Precision medicine and pharmacogenomics in community and primary care settings

Over the last 50 years, the scientific and medical community has seen the field of pharmacogenomics and precision medicine grow from concept to developing research discipline to an integral part of medical practice and application. Pharmacogenomics is the facet of clinical genomics that will eventually touch every patient in clinical practice.

Since ancestral genetic testing became widely available in large chain retail stores, individuals have had access to their unique genetic makeup, with information that reveals more about themselves than they have ever had before. As fascinating as a personalized ancestral history may be, however, there is little use for this information from a clinical standpoint in precision medicine. For example, there is more than a 20% difference in prevalence rates between African Americans and African/Ethiopians for being a CYP2D6 ultrarapid metabolizer, which could potentially mean the difference between a normal response to codeine or a fatal one. However, there is no way to guarantee an individual’s genotype without testing for it.

Today, we now know that variability within populations of the same ancestral history can occur because of a number of factors, including drug–drug interactions, age, organ dysfunction, and pharmacogenomics. The Precision Medicine Initiative describes precision medicine as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.” Pharmacogenomics—often also referred to as pharmacogenetics—is a major part of precision medicine because it is the study of how a person’s genetic makeup affects their response to medications. Using the concepts of precision medicine and pharmacogenomics, we can predict treatment and prevention strategies more accurately to ensure that medications are safe and effective.

Although many of the concepts and genetic variations were discovered more than 30 years ago, it has only been with the convergence of genomic technology and the electronic health record (EHR) that we now have the tools to utilize this science in clinical application. The EHR plays a critical role in the clinical use of pharmacogenetic testing because it is needed as the receptacle of the genetic information. It also provides the information to the medical provider at the correct time during point-of-care treatment.

Learning objectives

- Identify the three approaches to implementing pharmacogenetic testing for patients.
- Describe the workflow within each model of approach to implementing pharmacogenetic testing.
- List important questions to ask a pharmacogenetic laboratory to determine if they have the training, programs, and infrastructure to be a “good fit” to meet the goals of your pharmacogenetic program.
- Name at least five drug–gene implications that are mostly applicable to the community and primary care settings today.
- Use resources with evidence-based guidelines to support your recommendations to patients and other health professionals.
- Identify at least three challenges for developing a sustainable model for the practice of pharmacogenetics to support the pharmacist’s role in this innovative field.

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Accreditation information

Learning level: 1
Provider: APhA
Target audience: Pharmacists, pharmacy technicians
Release date: February 1, 2018
Expiration date: February 1, 2021
ACPE Universal Activity Number: 0202-0000-18-128-H04-P
CPE credit: 2 hours (0.2 CEUs)
Fee: There is no fee associated with this activity for members of the American Pharmacists Association (APhA). There is a $25 fee for nonmembers.

APhA is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education (CPE).

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Disclosures: Amina Abubakar, PharmD, AAHIVP; Olivia Bentley, PharmD, CFts, AAHIVP; Susan Kokura, PharmD; and APhA’s editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see www.pharmacist.com/apha-disclosures.

Development: This home-study CPE activity was developed by APhA.
Preassessment questions
Before participating in this activity, test your knowledge by answering the following questions. These questions will also be part of the CPE assessment.

1. Which guideline is considered to be the “gold standard” of pharmacogenetic guidelines?
   a. Pharmacogenomics Knowledge Base (PharmGKB)
   b. Dutch Pharmacogenetics Working Group (DPWG)
   c. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   d. Pharmacogenomics Research Network (PGRN)

2. CYP enzymes are primarily found in which of the following organs:
   a. Liver
   b. Small intestine
   c. Lungs
   d. Kidneys

3. CPIC guidelines recommend that ultrarapid metabolizers avoid use of codeine for the following reasons:
   e. Patients are unable to get the analgesic effect.
   f. Patients may require higher doses.
   g. Patients may have an increased risk for adverse effects.
   h. Patients may experience a higher risk for toxicity.

At present, we have evidence-based clinical guidelines for drug–gene cases with clinical utility. A challenge with implementation is the capabilities of the EHR. Medical centers today are using the EHR to notify physicians with clinical decision support (CDS) alerts at the point-of-care. If a genetic test is not on file, the CDS alert asks the provider, “Would you like to order a genetic test?”

However, is this really the best model for the most use of the science? Ideally, the patient has already received a genetic test preemptively, and their results are embedded in the EHR as part of their medical profile. Once the medical provider prescribes a medication with demonstrated pharmacogenetic clinical utility, the CDS alert informs the provider that the medication prescribed at the standard dose has an increased risk of severe adverse effects, or perhaps that it would be ineffective because of the genetic variations affecting patient response. Some medical centers have already adopted this new model of clinical decision support alerts, including both the Mayo Clinic and Mount Sinai in New York, and the journey has just begun. By increasing both access to and feasibility of pharmacogenetically based clinical guidance, prescribers can make immediate clinical decisions and provide the best treatments for their patients right from the start.

We developed this document as community pharmacists with extensive experience providing pharmacogenetic testing in the community and primary care setting and personalized education and training of other community pharmacists. The journey of pharmacogenetics in community pharmacy includes early adoption of genetic testing for a single gene or single drug and has expanded to the broad gene panel tests of today, which may cover more than 200 medications.

As logical as it may seem to pharmacists that we have the knowledge, skills, and expertise to be leaders in the field of pharmacogenetics, there has been ongoing research on and development of the best model for the safe and ethical delivery of pharmacogenetic information to the public. On March 2, 2016, FDA held a public workshop, “Patient and Medical Professional Perspectives on the Return of Genetic Test Results.” The purpose of this workshop was to understand and better define the specific information patients and providers prefer to receive, how those results should be returned, and what information is needed to understand the results so that they may be used effectively in medical decision making. The panel and participants consisted of FDA representatives, physicians, geneticists, and faculty members from prestigious schools of medicine. Only one pharmacist was present to share the value that pharmacists could bring to the medical team in the delivery and effective use of pharmacogenetic test results.

The presentation was well received such that it led to multiple meetings with different groups within FDA and finally with the White House Office of Science and Technology. As a result of recent changes in the Administration, there has been a change in priority and focus in the White House; however, efforts continue to ensure that pharmacists have a seat at the table in the precision medicine and pharmacogenomics initiative.

