Policy Statement

Cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®) versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel (Plavix®), is considered **investigational**.

Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered **medically necessary** for patients with either of the following conditions:

- Gaucher disease being considered for treatment with eliglustat
- Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day

CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered **investigational** for all of the following:

- Selection or dosing of selective serotonin reuptake inhibitors (SSRIs)
- Selection or dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SNRIs)
- Selection or dosing of tricyclic antidepressants
- Selection or dosing of antipsychotic drugs
- Selection or dosage of codeine
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection
- Dosing of immunosuppressants for organ transplantation
- Selection or dosing of β-blockers (e.g., metoprolol)
- Dosing and management of anti-tuberculosis medications

The use of genetic testing panels that include multiple CYP450 variants is considered **investigational**.

Policy Guidelines

This policy does not address the use of genetic panel testing that include tests for genes other than CYP450-related genes (e.g., the Genecept Assay), which are discussed in Blue Shield of California Medical Policy: Genetic Testing for Mental Health Conditions.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.
Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling
Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding
There following is specific CPT coding for CYP450 genotyping:

- **81225**: CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)
- **81227**: CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)

Effective January 1, 2018, the following CPT codes are specific to CYP450 genotyping. CYP3A4 and CYP3A5 were previously reported under code 81401:

- **81230**: CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22)
- **81231**: CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7)

There following are tier 2 CPT codes that include cytochrome P450 testing:

- **81402**: MOLECULAR PATHOLOGY PROCEDURE LEVEL 3 including:
  - CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (e.g., IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30- kb deletion variant)
- **81404**: MOLECULAR PATHOLOGY PROCEDURE LEVEL 5 including:
  - CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (e.g., primary congenital glaucoma), full gene sequence
- **81405**: MOLECULAR PATHOLOGY PROCEDURE LEVEL 6 including:
  - CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence
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- CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence
- CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., steroid 21-hydroxylase isofom, congenital adrenal hyperplasia), full gene sequence

**Description**

The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Testing for cytochrome P450 variants may assist in selecting and dosing drugs affected by these genetic variants.

**Related Policies**

- Genetic Testing for Mental Health Conditions
- Genetic Testing for Warfarin Dose
- Genetic Testing for Tamoxifen Treatment
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Diagnostic genotyping tests for certain CYP450 enzymes are now available. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Several testing kits for CYP450 genotyping have been cleared for marketing by the FDA (FDA product code: NTI). They include:

- AmpliChip® (Roche Molecular Systems) was cleared for marketing by the FDA in January 2005. AmpliChip® is a microarray consisting of many DNA sequences complementary to 2 CYP450 genes and applied in microscopic quantities at ordered locations on a solid surface (chip). The AmpliChip® tests DNA from a patient's white blood cells collected in a standard anticoagulated blood sample for 29 variants for the CYP2D6 gene and 2 variants for the CYP2C19 gene. The FDA cleared the test “based on results of a study conducted by the manufacturer of hundreds of DNA samples, as well as on a broad range of supporting peer-reviewed literature.” According to the FDA labeling, “Information about CYP2D6 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment doses for therapeutics that are metabolized by the CYP2D6 product.”
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- The xTAG® CYP2D6 Kit (Luminex Molecular Diagnostics, Toronto, ON) was cleared for marketing by the FDA in August 2010 based on substantial equivalence to the AmpliChip® CYP450 test. The xTAG® kit is designed to identify a panel of nucleotide variants within the polymorphic CYP2D6 gene on chromosome 22.
- The INFINITI CYP2C19 Assay (AutoGenomics, Vista, CA) was cleared for marketing by the FDA in October 2010 based on substantial equivalence to the AmpliChip® CYP450 test. INFINITI is designed to identify variants within the CYP2C19 gene (*2, *3, and *17).
- Verigene CYP2C19 Nucleic Acid Test (Nanosphere, Northbrook, IL), designed to identify variants within the CYP2C19 gene, was cleared for marketing by the FDA in November 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The Spartan RX CYP2C19 Test System (Spartan Bioscience, Redwood Shores, CA), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles), was cleared for marketing by the FDA in August 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The xTAG® CYP2C19 Kit v3 (Luminex Molecular Diagnostics, Toronto, ON), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles) was cleared for marketing by the FDA in September 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

Several manufacturers market diagnostic genotyping panel tests for CYP450 genes, such as the YouScript Panel (Genelex Corp., Seattle, WA), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4, and CYP3A5. Other panel tests include both CYP450 and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health, Mason, OH) and PersonaGene Genetic Panels (AIBioTech, Richmond, VA). These tests are beyond the scope of this evidence review.

Rationale

Background

Drug Efficacy and Toxicity

Drug efficacy and toxicity vary substantially across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Different factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics is the study of how an individual’s genetic inheritance affects the body’s response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse effects, and decrease medical costs.

Cytochrome P450 System

The cytochrome P450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (e.g., dextromethorphan, β-blockers, antiarrhythmics, antidepressants, and morphine derivatives), including most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.
Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultra rapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse events and PMs may not respond.

Many drugs are metabolized to varying degrees by more than 1 enzyme, either within or outside of the CYP450 superfamily. In addition, interaction between different metabolizing genes, interaction between genes and environment, and interactions among different nongenetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain interindividual differences in metabolism and consequent efficacy or toxicity.

Determining Genetic Variability in Drug Response
Genetically determined variability in drug response has been traditionally addressed using a trial-and-error approach to prescribing and dosing, along with therapeutic drug monitoring (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse events outside that range. However, TDM is not available for all drugs of interest, and a cautious trial-and-error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (e.g., in urine). However, testing and interpretation are time-consuming and inconvenient; as a result, phenotyping is seldom performed.

The clinical utility of CYP450 genotyping (i.e., the likelihood that genotyping will significantly improve drug choice, dosing, and patient outcomes) is favored when the drug under consideration has a narrow therapeutic dose range, when the consequences of treatment failure are severe, and/or when serious adverse reactions are more likely in patients with gene sequence variants. Under these circumstances, genotyping may direct early selection of the most effective drug or dose, and/or avoid drugs or doses likely to cause toxicity. For example, warfarin, some neuroleptics, and tricyclic antidepressants have narrow therapeutic windows and can cause serious adverse events when concentrations exceed certain limits, resulting in cautious dosing protocols. Yet, the potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed up the process of achieving a therapeutic dose and avoiding significant adverse events.

Literature Review
The most recent literature review was performed through April 25, 2017 (see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a variant that is present or
in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of a test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). The following is a summary of the key literature.

Genetic Testing for P450 Genotyping
Clinical Context and Test Purpose
The purpose of P450 genotyping is to tailor drug selection and dosing to patients based on their gene composition for drug metabolism. In theory, this should lead to early selection and optimal dosing of the most effective drugs, while minimizing treatment failures or toxicities.

The questions addressed in this evidence review are: (1) Is there evidence that P450 genotyping has clinical validity? and (2) Does P450 genotyping change patient management in a way that improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant populations of interest are patients being considered for treatment with clopidogrel, eliglustat, tetrabenazine, selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), antipsychotic drugs, codeine, efavirenz and other antiretroviral therapies for HIV infection, immunosuppressants for organ transplantation, β-blockers (e.g., metoprolol), and antitubercular medications.

