies and increased risk of adverse events. Consider non-SSRI antidepressant therapies such as SNRIs or TCAs.

Limitations and Concerns

Even with all the advances in PGt, there are several constraints that a pharmacist must be aware of and use their skills to overcome. Education is key to success. A pharmacist may see the benefit for a patient, and consult with the primary provider for authorization for the PGt; however, if the provider doesn’t have knowledge of the benefit, he or she may and decline your recommendation. A survey in 2012 showed that primary care providers do not feel well informed about PGt testing. The lack of knowledge about PGt that a provider has can limit the use of the genetic tests for patients who could benefit. It is vital that pharmacists educate themselves about the value of PGx and PGt and lead the effort to educate providers of the benefits of using this information in their prescribing decisions.

In addition, there can be patient concerns with this developing, personalized (“precision”) medicine technology. Patients worry about the cost of the tests, the security of their genetic information and what the results will mean for them. Most private insurance plans do cover some form of testing, especially if there is pharmacogenetic evidence to suggest increasing ADEs or lack of efficacy in specific patient populations (e.g., clopidogrel and CYP2C19 testing in ACS patients with stent placement). The pharmacist has a role in determining the best test for the patient, and also in explaining how the results will affect the patient’s medication choices in the future. The
The pharmacist will assure the patient of the security of their genetic information. The pharmacist plays an important role in the success and continued growth of personalized medicine through pharmacogenetic testing in the health care industry.

Lastly, patients may feel nervous about the results, not understand how genetic testing works or what it means for them. The pharmacist will need to educate the patient on the value of pharmacogenetic testing, what the testing entails and how the results might help determine better medication decisions in the future by their prescriber. There may be times the pharmacist will receive pharmacogenetic results from a patient that help identify that a medication will not work with in their body, but it may also be a biomarker that shows they have an increased risk for another disease state. These situations need to be handled with care and sometimes may require the pharmacist to refer the patient to a genetic counselor. For example, methylenetetrahydrofolate reductase gene (MTHFR) is an enzyme involved in folate metabolism that can be a marker for several diseases. MTHFR variants can demonstrate a possibility of increased risk of hyperhomocysteinemia, coronary artery disease or thrombosis. These results can be devastating for some patients, like a gene linked to Alzheimer’s Disease, yet other results may motivate the patient to make lifestyle changes to prevent their genetic disposition to something like coronary artery disease. It is important for the pharmacist to be knowledgeable of these markers, and be able to discuss the implications with their patients.

Summary

Personalized (precision) medicine seeks to reveal an individual’s genetic information to direct the clinical decision-making process. Personalized medication can reduce ADEs and treatment failures. Increased knowledge in pharmacogenetics and pharmacogenomics will continue to have an expanding impact on pharmacists and other health care professionals. PGt is already influencing medication management and it is important that pharmacists continue to be informed and prepare for how their specialty can embrace this personalized medicine movement.

References:
Continuing Education Self-assessment Questions

1. Which of the following best describes a poor metabolizer?
   a. An individual with two normal functioning alleles
   b. An individual with duplicate copies of an allele
   c. An individual with two loss-of-function alleles
   d. An individual with one loss-of-function allele

2. Which of the following best describes the effect on serum drug levels in a poor metabolizer versus a rapid metabolizer?
   a. Drug levels will be significantly increased
   b. Drug levels will be significantly decreased
   c. Drug sensitivity will be significantly decreased
   d. Drug sensitivity will be significantly increased

3. Which of the following is not affected by inherited genetic variations to CYP2D6?
   a. Atomoxetine
   b. Codeine
   c. Tamoxifen
   d. Abacavir

4. The initial dosing of Warfarin can be assisted with the use of VKORC1 and CYP2D9 genotypes by using the warfarin product labeling dosing chart.
   a. True
   b. False
5. A Ultrarapid Metabolizer (UM) of CYP2D6:
   a. may experience subtherapeutic doses with the use of codeine.
   b. may experience overdose symptoms with the use of codeine.
   c. may experience subtherapeutic doses with the use of clopidogrel.
   d. may experience overdose symptoms with the use of clopidogrel.

6. Patients who carry two non-functional alleles for CYP2C19 would be considered poor metabolizers (PM) and show reduced ability to convert clopidogrel into its active metabolite and, therefore:
   a. require the clopidogrel dose to be reduced
   b. require the clopidogrel dose to be increased
   c. choose a different drug because clopidogrel would be inactive
   d. do not need to adjust the dose. This allows for the drug to work as designed.

7. When referring to the nomenclature of the CYP450 enzyme system, which character in the enzyme system CYP2D6*4 denotes the “allele?”
   a. 6
   b. 2
   c. 2D
   d. 4

8. The most commonly identified mutations are single nucleotide polymorphisms, also called SNPs.
   a. True
   b. False

9. The abacavir product labeling recommends genetic testing to detect the presence of the TPMT allele to prevent serious hypersensitivity reactions.
   a. True
   b. False

10. Pharmacists can have an important role in PGx, allowing for a reduction in ADEs and possible drug therapy failures for our patients.
    a. True
    b. False