Developing and implementing a pharmacogenomics program
Regardless of the current landscape in which pharmacists may be recognized as leaders in this field, there is an urgent need for all pharmacists to be knowledgeable about the basics of pharmacogenetic testing and application of the test results. Growth in any technological science occurs rapidly, and pharmacists cannot afford to be caught off-guard when pharmacogenetic testing becomes mainstream in the community. Whether the setting is community pharmacy, primary care clinic, or institutional, many decisions need to be made when developing and initiating a pharmacogenomics program. Following are three important considerations when initiating a pharmacogenetics program at your site.

Selecting the right approach
Determining which patients should be the target population for your program is an important initial step because it sets the foundation for the policies, procedures, workflow, and complete coordination of care. Three main approaches are commonly used in a model pharmacogenetic program: preemptive, semi-preemptive, and reactive. Preemptive pharmacogenetic testing aims to optimize medication use by having genetic information at the point of prescribing for all patients regardless of demographic or risk parameters. Semi-preemptive pharmacogenetic testing uses the same principle except for a specifically defined “at-risk” population.

In both approaches, prescribers have the patient’s genetic results before a medication is needed. Reactive pharmacogenetic testing occurs after the patient has already been
diagnosed or an event has occurred and the patient requires a treatment that may have a pharmacogenetic implication. The major influencer in choosing between these approaches is cost. Most clinicians would agree that if the “blueprint” of our genetic information, complete with drug–gene implications, were readily available, it would be very valuable in both daily practice and in crisis situations where emergent treatment is needed.

The challenge becomes, who will pay for it? A few years ago, many insurance plans paid for this service—with astonishing reimbursements of around $10,000—but the clinical utility was minimal, and coverage soon ceased when payers saw no benefits. In working with primary care providers in our community, we came across stacks of pharmacogenetic test results that were not reviewed or utilized. When surveying these physicians, we learned that barriers to use included a lack of time to review lengthy test results and the lack of another high-level clinician in their office with the time to review these data on their behalf. By using a pharmacist trained in pharmacogenetics, our pharmacy was able to assist these providers in reviewing the results and identifying significant pharmacogenomic markers that may affect patient outcomes.

Currently, there is very limited insurance coverage for pharmacogenetic testing. However, because the cost has decreased significantly in recent years, now ranging from $200 to $500 depending on the size of the gene panel, individuals have been paying for the test themselves.

Following are recommendations for selecting the testing approach with the best fit for your organization.

- Compare the drugs on the FDA list with a high level of evidence and strong recommendations with the medications currently prescribed in your clinic or pharmacy’s database. For example, if you know you’ve prescribed X number of clopidogrel, then use prevalence factors to determine the potential impact you would have on patients taking this medication. If approximately 40% of CYP2C19 carriers are intermediate metabolizers and poor metabolizers and you have 200 patients on clopidogrel, then you potentially have 80 patients who could be affected by testing to avoid readmission or recurrent thromboembolic event. On the basis of cost of readmission or other surrounding events, this information can be used to build a business case for a pharmacogenetic program.

- Outside of the most common drug–gene implications, it may be relevant to your patient population to include genetic testing on rare yet significant genes with a high impact on morbidity and mortality. For example, HLA-B 15:02 and carbamazepine is a rare drug–gene implication most commonly found in Asian patients. The implication is fatal. For clinics or pharmacies that serve a majority of Asian patients, this may be an important gene to include on the genetic panel for testing.

Selecting the right lab partner or testing provider

Because a number of different tests are currently available on the market, you will need a process to determine which lab company or testing panel is the right fit for your program’s needs. The most important consideration when selecting a lab partner is to ensure the lab has the right infrastructure to support the needs of your organization. After performing an internal needs assessment, you may determine the need for education and training, clinical support, flexible spending accounts/health savings accounts eligibility, or drug information reference support.

When interviewing candidates, it is important to make sure the lab offers a testing panel that covers the class of drugs that fits the needs of your patient population. To ensure the quality of test results and answer any questions you might have about your patient’s test results, choose a lab partner that is certified by the appropriate governing bodies so you can rely on the data as well as the lab’s support team that interprets the data.

Obtaining training and education

There seems to be a general consensus that although pharmacists are highly trained and educated in pharmacokinetics, pharmacodynamics, and pharmacogenetics, the full application of these principles as part of daily practice may be lacking, and additional training and education may be required for best practices. Using the appropriate evidence-based resources is important for all pharmacists practicing in this field. A pharmacogenetic pharmacist does not have to know everything, but he or she must know where to find resources and information. Because pharmacists perform pharmacogenetic medication reviews with patients and their medical providers, they need to be able to translate complex information into an understandable and usable form. Drug prescribing and dosing suggestions using an evidence- and rule-based approach are essential when communicating recommendations to providers.

Resources are available to support all clinicians working in this field in the translation of pharmacogenetic concepts. Two commonly used resources include the Pharmacogenomics Knowledge Base (PharmGKB) and the Clinical Pharmacogenetics Implementation Consortium (CPIC). Together, these resources provide excellent tools for clinicians in pharmacogenetic translation and implementation in patient care. PharmGKB is a database of pharmacogenetic information that encompasses numerous resources, including genotype-based drug dosing/prescribing guidelines, drug labels with biomarker information, pharmacokinetics and pharmacodynamics drug-centric pathways, and summaries of important pharmacogenetics associations. The database is able to compile available primary and secondary data for genes as well as medications.

CPIC, a shared project of PharmGKB and the Pharmacogenomics Research Network (PGRN), is known among experts in the field as the “gold standard” of pharmacogenetic guidelines. These guidelines address the need for practice guidance that enables the translation of genetic results into actionable prescribing decisions for specific medications. CPIC guidelines were written with the intent that patient genotypes are already avail-
able and do not provide recommendations as to whether to perform a pharmacogenetic test. CPIC guidelines are cited by the National Institute of Health’s Genetic Test Registry and are endorsed by the American Society of Health System Pharmacists and the American Society for Clinical Pharmacology and Therapeutics.7

Clinical application for the top disease states pharmacists may encounter

The following clinical section is not meant to address decisions about whether or not to test a patient, but rather to provide the recommended actions from evidence-based guidelines if the patient’s genetic information is known. The clinical application for pharmacogenetics is a broad topic that touches on many disease states and specialties. We have narrowed the drug–gene implications to those that have been shown to have clinical utility and those we have commonly encountered through our work in providing pharmacogenetic reviews to more than 400 patients in the community and primary care settings.5

When most clinicians think of genetic testing, use in the field of oncology has been most promising; however, despite such advances, there is still not much integration between genomics and clinical practice.9 In addition, some patients often confuse genetic testing for risk of cancer with pharmacogenetic testing for medication utilization. As we discuss a patient’s pharmacogenetic results for a panel of medications, it’s important to take the time to educate patients and distinguish between a pharmacogenetic test and other genetic testing, which can assess the patient’s risk for disease. Another important disclaimer to share with patients is that a pharmacogenetic test is only one piece of the puzzle. Many other factors affect drug metabolism and drug transport from one organ system of the body to another. An individual’s liver function, kidney function, eating habits, smoking status, gender, age, and current medication list can all affect a person’s drug response.