Interventions
Commercial tests for individual genes or panels are available and are listed in the Regulatory Status section. Only those panels that include CYP450 genes are listed in that section.

Comparators
The comparator of interest is standard clinical management without genetic testing.

Outcomes
Specific outcomes of interest are listed in the Table 1.

Table 1. Outcomes of Interest for Individuals with Altered Drug Metabolism

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel therapy</td>
<td>• Initial and maintenance dose selection</td>
</tr>
<tr>
<td></td>
<td>• Decrease in platelet reactivity</td>
</tr>
<tr>
<td></td>
<td>• Myocardial infarction, cardiovascular or all-cause death, revascularization, fatal/nonfatal cerebrovascular accident, aortic event</td>
</tr>
<tr>
<td>Eliglustat</td>
<td>• Avoidance of treatment failure</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events due to overtreatment</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>• Initial and dose titration selection</td>
</tr>
<tr>
<td></td>
<td>• Reduction in time taken for appropriate dose titration</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events due to overtreatment</td>
</tr>
<tr>
<td>Serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotic drugs</td>
<td>• Dose selection</td>
</tr>
<tr>
<td></td>
<td>• Reduction in depressive or psychosis symptoms</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events due to overtreatment</td>
</tr>
<tr>
<td>Codeine</td>
<td>• Dose selection</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events including death due to overtreatment</td>
</tr>
<tr>
<td>Highly active antiretroviral agents</td>
<td>• Dose selection</td>
</tr>
<tr>
<td></td>
<td>• Avoidance of treatment failure</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events</td>
</tr>
</tbody>
</table>
Drug Outcomes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressant therapy for organ</td>
<td>• Dose selection</td>
</tr>
<tr>
<td>transplantation</td>
<td>• Avoidance of organ failure</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse events</td>
</tr>
<tr>
<td>β-blocker(s)</td>
<td>• Dose selection</td>
</tr>
<tr>
<td></td>
<td>• Superior control of blood pressure</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of adverse effects due to overtreatment</td>
</tr>
<tr>
<td>Antitubercular medications</td>
<td>• Dose selection</td>
</tr>
<tr>
<td></td>
<td>• Avoidance or reduction of hepatotoxicity due to overtreatment</td>
</tr>
</tbody>
</table>

Potentially harmful outcomes are those resulting from a false-test result. False-positive or false-negative test results can lead to initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

**Timing**

Genetic testing may be used for drug selection before treatment initiation.

**Setting**

Consultations about choice of drug generally occur in outpatient setting and a variety of specialists may be involved including primary care providers (HIV, β-blockers, tuberculosis and cough medications), cardiologists (clopidogrel), psychiatrists (antidepressants and antipsychotics), neurologists (Huntington disease), and endocrinologists (Gaucher disease).

**Analytic Validity**

Measures of analytic validity include sensitivity (detection rate), specificity (1 – false-positive rate), reliability (repeatability of test results), and assay robustness (resistance to small changes in preanalytic or analytic variables).

The analytic validity of the AmpliChip test was reported by Chau and Thomas (2015) who summarized data from 4 studies reported by Roche, the manufacturer of AmpliChip, in the manual on the diagnostic test. It is reproduced in Table 2. Chau and Thomas also reported that there was minimal research on the reliability of the AmpliChip outside of Roche in-house testing. The in-house data reported high reliability with CYP2D6 (99.2%) and CYP2C19 (99.6%) testing based on 246 specimens. However, another study, based on a small sample size of 13 specimens, reported 84.6% reliability.

AmpliChip was designed for the North American population and detection problems have been reported when applied to different populations. In South Africa, certain alleles are more prevalent and the AmpliChip is less accurate for CYP2D6 assessment, with an average failure rate of 22.4%.

**Table 2. Studies Assessing the Genotyping Accuracy of the AmpliChip**

<table>
<thead>
<tr>
<th>Genotyping Accuracy</th>
<th>Measure of Reliability</th>
<th>Risk of Biases</th>
</tr>
</thead>
</table>
| The AmpliChip miscalled or no called 24.1% of diabetics and 29% healthy volunteers for CYP2D6. CYP2C19 had a near 98.8% success rate for diabetics and 100% for healthy | For CYP2D6, 13 failed samples from the healthy group were repeated, yielding 2 successes and 11 repeat fails. Two successful samples were also retested yielding concordant results. | • Small sample size  
• Selection bias of individuals from a diabetic clinic because of convenience |
| 152 (95.6%) of 159 blood samples showed concordance with PCR-RFLP. In 6 of 7, differences between PCR-RFLP and AmpliChip not due to assignment of different alleles but assignment of duplicated genes. In the 1 allele discrepancy, DNA sequencing showed concordance with AmpliChip. | NA | • AmpliChip product was provided by Roche at no cost (possible conflict of interest)  
• Small sample size |
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<table>
<thead>
<tr>
<th>Genotyping Accuracy</th>
<th>Measure of Reliability</th>
<th>Risk of Biases</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 samples were tested for 4 CYP2D6 alleles by PCR-RFLP and compared to Amplichip. 41 individuals contained the test alleles and showed 100% concordance.</td>
<td>NA</td>
<td>• Small sample size</td>
</tr>
<tr>
<td>100% specificity for detection of previously known wild-type genes (*1, *2, or *35) For CYP2D6, 99% agreement between Amplichip and PCR-RFLP or DNA sequencing for all 25 genotypes (CYP2D6 and CYP2C19)</td>
<td>• CYP2D6 sequencing concordance of 99.2%  • CYP2C19 sequencing concordance of 99.6%</td>
<td>• Only looked at 4 of the most common alleles to compare and not all</td>
</tr>
</tbody>
</table>

Reproduced From Chau and Thomas (2015).¹
NA: not available; PCR-RFLP: polymerase chain reaction with restriction fragment length polymorphism.

Clinical Validity
The 2004 TEC Special Report provided background on cytochrome P450 (CYP450) enzymes and on genotyping applications for drugs then available.³ Data suggested a strong association between specific variant alleles and increased adverse events related to specific drugs or between specific variant alleles and final doses for specific drugs (clinical validity). Such associations, however, do not explain most of the interindividual variability in drug response. For example, although CYP2C9 genotype is an independent predictor of final warfarin dose, CYP2C9 genotype in combination with other known genetic and nongenetic significant confounders statistically explain up to 60% of the variation in final dose.⁴⁻⁹ Whether that is sufficient to improve patient outcomes after genotype-directed dosing is, at present, unknown.

The following are brief synopses of the literature on clinical validity for the clinical indications discussed herein.