Most genes reported in a pharmacogenetic test are pharmacokinetic genes that provide insight on how an individual metabolizes a drug. However, some genes code for transporters or enzymes that affect a drug’s pharmacodynamics. As a pharmacist works with patients to provide pharmacogenetic reviews, it is important for pharmacists to understand the difference and to be able to explain that difference clearly and concisely to patients.

CYP450 has more than 50 enzymes that are essential for the metabolism of many medications. However, these six—CYP 1A2, 2C9, 2C19, 2D6, 3A4, and 3A5—metabolize 90% of drugs.8,11 Although these enzymes are found primarily in the liver, they also occur in the small intestine (reducing bioavailability), lungs, placenta, and kidney.11 Genetic polymorphisms in these enzymes may influence a patient’s response to commonly prescribed medications, including beta blockers, antidepressants, warfarin, clopidogrel, opioids, NSAIDs, and proton pump inhibitors (PPIs). Non-CYP–related genetic implications include catechol-O-methyltransferase (COMT) for ADHD medications and the transporter protein SLCO1B1 for statins. Knowledge of the most important drugs metabolized by CYP450 enzymes and potent CYP inducers and inhibitors can help minimize the possibility of adverse drug events or poor efficacy.

Psych: Antidepressants and antipsychotics

In psychiatry, there has been considerable interest centered on pharmacogenetics to predict drug response, especially since the major CYP450 classes account for 60% of the psychiatric drug metabolism.12 Despite the potential of psychiatric pharmacogenomics to reduce adverse events, optimize drug dosing, and guide treatment decisions, pharmacists have been slow to accept it. As pharmacists emerge as leaders in this field, it will be crucial to know the evidence-based guidelines for the most widely used psychiatric medication, such as SSRIs and tricyclic antidepressants (TCAs), for the utility of pharmacogenetic testing to potentially reduce suffering from depression, decrease the delay in effective treatment, and avoid adverse reactions.

Treatment of depression and psychiatric disorders can be very complex, so as a clinician working with these patients, a pharmacogenetic report may provide insight for a good starting point. Continuing to treat the patient on the basis of patient response and clinical judgment will also play a role in the proper course of individualized treatment.

For the purposes of this discussion, we have narrowed the drug classes to focus on two main groups, TCAs and SSRIs. However, many other classes of antidepressants and antipsychotics also have clinical utility in pharmacogenetics.

Amitriptyline, classified as a TCA, is used in the treatment of several psychiatric disorders, including major depression, obsessive–compulsive disorder (OCD), panic attacks, generalized anxiety disorder, posttraumatic stress disorder, and bulimia. Amitriptyline has many off-label uses as well, including treatment for migraine and fibromyalgia and as a sleep aid. The primary metabolic pathway for amitriptyline is through CYP2C19 and CYP2D6; however, clinicians focus mainly on CYP2C19 because this pathway leads to another active TCA metabolite, nortriptyline. Although metabolism through CYP2D6 results in a less active metabolite, it is important to consider this pathway because it may cause a disequilibrium with CYP2C19, depending on the overall phenotypic status of the patient. This has led to the FDA-approved amitriptyline drug labeling stating that CYP2D6 poor metabolizers may have higher-than-expected plasma concentrations of TCA at usual doses. FDA further recommends monitoring plasma concentrations whenever a TCA is coadministered with a CYP2D6 inhibitor.12

Interestingly, CYP2C19 is not mentioned on the FDA-approved drug label, but CPIC guidelines include dosing recommendations for TCAs based on both CYP2C19 and CYP2D6 genotypes.13 The CPIC guidelines for both pathways include specific dosing guidance information for reducing or increasing the starting dose, based on the patient’s phenotype. Use of a TCA is avoided in CYP2D6 ultrarapid metabolizers for lack of efficacy and in poor metabolizers because of the potential for adverse effects. The CPIC guidelines recommend avoiding tertiary amines like amitriptyline in ultrarapid and poor metabolizers of CYP2C19 as well;
however, the reasons are reversed. In summary, for patients who may be candidates for initiation on a TCA, it is recommended to consider their metabolic status for both CYP2D6 and 2C19. On the PharmGKB website for amitriptyline under the PGx prescribing info section, a useful table provides recommendations on a combined CYP2D6 and 2C19.

**Patient case #1**

A.O. is a 34-year-old female patient receiving her pharmacogenetic review with her community pharmacy. After confirming her current medication list, the pharmacist finds no pharmacogenetic implications for these medications. As part of preventive care counseling, the pharmacist informs the patient of medications that could have major genetic implications if she were prescribed them in the future. The pharmacist shows the patient the section on antidepressants in her profile, which indicates strong drug–gene implications with amitriptyline and other TCAs. The patient tells the pharmacist that she had taken amitriptyline in the past for neuropathy after a knee injury. After one dose, she experienced hallucinations. Her physician said that she must have taken too much or the pharmacy gave her the wrong dose. The pharmacist explains that the patient is a CYP2C19 ultrarapid metabolizer. How would the pharmacist best explain what likely happened to the patient after one dose of amitriptyline?

A potential pharmacist response is “amitriptyline gets changed into strong active drug when it is broken down by CYP2C19. Since you are an ultrarapid metabolizer of CYP2C19, you are ‘activating’ or ‘turning on’ this medication faster than normal, which leads to higher response to this medication in your body and explains why you experienced severe adverse effects. Now that you have this information, going forward it is very important that you share your pharmacogenetic report with all of your medical providers so they can be aware of your metabolic status before they prescribe medications that may pass through similar pathways in your body.”

SSRIs are the primary treatment options for major depressive and anxiety disorders. Approximately 50% of patients initiated on SSRI therapy will experience treatment failure. In the United States, an estimated 25,000 patients per year are hospitalized as a result of adverse events associated with antidepressants. Clinical evidence shows that genetic variants of CYP2D6 and CYP2C19 influence the metabolism and dosing recommendations of SSRIs such as citalopram, escitalopram, fluvoxamine, paroxetine, and sertraline. There is a high potential for clinical utility within this class of medications to improve treatment response and decrease the occurrence of adverse events. The most common adverse effects are on the central nervous system and include insomnia, headache, gastrointestinal (GI) dysfunction, and sexual dysfunction. However, the serious adverse effect of major concern is QT prolongation, which potentially could be fatal.

Patients who experience poor therapeutic response and outcomes on SSRIs are good candidates for genetic testing because the likely causes are CYP2D6 and CYP2C19 polymorphisms. SSRIs like paroxetine and fluvoxamine may result in changes in exposure to the drugs as a result of variations in CYP2D6. Both of the R- and S-enantiomers of citalopram are extensively metabolized by CYP2C19 to less-active metabolites, which results in less serotonin reuptake inhibition. Sertraline and fluoxetine have complex pharmacogenetic implications because both CYP2D6 and CYP2C19 pathways affect the conversion to active metabolites.

**Patient case #2**

A case report of a 9-year-old boy with ADHD, OCD, and Tourette disorder revealed the patient taking methylphenidate, clonidine, and fluoxetine. His initial symptoms consisted of nausea, vomiting, and headache, which developed slowly over the first few weeks of his starting this regimen. The patient’s parents tell you they purchased an OTC genetic test for the patient and ask you to review the results. The patient turns out to be a CYP2D6 poor metabolizer. Which medication do you suspect is causing the patient’s symptoms, based on a drug–gene implication?

The above case report was real except the patient did not have a pharmacogenetic report. Unfortunately, over the previous 10 months, the patient experienced signs and symptoms suggestive of metabolic toxicity, marked by GI distress, low-grade fever, incoordination, and disorientation. Generalized seizures were observed, and eventually the patient lapsed into status epilepticus followed by cardiac arrest and subsequently died. The autopsy report revealed that the patient experienced fluoxetine and norfluoxetine concentrations that were several-fold higher than expected for overdose situations. The child’s adoptive parents were under investigation by social services to determine their level of control for medication access. Further genetic testing of tissue revealed the child was a CYP2D6 poor metabolizer, and these results ended the investigation of the adoptive parents. This was the first confirmed report of a fluoxetine CYP2D6 polymorphism–related death of a child from impaired drug metabolism.

**ADHD**

In children, ADHD, a common neurodevelopmental and behavioral disorder, is typically treated with stimulants such as methylphenidate. Common adverse effects and risks from these medications include restlessness, headache, stomach pain, and decreased appetite, which are usually reduced by controlling the dose. Other medications that may be part of a child’s regimen include antidepressants and antipsychotics. Approximately, 20% to 50% of these medications are metabolized by CYP2D6 and CYP2C19. According to a study conducted by Mayo Clinic physicians, children who are treated without the benefit of individualized molecular genotyping have only a 60% chance of successful long-term treatment.

In our experience, we have seen much success with pharmacogenetic testing in the community setting with parents who have been searching for answers on providing the best care for their children with autism and/or ADHD. One of our customers who purchased the pharmacogenetic test was a physician and the mother of a nonverbal child with autism who was struggling with his ADHD medication. The genetic test revealed polymorphisms that in supporting literature have been linked to poor responses to methylphenidate, dexamethasone, Adderall, and other medications for which the patient had previously experienced treatment failure. She stated that she wished she had known about this test earlier because it could have helped her family avoid initiating unnecessary therapy.

Pharmacogenetic testing has the potential to identify a more comprehensive, individualized risk profile, allowing
for precision therapeutics with medications and doses adjusted appropriately based on an individual’s personal genetic results.

**Patient case #3**
A case report of a 6-year-old boy with ADHD revealed the patient being started on methylphenidate 5 mg twice daily for symptom control. The parents reported compliance with medication administration, and after the first full day of treatment the child began portraying extremely aggressive behaviors. These behaviors included agitation, insomnia, and poor appetite. The patient was then given additional medications, including antipsychotics, with the hope of reducing these behaviors. However, the behaviors worsened, which resulted in genetic testing that reported the patient as an intermediate metabolizer of CYP2D6. The medical provider withdrew the additional medications and decreased the dose of the methylphenidate to 2.5 mg once daily, and the aforementioned behaviors ceased. The child was then able to respond appropriately, and his appetite returned.23

**Opioids**
Opioids are the most potent and commonly prescribed analgesics for pain management. As a result of multiple disease and pharmacological factors, a patient’s drug response to opioids may be complex to decipher. Adding pharmacogenetic factors further complicates the task of providing patients with personalized patient care. Using the pharmacogenetic test results as a tool to provide evidence-based recommendations and assess a patient’s risk of genetic implications on their current drug regimen, pharmacists can provide enhanced, personalized, and precise MTM services.

Many pharmacists are aware of the CYP2D6 and codeine genetic implication risk. Of all the genes of interest relative to opioid therapy, CYP2D6 is the one gene with the highest CPIC level of evidence. CPIC has a C/D level of evidence for OPRM1, the gene that codes for the opioid receptor mu 1, which may affect efficacy of fentanyl, hydrocodone, and other opioids. Limited studies have been conducted on efflux transporters like ABCB1 and pain sensitivity genes like COMT and MC1R; however, clinical evidence for them is lacking at this time.

In early 2013, FDA added a black box warning to the codeine drug label cautioning against prescribing codeine to children of any age for treatment of pain after surgery to remove tonsils or adenoids. In the following years, FDA warned of the risk of serious breathing problems in some children who are CYP2D6 ultrarapid metabolizers. Potentially fatal levels of codeine may occur because their bodies metabolize the drug too quickly. After a review of adverse event reports that identified 64 cases of respiratory depression, including 24 deaths, with codeine-containing medicines in children younger than 18 years of age in April 2017, FDA restricted the use of prescription codeine pain and cough medicine and tramadol pain medicines in children, and recommended against use in breastfeeding women.