Selection and Dosing of Clopidogrel
Guidelines from the American Heart Association and the American College of Cardiology have recommended the use of dual antiplatelet therapy with aspirin and a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor, for the prevention of atherothrombotic events after acute myocardial infarction (MI). However, a substantial number of subsequent ischemic events still occur, which might be at least partly due to interindividual variability in the response to clopidogrel. Clopidogrel is a prodrug that is converted by several CYP450 enzymes, CYP2C19 in particular, to an active metabolite. For this reason, genetic variants that inactivate the CYP2C19 enzyme are associated with impaired pharmacodynamic response in healthy individuals. Previous studies have shown that persistent high platelet reactivity, despite clopidogrel treatment at standard dosing, is associated with CYP2C19 variants that code for inactive enzymes⁵⁰; higher loading and/or maintenance doses decrease reactivity even in initial nonresponders, presumed to be CYP2C19 poor metabolizers (PMs).¹¹⁻¹³ Higher platelet reactivity has also been associated with a higher rate of subsequent thrombotic events.¹⁴ A 2014 meta-analysis of 8 studies reporting on the association between the CYP2C19*2 genotype and clopidogrel resistance using measures of platelet function concluded that CYP2C19 genotype is probably associated with changes in platelet reactivity.¹⁵ However, the intrinsic variability of platelet monitoring is a known limitation of all tests measuring platelet aggregation, making it difficult to use these tests to modulate treatment.¹⁶

In 2009, the U.S. Food and Drug Administration (FDA) expanded the pharmacogenetics section of the clopidogrel label to include information on the metabolic impact of polymorphic CYP450 enzymes. However, no dosing or drug selection recommendations were made. In March 2010, based on the available data at that time, the FDA issued a safety communication indicating it was adding a boxed warning to the label of Plavix. This warning included information to:

• Warn about the reduced effectiveness in PMs of Plavix (patients with CYP2C19*2/2, *3/3, or *2/3 genotypes)
• Indicate tests are available to identify genetic differences in CYP2C19 function that will help identify PMs
• Advise health care professionals to consider alternative dosing or use of other medications in patients identified as potential PMs

Systematic Reviews
Studies on the association between CYP2C19 genotype and clopidogrel response have been summarized in a number of systematic reviews and meta-analyses, some of which have come to opposing conclusions.

Wang et al (2016) reported results of a meta-analysis assessing 12 studies involving 8284 patients to delineate association between CYP3A5 variants and the risk of adverse events in patients undergoing clopidogrel therapy. The CYP3A5 variant was classified as a wild-type, heterozygote, or homozygous variant. There were no statistically significant differences in the odds of major adverse cardiovascular events in the 3 groups classified by CYP3A5 variant (wild-type plus heterozygote vs homozygous variant: odds ratio [OR], 1.032; 95% confidence interval [CI], 0.583 to 1.824; p = 0.915; wild-type vs heterozygote plus homozygous variant: OR=1.415; 95% CI, 0.393 to 5.094; p = 0.595). There was also no significant relation between CYP3A5 variants and bleeding (homozygous vs wild-type plus heterozygote: OR=0.798; 95% CI, 0.370 to 1.721; p = 0.565) or clopidogrel resistance (wild-type plus heterozygote vs homozygous variant: OR=1.009; 95% CI, 0.685 to 1.488; p = 0.963; wild-type vs heterozygote plus homozygous variant: OR=0.618; 95% CI, 0.368 to 1.039; p = 0.069).

In 2015, Osnabrugge et al on reported a systematic review of 11 meta-analyses that summarized studies evaluating the associations between CYP2C19 genetic status and outcomes in clopidogrel-treated patients. The 11 meta-analyses included 30 primary studies, but not all studies were included in all meta-analyses. Among the 30 primary studies, there were 23 cohort studies and 7 post hoc analyses of RCTs. Eight of 11 meta-analyses on clinical end points reported a statistically significant association between CYP2C19 genotype and outcomes, with mean effect sizes ranging from 1.26 to 1.96. Five of these 8 concluded that there was an association between CYP2C19 genotype and the clinical end point, 2 inferred a possible association, and 1 concluded that the association was not proven because of publication bias. For the outcome of stent thrombosis, all 11 meta-analyses reported a statistically significant association between CYP2C19 genotype and stent thrombosis, with mean effect sizes ranging from 1.77 to 3.82.

Examples of the available systematic reviews on the association between CYP2C19 genotype and clopidogrel response follow.

Bauer et al (2011) assessed 15 studies in a meta-analysis. In a comparison of carriers with at least 1 reduced-function CYP2C19 allele with noncarriers, they reported the unadjusted odds of major adverse events were higher in 3 studies, lower in one, and not significantly different in 8. For stent thrombosis, the odds associated with reduced-function allele carrier status was lower in 4 studies but showed no significant difference in 5. No studies showed a significant positive or negative influence on outcomes from the results of CYP2C19*17 testing.

Holmes et al (2011) identified 32 studies (total N=42,106 participants) linking CYP2C19 testing to clopidogrel treatment. Twenty-one studies included patients with acute coronary syndromes, and 8 studies included patients with stable coronary heart disease. While reviewers observed a decrease in the measurable concentration of clopidogrel metabolite in patients with a loss-of-function gene on clopidogrel 75 mg, they were unable to show that this loss resulted in a clinically meaningful change in outcomes. When studies were stratified by numbers of outcome events, there was a clear trend toward the null in larger studies, consistent with small-study bias. The strongest data supporting use of testing was to predict stent thrombosis using fixed-effects (relative risk [RR], 1.75; 95% CI, 1.50 to 2.03) and using random-effects modeling (RR=1.88; 95% CI, 1.46 to 2.41). There was also a trend toward the null in larger studies. Assuming an event risk of 18
per 1000 in the control group, they calculated that this corresponded to an absolute increase of 14 stent thromboses per 1000 patients. Reviewers also noted a trade-off between decreased risk of bleeding with loss of function that in part appeared to mitigate increased susceptibility to thrombosis. They cautioned that efforts to personalize treatment in the loss-of-function setting should be considered carefully because efforts to improve efficacy might be offset by risks of harms such as bleeding.

Mao et al (2013) conducted a meta-analysis of studies assessing the effect of CYP2C19 variants on clinical outcomes in patients with coronary artery disease treated with clopidogrel. Reviewers included 21 studies (total N=23,035 patients), including prospective cohort studies and post hoc analyses of RCTs involving patients with coronary artery disease. Carriers (n=6868) of the CYP2C19 variant allele had a higher risk of adverse clinical events than the 14,429 noncarriers (OR=1.50; 95% CI, 1.21 to 1.87; p<0.000). Patients with a loss-of-function CYP2C19 allele had a higher risk of MI (OR=1.62; 95% CI, 1.35 to 1.95; p<0.000) and a higher risk of in-stent thrombosis, among those who underwent stent implantation (OR=2.08; 95% CI, 1.67 to 2.60; p<0.000).

In an older meta-analysis, Mega et al (2009) evaluated 9 studies (total N=9685 patients) comparing CYP2C19 genotype to clinical outcomes in patients treated with clopidogrel. Most patients (91.3%) had undergone percutaneous coronary intervention (PCI), and 54.5% had an acute coronary syndrome. Reviewers observed a significantly increased risk of cardiovascular death, MI, stroke, or stent thrombosis in patients with 1 and 2 reduced-function CYP2C19 alleles as compared with noncarriers.

Secondary Analyses of Randomized Controlled Trials
Pare et al (2010) retrospectively genotyped 5059 patients from 2 large randomized trials (the Clopidogrel in Unstable Angina to Prevent Recurrent Events [CURE] trial, the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events [ACTIVE] trial) that showed clopidogrel reduce the rate of cardiovascular events compared with placebo in patients with acute coronary syndromes and atrial fibrillation. Genotyping was performed for *2, *3, and *17 of the CYP2C19 allele. These investigators observed that the efficacy and safety of clopidogrel compared with placebo was not affected by CYP2C19 loss-of-function alleles. Even when data were restricted to patients homozygous for loss of function, no increased risk of cardiovascular events was observed. Although the reason for these divergent findings remains unclear, it was noted that, in the populations studied, use of stents was substantially lower than in previous reports (19% of patients with acute coronary syndromes and 14.5% in patients with atrial fibrillation).