CYP2D6 metabolizes approximately 25% of the most commonly prescribed medications, including codeine, tramadol, tamoxifen, fluoxetine, metoprolol, and risperidone. There is a high level of interindividual variation with CYP2D6.

**Figure 1.** Metabolic pathways of commonly prescribed opioid medications. Drugs and metabolites in white have little to no analgesic effects, green indicates those having analgesic effects, yellow enzymes are major metabolic pathways, and blue enzymes indicate a minor metabolic pathway.

Source: Adapted from Reference 25.
More than 105 different alleles or variations of CYP2D6 have been reported, and each encodes for a functionally different enzyme. Whole gene duplications and multiplications are common in CYP2D6, which may be referred to as copy number variation. On a genetic report, these may be shown in the patient’s genotype as “x2,” meaning two copies of the allele are present; “xN,” meaning a duplication exists but does not indicate the number of alleles present; or “DUP,” meaning a duplication exists but does not indicate which allele is duplicated or the number of alleles. Up to 13 copies of a CYP2D6 allele have been reported.24

Codeine produces antitussive properties, but all of its analgesic properties stem from its metabolites via CYP2D6. The CYP2D6 pathway leads to morphine and morphine-6-glucuronide, which are the first and second active metabolites, respectively. If this conversion occurs too rapidly, the patient is at higher risk of serious adverse drug reactions such as respiratory depression, circulatory depression, respiratory arrest, shock, and cardiac arrest.24

Figure 1 shows the other opioid substrates that are metabolized by CYP2D6. In all cases, the metabolite conversion through this pathway leads to a more potent metabolite that has a high affinity for the opioid receptor (codeine < morphine, tramadol < M1, dihydrocodeine < dihydromorphone, and oxycodone < oxymorphone).24

On the basis of the evidence, the CPIC guidelines recommend that ultrarapid metabolizers should avoid codeine use because of potential toxicity and, to a lesser extent, avoid tramadol, hydrocodone, and oxycodone (Table 1).

What are appropriate alternative medications for CYP2D6 ultrarapid metabolizers for pain management? Depending on the patient’s diagnosis and the appropriateness of administration, pharmacists may recommend NSAIDs, steroids, analgesics, and other opioids that do not pass through CYP2D6 metabolism, topical pain relief, and nonpharmacological suggestions.

On the opposite end of the spectrum, poor metabolizers are unable to get the analgesic response expected from codeine, tramadol, hydrocodone, and oxycodone. This means these patients may not be getting the full benefit from these medications, requiring higher doses that put them at risk of adverse effects.

The alleles of CYP2D6 have been very well studied. Each allele has been assigned an activity score that leads to either increased function, normal function, decreased function, or no function. Using a patient’s genotype, a clinician can use the CYP2D6 activity score tables (Tables 2 and 3) to determine whether a patient is a poor, intermediate, normal, or ultrarapid metabolizer. Fortunately, most pharmacogenetic reports translate this information into the phenotype for ease of review. However, Tables 2 and 3 show how phenotypes are determined from a patient’s genotype. If a patient’s report shows that he or she is a CYP2D6 *1/*17 genotype, to determine which one of the four categories of metabolizer types the patient possesses, a pharmacist has to find the activity value for each allele, add them, and find the resulting value in the corresponding table.

Without having a tool like a pharmacogenetic test, clinicians may consider a patient’s race and ethnicity to guide drug selection. The prevalence of phenotypes in CYP2D6 based on race and ethnicity is a prime example of when this method may not yield the desired results. For example, ultrarapid metabolizers of East African descent such as Ethiopians have a prevalence rate of approximately 29%, whereas ultrarapid metabolizers for African Americans have a prevalence rate of 3.4% to 6.5%.5,46 There is an approximately 24% difference in prevalence, supporting that race and ethnicity are not the most reliable guides for determining a patient’s phenotypic status.

Pharmacists use many skills when performing pharmacogenetic medication reviews with patients that sets the experience apart from the skills other health professionals can provide. As medication experts, pharmacists can showcase their value when discussing a patient’s pharmacogenetic re-

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Table 1. CPIC guidelines dosing recommendations for CYP2D6 and codeine

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Genetic implications</th>
<th>Recommendations</th>
<th>Class</th>
<th>Considerations for alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid metabolizer</td>
<td>Increased formation of morphine leading to higher risk of toxicity</td>
<td>Avoid codeine use due to potential toxicity.</td>
<td>Strong</td>
<td>Morphine and nonopioid analgesics that are not affected by CYP2D6. Tramadol, hydrocodone, and oxycodone are not good alternatives.</td>
</tr>
<tr>
<td>Normal–extensive metabolizer</td>
<td>Normal morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing.</td>
<td>Strong</td>
<td></td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Reduced morphine formation</td>
<td>Use label-recommended age- or weight-specific dosing. If no response, consider alternative.</td>
<td>Moderate</td>
<td>Consider morphine or nonopioid. Monitor tramadol use for response.</td>
</tr>
<tr>
<td>Poor metabolizer</td>
<td>Greatly reduced morphine formation leading to insufficient analgesia</td>
<td>Avoid codeine use due to lack of efficacy.</td>
<td>Strong</td>
<td>Morphine and nonopioid analgesics that are not affected by CYP2D6.</td>
</tr>
</tbody>
</table>

Source: Adapted from Reference 44.
Table 2. CYP2D6 functional status of alleles chart using activity scores

<table>
<thead>
<tr>
<th>Functional status</th>
<th>Activity value</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased function</td>
<td>&gt;1</td>
<td>*1 x N, *2 x N, *35 x N, *45 x N</td>
</tr>
<tr>
<td>Normal or increased function</td>
<td>1 or &gt;1</td>
<td>*9 x N, *10 x N, *17 x N, *29 x N, *41 x N</td>
</tr>
</tbody>
</table>

Source: Adapted from Reference 5.