Observational Studies
A number of studies have evaluated outcomes in patients treated with clopidogrel by CYP2C19 genetic status. These studies showed that patients with genetic variants had worse outcomes than those without genetic variants. These data suggest that the efficacy of clopidogrel is reduced in patients with genetic variants.

Section Summary: Selection and Dosing of Clopidogrel
Multiple observational studies have reported that genetic variants associated with CYP2C19 may be associated with a modest increase in the rate of stent thrombosis and increased incidence of adverse events. However, 2 large meta-analysis that included patients treated with and without PCI showed conflicting results on the impact of CYP2C19 variant selection on clinical outcomes.

Selection or Dosing of Elaglustat
Gaucher disease is a rare autosomal recessive lipid storage disorder in which deficiency or absence of the enzyme β-glucocerebrosidase leads to lysosomal accumulation of the glycosphingolipid glucosylceramide. Untreated, this accumulation can lead to a range of effects, including anemia and thrombocytopenia, splenomegaly, bone disease, pulmonary
fibrosis, and central nervous system involvement. Gaucher disease has been treated using enzyme replacement. Treatments for Gaucher disease include the use of enzyme replacement therapy (imiglucerase, velaglucerase alfa, taliglucerase alfa) or substrate reduction therapy (miglustat, eliglustat tartrate). Eliglustat tartrate is an orally administered selective inhibitor of glucosylceramide synthase that received FDA approval in 2014 and, in 3 phase 3 clinical trials, led to improvements in hematologic metrics and organomegaly.

Eliglustat tartrate is primarily metabolized by the CYP2D6 enzyme. FDA labeling requires that patients be tested for CYP2D6 metabolizer status as determined by genotype and that ultrarapid metabolizers (UMs) not be given eliglustat because these patients may not achieve adequate concentrations to achieve a therapeutic effect. FDA reviews have reported that, at doses as high as 200 mg twice daily, the exposure in UM was about 57% and about 82% lower than the exposures for extensive metabolizers (EMs) and intermediate metabolizers (IMs) at 100 mg twice daily, respectively. The approved dose is 84 mg twice daily for EMs and IMs and 84 mg once daily for PMs.

Section Summary: Selection or Dosing of Eliglustat
We did not identify any published studies that showed CYP2D6 and CYP3A variants may be associated with differential rates of drug metabolism or drug-related adverse events compared to nonvariant status. Information submitted to the FDA by the manufacturer as part of regulatory approval have shown that patients classified as UMs by CYP450 genotype testing may fail to achieve adequate therapeutic concentrations and therefore should not be prescribed eliglustat.

Selection or Dosing of Tetrabenazine
Huntington disease is an autosomal dominant genetic neurodegenerative disorder characterized by progressive cognitive and motor dysfunction, including chorea. In 2008, the FDA approved tetrabenazine, a centrally acting vesicular monoamine transporter inhibitor, as an orphan drug for the treatment of chorea in Huntington disease, based on evidence from a 2006 RCT of improved chorea symptoms in ambulatory patients with Huntington disease. Tetrabenazine is primarily metabolized by the CYP2D6 enzyme. FDA labeling (2015) for tetrabenazine includes recommendations for CYP2D6 genotyping in patients who require doses above 50 mg per day. The labeling states: “Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a PM or an EM. Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg. Maximum daily dose in EMs and IMs: 100 mg with a maximum single dose of 37.5 mg.”

Mehanna et al (2013) reported on the results of a cohort study in which CYP2D6 genotyping was performed sequentially on 127 patients receiving tetrabenazine. A reviewer blinded to the test results analyzed charts data to assess dose, titration, response to treatment and adverse effects. Treating physicians were not aware of the test results at the time of initiation or titration of tetrabenazine. A majority of patients were categorized as EMs (n=100) while the remaining were categorized as IMs (n=14), PMs (n=11), and UM (n=2). The mean duration of titration to achieve optimal benefit was longer for UM than for EMs, IMs, or PMs (8 weeks vs 3.3, 4.4, and 3 weeks, respectively; p<0.01) and required a higher average daily dose than the other patients (138 mg/d vs 63, 66 and 41 mg/d, respectively). Differences in dosage were not statistically significant. Authors concluded that there were no distinguishing features of patients with various CYP2D6 genotypes, and therefore the current recommendation to genotype systematically all patients prescribed tetrabenazine at doses more than 50 mg per day should be reconsidered.

Section Summary: Selection or Dosing of Tetrabenazine
We identified 1 published study that reported patients categorized as UM by a CYP450 genotyping required higher doses of tetrabenazine than those not categorized as UM. However, this finding was based in a sample with only 2 patients categorized as UMs, which makes conclusions uncertain.
Selection or Dosing of Selective Serotonin Reuptake Inhibitors

CYP2D6 and CYP2C19 are the primary CYP450 enzymes involved in the metabolism of selective serotonin reuptake inhibitors (SSRIs). Thus, understanding a patient’s metabolizer status might be helpful in choosing an initial SSRI and/or dose most likely to be effective.

Systematic Reviews

In 2007, an Agency for Healthcare Research and Quality systematic review evaluated the evidence on CYP450 testing for adults treated with SSRIs for nonpsychotic depression. Based on the review, the Evaluation of Genomic Applications in Practice and Prevention Working Group published the following recommendation: “The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.”

Observational Studies

A number of prospective and retrospective studies have evaluated the association between CYP450 genotype and response to SSRIs. Several studies have focused on specific drugs, including paroxetine and escitalopram. Gex-Fabry et al (2008) studied associations between paroxetine levels and clinical response in 71 patients with depression who had been genotyped for CYP2D6 and ABCBA variants. In this prospective observational study, CYP2D6 heterozygous EM phenotype showed a marginal impact on paroxetine levels and no impact on treatment response.

Ververs et al (2009), in a cohort study of 74 pregnant women, demonstrated that differences in CYP2D6 genotype produced differential effects on paroxetine plasma concentrations. EMs and UMs showed steady decreases in concentrations during pregnancy, with increase in depressive symptoms. IMs and PMs showed an increase in concentrations with no change in symptoms. It was suggested that data on CYP2D6 genotype status would be indispensable in this setting. However, no information on the use or outcome of use of such data was provided.

Tsai et al (2010) evaluated 100 patients diagnosed with major depressive disorder in an Asian population treated with escitalopram. These investigators evaluated 10 alleles involving CYP2D6, CYP2C19, and CYP3A4 and concluded genetic variants of cytochrome P450 enzymes appeared to influence drug metabolism and treatment response. However, results varied, and authors were unable to provide a confident estimate of the ability of various allelic combinations to predict drug levels or treatment outcomes.

Hodgson et al (2014) evaluated the association between CYP450 genotype, antidepressant serum concentration, and treatment response in patients taking escitalopram (n=223) or the tricyclic antidepressant nortriptyline (n=161). Genetic variation in CYP2C19 was significantly associated with serum escitalopram levels, while variation in CYP2D6 was significantly associated with serum nortriptyline and 10-hydroxynortriptyline. However, there was no significant relation between genotype and treatment response for either medication.