Table 3. CYP2D6 phenotype status based on activity score from an individual genotype

<table>
<thead>
<tr>
<th>Activity score</th>
<th>Phenotype</th>
<th>Prevalence</th>
<th>Genotype</th>
<th>Examples of diplotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.0</td>
<td>Ultrarapid metabolizer</td>
<td>1%–2%</td>
<td>Carrying more than two copies of functional alleles</td>
<td>*1/*1 x N, *1/*2 x N.</td>
</tr>
<tr>
<td>1.0–2.0</td>
<td>Normal (extensive) metabolizer</td>
<td>77%–92%</td>
<td>Carrying two alleles encoding full or reduced function or one full function allele together with either one nonfunctional or one reduced function allele</td>
<td>*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *10/*10</td>
</tr>
<tr>
<td>0.5</td>
<td>Intermediate metabolizer</td>
<td>2%–11%</td>
<td>Carrying one reduced and one nonfunctional allele</td>
<td>*4/10, *5/*41.</td>
</tr>
<tr>
<td>0</td>
<td>Poor metabolizer</td>
<td>5%–10%</td>
<td>Carrying no functional alleles</td>
<td></td>
</tr>
</tbody>
</table>

Source: Adapted from Reference 5.

Table 4. Common medications that are inhibitors of CYP2D6

<table>
<thead>
<tr>
<th>Strong inhibitors (&gt;5-fold increase in AUC or &gt;80% decrease CL)</th>
<th>Moderate inhibitors (2–5-fold increase in AUC or 50%–80% decrease in CL)</th>
<th>Weak inhibitors (1.25–2-fold increase in AUC or 20%–50% decrease in CL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Cincalcet</td>
<td>Amiodarone, celecoxib, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, <em>Echinacea</em>, escitalopram, febuxostat, gefitinib, hydralazine, hydrochloroquine, imatinib, methadone, oral contraceptives, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Duloxetine</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Terbinafine</td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: AUC, area under the curve; CL, clearance.  
Source: Adapted from Reference 46.
Cardiology: Beta-blockers, warfarin, clopidogrel, statins

Cardiology and pharmacogenetics encompass a wide variety of genetic markers and medications. Made popular from a single gene and single drug panel from pharmacy retailers, one of the most notable drug—gene implications in this class is clopidogrel and CYP2C19. CYP2C19 is responsible for the metabolism of clopidogrel to its active metabolite within hepatocytes. At least 35 CYP2C19 polymorphic variants have been identified and summarized in the CPIC guidelines. Alleles *2 through *8 indicate a loss of function. An individual with one normal *1 allele and one of any of the loss of function alleles will exhibit intermediate metabolizer status, and individuals with a double loss of function allele will exhibit poor metabolizer status. Intermediate and poor metabolizers have nearly a three to four times’ higher risk of experiencing a cardiovascular event. The *17 allele actually increases the expression of CYP2C19 and results in a gain of function. However, one *17 allele is not enough to overcome one allele with a loss of function (e.g., one *17 allele and one *2 allele would still result in loss of function).

In summary, genotypes leading to an expression of loss of function or intermediate/poor metabolizer phenotypes are associated with less-active metabolites and decreased antiplatelet effects. In a meta-analysis of nine trials and 9,685 patients treated with clopidogrel, the risk ratios for a major adverse cardiovascular event or stent thrombosis was statistically significant for intermediate and poor metabolizers versus extensive or normal metabolizers. However, another meta-analysis showed that if an individual was at a lower risk of experiencing a cardiovascular event, then the overall risk, regardless of the genotype, was also lower. Therefore, only patients who are considered high risk for a major cardiovascular event have the clinical outcomes to support use of a pharmacogenetic test for CYP2C19 and clopidogrel per the ACCF/AHA/SCAI guidelines.

Examples of patients considered “high risk” in these guidelines are those with a history of high-risk multivessel PCI, history of stent thrombosis, acute coronary syndrome, diabetes, and chronic kidney failure. These trials led to FDA’s box warning, which is focused primarily on poor metabolizers experiencing treatment failure on clopidogrel. However, there has been a great deal of supporting data for intermediate metabolizers as well. For details, refer to the official CPIC guidance for CYP2C19 and clopidogrel, as well as the alternative antiplatelet therapy options like prasugrel and ticagrelor on the PharmGKB website. Prasugrel’s mechanism of action is similar to clopidogrel except it is not a prodrug. It is metabolized to an intermediate metabolite through hydrolysis. Ticagrelor is an active drug. Both drugs have been shown to be more effective than clopidogrel but with the potential for increased risk of bleeding in addition to being more expensive medications. Also, these medications are not always appropriate to initiate in all patients at risk for a cardiovascular event.

Although there are many newer agents on the market for anticoagulation, warfarin remains a first-line option for treatment of venous thromboembolism and prevention of stroke in persons with atrial fibrillation, atrial flutter, or valvular heart disease. When assessing whether warfarin is appropriate for a patient on the basis of their genetic compatibility with the medication, CYP2C9 and vitamin K epoxide reductase complex 1 (VKORC1) genotypes have shown strong and consistent effects on patient response. CPIC guidelines and FDA-approved labeling have incorporated dosing algorithms and genetic clinical information for predictive and stable warfarin dosing.

To better understand the dosing guidance for warfarin and these two genetic interactions, it is important to know the mechanism of action of warfarin on the vitamin K cycle as well as the metabolism of warfarin through CYP2C9. CYP2C9 metabolizes warfarin as a method of clearing the drug from the system. Variations in CYP2C9 cause decreased clearance of warfarin as well as increased exposure time and concentration levels. Warfarin binds to VKORC1 and blocks the reduction of vitamin K, which leads to its anticoagulant effects. Variations in VKORC1 affects how much VKORC1 is available for warfarin to bind to and block. Theoretically, if an individual has lots of VKORC1, then they would need
more warfarin to block it, but if they have less VKORC1, then they would need a lower dose of warfarin.

The FDA-approved labeling for warfarin now includes a table that shows the appropriate initial starting dose for warfarin using an individual’s VKORC1 and CYP2C9 genotypes. Using both genotypes, clinicians can find the appropriate starting dose of warfarin for a patient provided that no other nongenetic extrinsic factors cause contraindications. Despite the amount of genetic information and clinical support available for genetically based dosing of warfarin, clinical trials have produced mixed results, a factor that further complicates the translation of pharmacogenetic data into clinical practice. We suspect that these variable results are likely due to the variety of other factors that affect warfarin clearance and patient response, such as vitamin K intake, age, drug–drug interactions, environmental factors, etc. Ongoing trials and observational studies are expected to provide more insight and shape future guidance on clinical utility of genotyped-guided warfarin dosing.