Chang et al (2014) evaluated the relation between CYP2C19 variants and exposure to escitalopram and citalopram measured by serum or plasma levels in a meta-analysis of 14 studies. Compared with EM homozygotes, citalopram or escitalopram concentrations differed significantly for other metabolizer states, as shown in Table 3.

Table 3. (Es)citalopram Serum Concentration by CYP2C19 Genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Change in Serum (Es)citalopram Level, %</th>
<th>95% CI, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM/PM (CYP2C19*2 or *3/*3 or *3)</td>
<td>95</td>
<td>40 to 149</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EM/PM (CYP2C19*1/*2 or *3)</td>
<td>30</td>
<td>4 to 55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UM/PM (CYP2C19*17/*2 or *3)</td>
<td>25</td>
<td>1 to 49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UM/UM (CYP2C19*17/*17)</td>
<td>-36</td>
<td>-46 to 27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UM/EM (CYP2C19*17/*1)</td>
<td>-14</td>
<td>-27 to -1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
CI: confidence interval; EM: extensive metabolizer; PM: poor metabolizer; UM: ultrarapid metabolizer.

Other studies have evaluated the association between P450 genotype variants and response to multiple antidepressants. Serretti et al (2009), in a retrospective study of 287 patients on antidepressants, demonstrated no association between response and CYP1A2, CYP2C9, CYP2C19, and CYP2D6 allelic variations.42

Finally, Sim et al (2010) retrospectively studied 1472 Swedish subjects looking for associations between CYP2C19 variants and depressive symptoms.43 They concluded that PMs exhibited a significantly lower level of depressive symptoms than EMs. In the absence of drug-specific treatment outcomes or data related to drug levels, they suggested the need for further investigation into the functional link between CYP2C19 and depressive symptoms.

Section Summary: Selection or Dosing of Selective Serotonin Reuptake Inhibitors
SSRIs are primarily metabolized by CYP2D6 and CYP2C19 enzymes and therefore it has been hypothesized that understanding a patient’s metabolizer status might help choose an initial SSRI and/or dose that is most likely to be effective. Multiple retrospective and prospective studies have evaluated this association with conflicting results. Based on a systematic review, EGAPP concluded that there was insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for nonpsychotic depression.

Selection and Dosing of Serotonin-Norepinephrine Reuptake Inhibitors
SNRIs are used most commonly as antidepressants. Available agents in the United States include venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran, and sibutramine. All are metabolized by the cytochrome P450 system, and medication levels vary according to cytochrome P450 status.44 Some of these agents (eg, venlafaxine) are metabolized to an active metabolite by the CYP2D6 enzyme, while other agents (eg, duloxetine) are inhibitors of cytochrome P450 activity. There also exist a number of selective norepinephrine reuptake inhibitors, 2 of which (atomoxetine and maprotiline) are approved for use in the United States.

Lobello et al (2010) tested patients from 4 RCTs comparing venlafaxine with placebo to evaluate the relation between CYP2D6 enzymatic status and correlated genetic status, defined as either EMs or PMs, and response to treatment.45 There were no significant differences in drug doses according to genetic status. In 4 of 5 comparisons, patients who were EMs had a better treatment response, as determined by depression rating scales. There was also a significantly greater percentage of responders in the EM group compared with the PM. There were no differences in discontinuation of therapy or adverse event rates between the EM and the PM groups.

Waade et al (2014) retrospectively evaluated the association between age, serum levels of venlafaxine, and the SSRI escitalopram for different CYP2D6 and CYP2C19 genotype subgroups.46 The study included 462 serum concentration measurements from 255 patients treated with venlafaxine and 953 serum concentration measurements from 541 patients treated with escitalopram. Patients were divided into 3 CYP2D6 (venlafaxine) or CYP2C19 (escitalopram) phenotype subgroups according to inherited genotype (PMs, heterozygous EMs, and EMs). In CYP2D6 PMs, the mean dose-adjusted serum concentration of venlafaxine was 8-fold higher in patients older than 65 years compared with those younger than 40 years (p<0.001). By comparison, the respective age-related differences in mean dose-adjusted serum concentrations of venlafaxine were much less pronounced in CYP2D6 heterozygous EMs and EMs (~2-fold differences between age groups). A similar genotype-related effect of age was not observed for escitalopram (~1.5-fold age differences in all CYP2C19 subgroups).

For duloxetine, the inhibitory effects on cytochrome P450 activity are manifested by higher drug concentrations for other medications metabolized by cytochrome P450, such as TCAs and/or SSRIs. Similarly, other inhibitors of cytochrome P450 (eg, paroxetine) will increase levels of duloxetine.47
Atomoxetine is an SNRI that is approved to treat attention-deficit/hyperactivity disorder (ADHD). Atomoxetine, the active moiety, is primarily metabolized by the CYP2D6 enzyme. The therapeutic window for atomoxetine is wide, and dosing is weight-based, initiated at a standard dose per kilogram and adjusted thereafter according to clinical response and adverse events. At steady-state dosing, CYP2D6 PMs have substantially higher atomoxetine plasma concentrations than EMs, although because it is generally well-tolerated across a wide range, adverse events do not appear to be significantly associated with PMs. After titration, mean doses for EMs and PMs also do not differ significantly. However, more EM patients discontinued in 1 trial due to lack of efficacy, and PMs improved inattention scores more than EMs in another, perhaps suggesting a need to reexamine recommended dosing limits. The FDA decided not to include a recommendation to perform genotyping before prescribing atomoxetine. Dosing directions recommend a low starting dose to be increased to the target dose if well-tolerated. Thus, genotyping for CYP2D6 PMs of atomoxetine is not recommended because the margin of safety is not exceeded and evidence to support guidelines for dosing such that patient outcomes are improved has not been collected. Indeed, Ramoz et al (2009) reported on 2 independent cohorts of 160 and 105 children with ADHD treated for 6 weeks with atomoxetine. Interindividual response to the drug appeared independent of the CYP2D6 variants. The authors observed drug treatment and genomic associations, but these were found between drug response and a haplotype of the norepinephrine transporter gene (Slc6a2). It was suggested further study assess this region of the gene to better manage patients being treated with atomoxetine. Ter Laak et al (2010) evaluated 100 patients treated for ADHD with standard doses of atomoxetine. A neurologist identified 10 patients who, based on late response or adverse events, underwent CYP450 testing. Eight of the 10 were found to have a nonfunctional or less functional 2D6 allele. Four of these children showed improved responses with lower doses of atomoxetine; 4 were taken off treatment because of initial adverse events. While pretreatment testing could yield improved results, the study was not designed to evaluate the actual effect of testing on treatment outcomes.

Section Summary: Selection and Dosing of Serotonin-Norepinephrine Reuptake Inhibitors
SNRI metabolism is affected by genetic status of cytochrome P450, with the greatest potential clinical effect seen for venlafaxine. For this agent, EMs with the CYP2D6 variant have higher levels of the active metabolite, and gene status may have an impact on treatment response. A post hoc reanalysis of data from multiple RCTs has correlated treatment response to venlafaxine with gene status. Atomoxetine is an SNRI used to treat ADHD. Although it has a wide therapeutic window, there is potential for PMs who require relatively high doses to reach serum levels that may be toxic. However, current recommendations for starting atomoxetine at a low dose and watching closely for adverse events while titrating higher should minimize the risk of toxicity for PMs.