Up to this point, we’ve discussed pharmacokinetic and drug target genetic implications. Now we will discuss a pharmacodynamic genetic implication between statins and the drug transporter gene SLCO1B1. SLCO1B1 codes for a transporter protein found on hepatocytes that moves compounds from the blood into the liver so that they can be cleared from the body. Drugs transported by this protein include enalapril, olmesartan, valsartan, nateglinide, metformin, and most statin medications. This protein may also be inhibited by medications such as gemfibrozil, cyclosporine, clarithromycin, protease inhibitors, bimoreprevir, and boceprevir. However, clinical evidence is lacking for these interactions except for statins.

Reduced or poor transporter function of the protein from SLCO1B1 is associated with decreased statin clearance and increased exposure time to statin medications in blood and tissues, which has been associated with statin-induced myopathies. At 221%, simvastatin has the highest rate of exposure time to tissues among all of the statins tested, with fluvastatin being the lowest at 19%. The CPIC guidelines for simvastatin and SLCO1B1 indicate a high myopathy risk for patients on simvastatin who have the low functioning transporter genotype, CC. Individuals with intermediate function (TC genotype) and normal function (TT genotype) have an intermediate and normal risk of myopathy, respectively. With so many other alternatives available, most providers are very accepting of switching CC patients to an alternative statin medication with less dependence on SLCO1B1 for clearance. Currently, there is no CPIC guidance on this drug–gene interaction. However, the Royal Dutch Pharmacists Association Pharmacogenetics Working Group (DPWG) guidelines on the PharmGKB website evaluate the therapeutic dose recommendations for metoprolol based on CYP2D6 genotypes. For patients who are CYP2D6 poor and intermediate metabolizers, DPWG recommends selecting an alternative medication or reducing the dose because decreased clearance of metoprol potentially leads to beta-blockade or other serious adverse events.

Although metoprolol and CYP2D6 are not in the CPIC guidelines, in our clinical experience we encountered a 55-year-old female patient who was discharged from the hospital post-MI on a regimen that included metoprolol. Within 2 days of starting the metoprolol at home, the patient returned to the emergency department (ED) with severe heart block and circulatory depression. Fortunately, the ED staff was able to resuscitate the patient and restore her vital functions. Five years later, the patient found out that she was a CYP2D6 poor metabolizer. Had this information been available preemptively, the patient could have avoided the traumatizing experience and financial burden from this severe adverse drug reaction.

**Gastroesophageal reflux disease and PPIs**

PPIs are used for treatment of gastroesophageal reflux disease and other acid-related disorders. Drugs in this class are acid-activated prodrugs that are converted in the lumenal surface of the stomach. Although PPIs are active in the stomach, they are metabolized primarily by CYP2C19 and CYP3A4 in the liver, with CYP2C19 causing a majority of the individual pharmacokinetic variations. All PPIs undergo CYP2C19 metabolism. This includes rabeprazole, but only to a minor extent; therefore, rabeprazole may be a suitable alternative for patients with CYP2C19 polymorphism who require an alternative.

Omeprazole and pantoprazole have the most significant clinical evidence. CPIC guidelines do not cover this drug–gene implication, but dosing guidance may be found in the DPWG. For CYP2C19 ultrarapid metabolizers, PPIs may have an insufficient response. The recommendation is to increase the dose by 100% to 200% for omeprazole and up to 400% for pantoprazole. However, based on clinical experience, we believe it may be better for ultrarapid metabolizers to consider alternative therapies like rabeprazole, which is less affected by CYP2C19 metabolism or other pharmacologic and nonpharmacological treatments.

**Nutrigenomics: MTHFR**

Nutrigenomics is the study of the interaction of nutrition and genes, especially with regard to the prevention or treatment of disease. The MTHFR gene codes for an enzyme called methylenetetrahydrofolate reductase, which plays a role in processing amino acids. In general, this enzyme performs the methylation step in vital pathways in the body related...
to DNA synthesis and vitamin B activation. This gene is of interest in the nutrigenomics community because of studies on the interactions between dietary folate and MTHFR variation and disease development. Through MTHFR, folic acid is methylated to its active form, folate, which makes it usable in the body.

This enzyme is also involved in activating vitamin B₁₂ to methylcobalamin and converting homocysteine to methionine, which the body needs for energy, proper metabolism, and muscle growth. The T allele for MTHFR may benefit from taking activated folate and activated B₁₂ vitamins as opposed to most vitamins on the market. By taking the already activated form, these individuals will be able to utilize the vitamins for all the essential processes in the body without depending on the methylation through MTHFR. Educating patients with these genetic variations on how to read OTC labels is important to ensure they obtain the right types of B vitamins to fit their needs.

Summary and conclusion
We discussed how the three approaches to launching a pharmacogenetics testing program affects costs and workflow to any clinical setting. It is important for project managers to assess their setting, the needs of the patient population, and the costs and workflow in order to have a sustainable model for pharmacogenetic testing in their practice. Once a model is in place, using a systematic approach within the EHR for the clinical utility of the test will be essential for diligent storage of data and provider uptake of the program. If pharmacist-led pharmacogenetic testing programs are to be successful, pharmacists must educate themselves on the top drug–gene pairs with clinical utility and be able to share this information with patients and medical providers clearly and concisely.

Although we’ve shared our journey and experience using pharmacogenomics in daily practice, we have only scratched the surface for the clinical utility of this elegant science. In addition to needing more research and clinical evidence to support our assumptions, the medical community will need to overcome cost and health information exchange barriers from a technological standpoint. Ideally, pharmacogenetic preemptive testing will be a standard covered medical benefit for all patients. All electronic medical records from the primary care office, to the hospital, to the pharmacy will be able to hold genotypic and phenotypic status as part of the patient’s demographic profile, with CDS alerts readily available for clinicians to act on these results at the point-of-care. We have a long way to go, but based on the speed at which this field has grown within the last decade, we may not have to wait very long to be fully equipped to transition to precision medicine.

References
CPE information

To obtain the 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online assessment with a passing grade of 70% or better, the evaluation, and CLAIM credit at http://apha.us/CPE0218. You will have two opportunities to successfully complete the assessment. The current policy of the APhA Education Department is not to release the correct answers to any of our CPE tests. This policy is intended to maintain the integrity of the CPE activity. Learners who successfully complete this activity by the expiration date can receive CPE credit. Please visit CPE Monitor for your statement of credit/transcript.