Selection and Dosing of Tricyclic Antidepressants
Nortriptyline and other TCAs are metabolized by the CYP2D6 enzyme. Patients who are PMs will develop serum concentrations of nortriptyline that are 3- to 10-fold higher than patients who are EMs. De Vos et al (2011) studied 678 patients treated with TCAs and reported that EMs had increased metabolism and lower serum levels of amitriptyline and citalopram, but not clomipramine. However, these authors reported that the differences observed were not likely to have clinically important effects. In the study by Hodgson et al (2014) (discussed previously), CYP2D6 genotype was associated with nortriptyline levels, but not with clinical improvement in 161 patients treated with nortriptyline.

It has been reported that patients with TCA overdose may have different risk depending on cytochrome P450 genetic status. Simulations and case reports have reported that PMs may be at higher risk for toxic levels of nortriptyline and that toxic levels are maintained for longer periods of time. There are no clinical studies demonstrating that measuring genetic status improves outcomes for patients who have had a TCA overdose.
Section Summary: Selection and Dosing of Tricyclic Antidepressants
Cytochrome P450 genetic status affects the metabolism and serum levels of multiple TCAs, including nortriptyline, but the clinical impact of these differences on metabolism are not clear. There is some evidence that patients who are PMs are more prone to TCAs toxicity.

Selection or Dosing of Antipsychotic Drugs
Classical antipsychotic agents (e.g., haloperidol, perphenazine, risperidone) have narrow therapeutic ranges, more severe adverse events, and highly variable clinical responses. Case reports and small studies have reported associations between clinically significant adverse reactions or clinical responsiveness and specific CYP450 genotypes (e.g., CYP2D6 and CYP3A4 variants), but most studies are small and results are inconsistent. Moreover, plasma concentration of antipsychotic drugs may not correlate with treatment outcome or adverse events. Because most patients with schizophrenia take combinations of psychoactive agents for extended periods of time, drug-drug and drug-environmental interactions may influence the CYP450 metabolic phenotype in addition to genotype. For example, carbamazepine, phenytoin, smoking, and alcohol consumption can induce CYP450 enzymatic activity, whereas caffeine and fluvoxamine are inhibitors of CYP1A2 enzymatic activity. Some antipsychotic medications are metabolized by multiple CYP450 enzymes, and dominant pathways may vary. Several classical antipsychotic drugs inhibit the CYP450 enzyme required for their metabolism and may render the patient a phenotypic PM, despite an EM genotype. Thus, initial dosing algorithms need to accommodate both genetic influences and other interactions; therapeutic drug monitoring may be needed to reflect the metabolic phenotype during ongoing treatment.

Systematic Reviews
Fleeman et al, in a 2010 health technology assessment, reviewed published articles on clinical validity of testing for cytochrome P450 in patients with schizophrenia treated with antipsychotic medications. Reviewers concluded that patients with heterozygous or homozygous CYP2D6 variants were at increased risk for tardive dyskinesia (odds ratio [OR], 2.08 and 1.83, respectively) and patients with homozygous variants at increased risk for parkinsonism syndromes (OR=1.64). Reviewers concluded “further evidence is required to link phenotype to genotype.” This assessment included 47 articles on clinical validity. It also reported no convincing association between test results and either drug efficacy or toxicity. Differences when seen (e.g., an association with tardive dyskinesia) were considered too small to be clinically meaningful.

Observational Studies
Other studies have reported on CYP2D6 variants and response to risperidone. Jovanovic et al (2010) evaluated the role of the CYP2D6 variant in 83 drug-naive patients undergoing a first episode of psychosis who were treated with risperidone. While significant improvements were observed in positive and general symptoms using this drug, the investigators were unable to identify an association between treatment response and variations in either genetic or drug concentration findings. Locatelli et al (2010) evaluated CYP2D6 genotypes in 50 patients hospitalized for acute schizophrenia who were also treated with risperidone. They found elevations in risperidone plasma levels in patients classified as PMs or IMs based on genotyping. Drug efficacy was not reported, but authors observed an association among genotype, levels of risperidone, and the occurrence of extrapyramidal syndromes. In a study of 76 white adult males with schizophrenia being treated with risperidone, Almguer et al (2013) reported that CYP2D6 phenotype was associated with improved scores on the total and negative symptoms scales of the Positive and Negative Syndrome Scale.

Van der Weide and van der Weide (2015) retrospectively evaluated CYP2D6 and CYP3A4 variants and serum drug concentrations among 834 adults treated with aripiprazole, haloperidol, pimozide, or risperidone (n=130, 312, 86, and 396, respectively). CYP3A4 genotype was not associated with dose-corrected serum antipsychotic concentration. However, CYP2D6
genotype was associated with dose-corrected concentrations of all 4 antipsychotics. Clinical outcomes were not reported.

Section Summary: Selection or Dosing of Antipsychotic Drugs
Multiple observational studies have suggested that CYPD6 variants may be associated with differential risk for adverse events antipsychotic drugs, particularly extrapyramidal effects (e.g., tardive dyskinesia). A large systematic review and meta-analysis of 47 studies found no convincing evidence of an association between test results and either drug efficacy or toxicity. Differences when seen (e.g., an association with tardive dyskinesia) were considered too small to be clinically meaningful.

Selection or Dosing of Codeine
Codeine is metabolized by the CYP2D enzyme to morphine. Enhanced CYP2D activity (i.e., in CYP2D6 UMs) predisposes to opioid intoxication. In August 2007, the FDA issued a warning on codeine use by nursing mothers. Nursing infants “may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of codeine.” Information about genetic variation and risk of accelerated codeine metabolism is now included in package insert information. The warning was prompted by a 2006 case report about an infant who died of morphine overdose. The mother, prescribed codeine for episiotomy pain, was a CYP2D6 UM, with high levels of circulating morphine. Not mentioned in the original case report, but noted later, is that the mother was also homozygous for the UGT2B7*2 metabolizing variant, which is believed also to contribute to higher than normal production of active opioids from codeine. Currently, the FDA is not recommending genotyping for any population before prescribing codeine because “there is only limited information about using this test for codeine metabolism.” Information is limited to associations of genotype with morphine exposure and adverse events (e.g., sedation in adults), and association of mothers’ genotype with morphine exposure in women with infant central nervous system (CNS) depression. Studies have been small, with correspondingly few PMs and UMs for drawing conclusions. Madadi et al (2011) have more recently described the use of a pedigree approach to aid in diagnosis, identification of other at-risk family members, and simplification of pharmacogenomic analysis. However, they noted that, for most medical centers, the framework for performing this work may not exist, and its applicability and relevance to general use remain unestablished.

In 2016, the American Academy of Pediatrics released a clinical report on codeine, expressing concerns about the dangers of codeine use in children and requiring for formal restrictions of its use in children younger than 12 years of age. Subsequently, the FDA changed the labels of medications containing codeine. Codeine is now contraindicated to treat pain or cough in children under 12 years of age and codeine is not recommended for use in adolescents ages 12 to 18 who are obese or have conditions such as obstructive sleep apnea or severe lung disease. There is an additional warning to mothers to not breastfeed when taking codeine.

Section Summary: Selection or Dosing of Codeine
Enhanced CYP2D6 enzymatic activity is associated with risk of accelerated codeine metabolism to high levels of circulating morphine in UMs, which is thought to have contributed to deaths of infants of nursing mothers prescribed codeine and of pediatric patients after tonsillectomy. Few case reports have described the association between CYP2D6 variant status and risk of death. There is limited evidence about the clinical validity of testing for CYP2D6 genotype.