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CPE assessment
This assessment must be taken online; please see “CPE information” in the sidebar on page 66 for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question. Use the patient case below to answer the questions. You may also need to refer to Tables 1 through 4 to answer questions 1 through 5.

Patient case
S.B. is an urgent care patient with an open wound on his right foot that has been slow to heal. It’s clean and dry. There is health granulation tissue surrounding the wound. The wound is stapled together. The patient just filled a prescription for hydrocodone yesterday. The patient tells the provider that tramadol and hydrocodone do not work for him, and he wants something stronger. Given this information and based on the patient’s prescription history, the medical provider suspects diversion. Upon checking the patient’s profile, they see that the patient is a CYP2D6 *3/*5 and CYP2C19 *1/*1. The physician asks you to provide your recommendation for pain management based on this information.

1. Considering the level of evidence and the genotype, which gene(s) is of interest for this patient’s pain management?
   a. CYP2D6
   b. CYP2C19
   c. Both have a high level of evidence for pain management, and the patient’s genotype in both cases will affect your decision.
   d. Neither of these genes has an impact for management of pain in this patient.

2. What is the activity score for CYP2D6 in this patient?
   a. 0
   b. 0.5
   c. 1.5
   d. 3

3. What is the phenotype of the gene that has clinical utility in this case?
   a. Ultrapid metabolizer
   b. Extensive or normal metabolizer
   c. Intermediate metabolizer
   d. Poor metabolizer

4. Based on your answer in question 3, which recommendation would you NOT provide to the physician on use of medications for pain management?
   a. The drug–gene implication has been shown to lead to increased morphine formation following a codeine administration, resulting in insufficient pain relief.
   b. Avoid tramadol in this patient and to a lesser extent hydrocodone and oxycodone because the patient’s metabolism is also affected.
   c. Perform a urine drug screen on this patient to check for drug and metabolites.
   d. Recommend morphine, oxymorphone, or a nonopioid analgesic.

5. Which of the following medications may NOT cause phenoconversion in this patient?
   a. Paroxetine
   b. Terbinafine
   c. Verapamil
   d. Levoxoxacin

6. Which of the following can affect an individual’s risk for adverse reactions?
   a. Drug–drug interactions
   b. Age
   c. Pharmacogenomics
   d. All of the above

2. This type of pharmacogenetic testing aims to optimize medication use by the utilization of genetic information at the point of prescribing.
   a. Reactive
   b. Preemptive
   c. Semi-preemptive
   d. Sensitive

3. Which guideline is considered to be the “gold standard” of pharmacogenetic guidelines?
   a. Pharmacogenomics Knowledge Base (PharmGKB)
   b. Dutch Pharmacogenetics Working Group (DPWG)
   c. Clinical Pharmacogenetics Implementation Consortium (CPIC)
   d. Pharmacogenomics Research Network (PGRN)

4. CYP enzymes are primarily found in which of the following organs?
   a. Liver
   b. Small intestine
   c. Lungs
   d. Kidneys

5. The CPIC guidelines recommend that ultrapid metabolizers avoid use of codeine for the following reasons:
   a. Patients are unable to get the analgesic effect.
   b. Patients may require higher doses.
   c. Patients may have an increased risk for adverse effects.
   d. Patients may experience a higher risk for toxicity.

6. For CYP2D6 poor metabolizers, which of the following might you expect?
   a. Higher plasma concentrations of levothyroxine
   b. Lower plasma concentrations of levothyroxine
   c. Higher plasma concentrations of TCA at usual doses
   d. Lower plasma concentrations of TCA at usual doses
7. Approximately 20% to 50% of ADHD medications are metabolized by which of these enzymes?
   a. CYP1A2 and CYP3A5
   b. CYP2D6 and CYP3A5
   c. CYP2C19 and CYP1A2
   d. CYP2D6 and CYP2C19

8. FDA issued a warning about the risk of serious breathing problems in some children who are CYP2D6 ultrarapid metabolizers if they are taking this medication.
   a. Thalidomide
   b. Codeine
   c. Amitriptyline
   d. Propafenone

9. Select the appropriate match for genetic implication and medication class.
   a. VKORC1 and clopidogrel
   b. SLCO1B1 for statins
   c. MTHFR and warfarin
   d. COMT and metoprolol

10. Which mutations are commonly observed in CYP2D6?
    a. Copy number variation
    b. Single point mutations
    c. Missense mutations
    d. Frameshift mutations

11. The guidelines recommend using an alternative antiplatelet instead of clopidogrel for this metabolizer group.
    a. Extensive metabolizer
    b. Ultrarapid metabolizer
    c. Normal metabolizer
    d. Poor metabolizer

12. Reduced transporter function due to genetic variations is associated with decreased clearance of statins and increased risk for statin-induced myopathies. Which statin has the highest rate of exposure?
    a. Fluvastatin
    b. Atorvastatin
    c. Simvastatin
    d. Lovastatin

13. Which guidelines have guidance on the drug–gene interaction for metoprolol?
    a. Pharmacogenomics Knowledge Base (PharmGKB)
    b. Dutch Pharmacogenetics Working Group (DPWG)
    c. Clinical Pharmacogenetics Implementation Consortium (CPIC)
    d. Pharmacogenomics Research Network (PGRN)

14. What modification is the MTHFR gene responsible for?
    a. Methylation
    b. Sulphation
    c. Acetylation
    d. Glucuronidation

15. If there is a decrease in function of the MTHFR gene, which vitamin recommendations might you change?
    a. Vitamin C
    b. Vitamin E
    c. Vitamin A
    d. Vitamin B₁₂

16. Which PPI would you recommend for a patient with a CYP2C19 polymorphism?
    a. Omeprazole
    b. Esomeprazole
    c. Rabeprazole
    d. Pantoprazole

17. Which patient population would require the highest dose of warfarin, based on their genetics?
    a. High levels of VKORC1 and CYP2C9 extensive metabolizer
    b. Low levels of VKORC1 and CYP2C9 poor metabolizer
    c. High levels of VKORC1 and CYP2C9 poor metabolizer
    d. Low levels of VKORC1 and CYP2C9 extensive metabolizer