Selection and Dosing of Highly Active Antiretroviral Agents
Dosing of Efavirenz
Current guidelines recommend efavirenz as a preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for HIV-infected patients. Forty to 70% of patients report adverse CNS events. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects. Efavirenz is primarily metabolized by the CYP2B6 enzyme, and inactivating variants are associated with higher efavirenz exposure, although plasma levels appear not to correlate with adverse events. Limited
reports suggest that CYP2B6 PMs have markedly reduced adverse events while maintaining viral immunosuppression at substantially lower doses. Simulations of such dose adjustments support this position.

Cabrera et al (2009), who evaluated in 32 patients, reported on the relation between CYP2B6 variants and efavirenz clearance. Although they reported that CYP2B6 variants could be used to account for only 27% of interindividual variability, they noted decreased clearance of 50% in the patient group with the G/T genotype and 75% with the T/T genotype. Based on this observation, they suggested a gradual reduction in efavirenz dose be considered in patients with these phenotypes. They proposed use of a model to incorporate factors that affect drug levels. However, based on the complexity of factors involved in dosing, they concluded drug treatment should be carefully evaluated using therapeutic drug monitoring and assessment of clinical efficacy.

Two other studies have been published, one evaluating 373 patients for CYP2B6 variants and constitutive androstane receptor, and one evaluating genotyping for 23 markers in 15 genes. Both demonstrated an association between markers and early efavirenz discontinuation. Both articles recommended further study to determine the clinical utility of these associations.

Lee et al (2014) evaluated the effect of CYP2B6 G516T variants on the plasma efavirenz concentrations in 171 HIV-infected patients, with or without concomitant rifampicin use. The study included 171 HIV-infected patients, including 18 (10.5%) patients with tuberculosis, 113 (66.1%) with CYP2B6 G516G, 55 (32.2%) with the GT genotype, and 3 (1.8%) with the TT genotype. Patients with GT or TT genotype had a significantly higher plasma efavirenz concentration than those with GG genotype (2.50 vs 3.47 mg/L for GT genotype; 8.78 mg/L for TT genotype; p<0.001).

Bienvenu et al (2014) evaluated the effect of single-nucleotide variants (SNVs) in 5 drug metabolizing enzymes on plasma efavirenz levels and treatment response in patients treated with efavirenz alone (n=28) and cotreated with efavirenz plus rifampicin in-based tuberculosis treatment (n=62). Serum efavirenz levels differed based on CYP1A2 genotype (T/G vs T/T) when patients were cotreated with efavirenz plus rifampicin, but not when patients only received efavirenz. High serum efavirenz levels were associated with CYP2B6 516T/T genotype, both with and without rifampicin in treatment. CYP2B6 5167/T and 9837/T genotypes predicted supratherapeutic efavirenz levels (positive predictive value, 100%), particularly in the absence of rifampicin.

Other Antiretroviral Therapies
While the preponderance of the evidence on CYP450 testing for antiretroviral therapies has focused on efavirenz, there has been some investigation of pharmacogenomic testing for other antiretroviral therapies. In a case-control analysis of 27 patients with nevirapine-induced Stevens-Johnson syndrome induced by the non-nucleoside reverse transcriptase inhibitor nevirapine and 78 controls, Ciccacci et al (2013) found that CYP2B6 variants, but not CYP3A4 and CYP3A5, were associated with Stevens-Johnson syndrome risk. In a prospective cohort study including 66 women receiving nevirapine, Oluka et al (2015) reported that CYP2B6 genotype was associated with serum nevirapine concentration and CD4 counts. Lu et al (2014) reported that CYP3A5 variants were associated with serum concentrations of maraviroc, a CCR5 receptor antagonist used for HIV treatment, in healthy control subjects.

Section Summary: Selection and Dosing of Highly Active Antiretroviral Agents
CYP2B6 variants are associated with increased adverse events for patients treated with antiretroviral agents particularly efavirenz. Multiple small and large observational studies have shown association between CYP2B6 variants and higher efavirenz drug levels, CNS adverse events, and treatment discontinuation. Preliminary evidence from 2 studies has suggested that CYP450 variants may be associated with nevirapine-induced Stevens-Johnson syndrome.
Dosing of Immunosuppressants for Therapy for Organ Transplantation

Immunosuppressive drugs administered to organ transplant patients have a narrow therapeutic index with the consequences of rejection or toxicity. In addition, there is variability in patient response, requiring close clinical follow-up and routine therapeutic drug monitoring to maintain safety and efficacy. Results of a systematic review (2015) reported on 187 studies that have explored associations between CYP3A5 variants and clinical outcomes (nephrotoxicity, transplant rejection) or pharmacokinetic data. \(^90\) Tacrolimus blood levels were related to CYP3A5 variants, with an approximately 2.3-fold difference in daily dose required to maintain target concentrations between CYP3A5*3 and CYP3A5*1 homozygous variants. \(^91\) CYP3A5*1 carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared with noncarriers; although the overall rate of acute rejection episodes was not higher in CYP3A5*1 carriers, their rejection episodes occurred earlier. \(^92\) Studies have also reported on associations between CYP3A5 genotype and tacrolimus exposure in pediatric renal transplant recipients and the required tacrolimus dose in heart transplant recipients. \(^93\) In a 2015 systematic review and meta-analysis of 37 studies evaluating the effect of CYP3A5 variants on outcomes in kidney transplant recipients treated with tacrolimus, Rojas et al found that CYP3A5*1 carriers had significantly lower plasma tacrolimus concentrations per daily dose per body weight than carriers of the CYP3A5*3/*3 genotype. \(^94\)

Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adults and children. \(^95\), \(^96\) These models predict clearance based on CYP3A5*3/*3 genotype, as well as clinical factors, including body weight, hematocrit levels, and time since transplant. Although the developers of predictive models for tacrolimus clearance applied a number of bootstrap techniques to validate their models, they did not perform an independent clinical validation of their models and concluded “a prospective study in a larger number of patients is warranted to evaluate the clinical benefits of individualizing tacrolimus dosage in the immediate post-transplantation period on the basis of a pretransplant determination of CYP3A5 polymorphism.”

Passey et al (2011) used tacrolimus blood trough and dose information from 681 kidney transplant recipients to develop a predictive tool for tacrolimus apparent clearance, from which individual tacrolimus dosing could be extrapolated. \(^97\) The study’s final model included CYP3A5 genotype, along with other clinical factors, but was not validated in an independent population. In a subsequent study, Boughton et al evaluated the previously-developed model in a single-center cohort of renal transplant recipients. \(^98\) The (2013) found a weak correlation (R=0.431) between clearance based on dose-normalized tacrolimus trough concentrations and the algorithm-predicted clearance.

Less evidence is available for other immunosuppressants, such as sirolimus and cyclosporine. Xue et al (2014) developed a pharmacokinetic predictive model based on data on cyclosporine blood trough and dose information, combined with demographics, hematologic indices, biochemical levels, concurrent drugs, and CYP3A4, CYP3A5, and ABCB1 variants, from 117 allogeneic hematopoietic cell transplant recipients. \(^99\) This model has not been validated in clinical populations.

Section Summary: Dosing of Immunosuppressant Therapy for Organ Transplantation

Individuals who express CYP3A5 (EMs, IMs) generally have decreased dose-adjusted trough concentrations of tacrolimus compared with those who do not (PMs), possibly delaying achievement of target blood concentrations. A systematic review has reported on 187 studies; reviewers showed an association between CYP3A5 variants and clinical outcomes (nephrotoxicity, transplant rejection) or pharmacokinetic data.

Selection and Management of Patients on \(\beta\)-Blockers

Several reports have indicated that lipophilic beta selective adrenergic receptor antagonists (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with CYP2D6 variants. \(^100\), \(^101\) Bijl et al (2009), in a population-based cohort study of 1553 patients,
noted an increased risk of bradycardia in patients found to be PMs (CYP2D6*4/*4). Wojtczak et al (2014) analyzed the association between CYP2D6 variants and metoprolol concentration in a cohort of 50 patients. Patients with PM genotypes had significantly higher plasma metoprolol concentrations (mean, 92.25 ng/mL) than patients with EM genotypes (mean, 168.22 ng/mL; p<0.000). However, the clinical consequences are uncertain. Other studies have not demonstrated similar associations. Baudhuin et al (2010) studied the relation between CYP2D6, ADRB1, and UGT1A1 variants and response in 93 heart failure patients treated with metoprolol or carvedilol; they observed no differences according to genotype. Similarly, Wu et al (2015) reported no significant associations between CYP2D6 variants and treatment outcomes (systolic blood pressure decrease of ≥10 mm Hg) in 93 patients with hypertension treated with metoprolol.

In a subanalysis of the MERIT-HF trial, Batty et al (2014) evaluated the role of variants in the CYP2D6 locus in metoprolol pharmacokinetics and clinical response. In the study population of 605 subjects, serum metoprolol concentrations were inversely associated with the number of functional CYP2D6 alleles; median serum metoprolol concentrations were 2.1- and 4.6-fold greater in the IM and PM groups, compared with the EM group, respectively (p<0.000). During dose titration, EMs had a smaller mean reduction in heart rate from baseline compared with IMs (7.9 vs 10.5 at 4 weeks, p=0.02; 9.7 vs 13.2 after 6 weeks, p=0.01).

Section Summary: Selection and Management of Patients on β-Blockers

Multiple large cohort studies and reanalysis of data from an RCT have suggested that CYP2D6 variants may be associated with impaired β-blocker metabolism, resulting in higher blood levels causing adverse events such as bradycardia. However, other studies, notably with smaller samples, have refuted such associations.

Dosing and Management of Antitubercular Medications

A number of studies have reported an association between CYP2E1 status and the risk of liver toxicity from antitubercular medications. Wang et al (2016) on reported a meta-analysis of 26 studies (total N=7423 participants) evaluating the association between CYP2E1 variants and susceptibility to antitubercular drug-induced hepatotoxicity. The overall odds favored an association between the CYP2E1 Rsal/PstI C1/C1 genotype and an elevated risk of liver toxicity (OR=1.32; 95% CI, 1.03 to 1.69; p=0.027), but not for the DraI variant (OR=1.05; 95% CI, 0.80 to 1.37; p=0.748). A meta-analysis of 17 available trials was reported by Deng et al (2012). Compared with wild-type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR=1.36; 95% CI, 1.09 to 1.69). Patients who were slow metabolizers had the highest risk of toxicity (OR=1.88, 95% CI, 1.14 to 3.09), and this overall risk was increased in Asian patients.

Section Summary: Dosing and Management of Antitubercular Medications

Two meta-analyses have reported that patients with CYP2E1 variant status had an increased risk of liver toxicity with antitubercular medication.

Clinical Utility

The potential clinical utility of genetic testing for CYP450 variants includes confirming a diagnosis and evaluating whether there is a modifiable treatment option that would aid in selecting and dosing of a particular drug that would lead to better outcomes compared to standard clinical management without genetic testing. Reduced activity in a particular CYP450 enzyme because of genotype may not affect outcomes when other metabolic pathways are available and when other confounders influence drug metabolism. Therefore, prospective studies of clinical utility are important to validate hypotheses generated by association studies. However, few prospective studies of genotype-directed dosing or drug choice have been conducted, and none has supported genotype-directed decision making.

Direct evidence of clinical utility would be provided by studies comparing health outcomes for patients managed with and without the test. Preferred evidence comes from RCTs.
Selection and Dosing of Clopidogrel

So et al (2016) reported on 102 patients undergoing PCI for ST-elevation myocardial infarction who received point of care testing for CYP2C19*2, ABCB1 TT, and CYP2C19*17 alleles. Of these, 59 tested as carriers and 43 as noncarriers. The 59 carriers were then randomized to prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg daily for 6 days and subsequently 75 mg daily). The noncarriers received clopidogrel with dosing as per treating physician. Thus, this study did not evaluate the clinical utility of genetic testing because patients were not randomized to management by genetic testing and to standard clinical management. The primary end point was proportion of patients with P2Y12 reaction unit (PRU) greater than 234 (a measure of high on-treatment platelet reactivity). Baseline platelet function testing showed that carriers compared to noncarriers had a higher mean PRU levels (183.5, SD=90.6 vs 147.3, SD=84.7, respectively, p=0.040). The proportion patients with PRU greater than 234 in the 3 groups—carriers randomized to prasugrel, carriers randomized to clopidogrel, and noncarriers who received clopidogrel as per treating physician—was 0%, 24%, and 5%, respectively. The difference between prasugrel-treated carriers and augmented clopidogrel-treated carriers was statistically significant (p=0.005) but not between prasugrel-treated carriers and clopidogrel-treated noncarriers (p=0.507). During 1-month follow-up, no major adverse cardiovascular events were observed among randomized patients. The number of patients with thrombolysis in myocardial infarction major and minor bleeding in the 3 groups (prasugrel, augmented clopidogrel, and clopidogrel as per treating physician) were 1 (3.3%), 1 (3.3%), and 1 (3.4%), and 0% (2.4%) and 5% (11.6%), respectively. Thus, this study showed that treatment of high-risk carriers with prasugrel resulted in a significant reduction in high on-treatment platelet reactivity after 1 month compared to augmented dosing of clopidogrel. Treatment of noncarriers with clopidogrel would suggest that it may be adequate among the vast majority of subjects who do not possess an at-risk genotype.

Shen et al (2016) reported results of a retrospective study of 628 Chinese patients with coronary artery disease who had undergone successful PCI. Patients were divided into routine group (n=319) and a CYP2C19 genetic testing group (n=309). The study did not report how patients were selected for genetic testing or how controls were selected. As such, methodologic limitations restrict the conclusions drawn from these data. Individuals in the genetic testing group were classified as EMs, IMs, and PMs according to CYP2C19 genotype. The EM group received clopidogrel 75 mg daily, IM group received clopidogrel 150 mg daily, and PM group received ticagrelor 90 mg twice daily. Routine group was treated with clopidogrel 75 mg daily conventionally. The primary end points were defined as major adverse cardiovascular events (composite of death from any cause, MI, or target vessel revascularization). All 628 patients were followed for an average of 12 months and clinical outcomes were analyzed at 1, 6, and 12 months after discharge. The percentage of patient that achieved the primary end point in genetic testing group was lower than in the routine group at 1, 6, and 12 months (1.3% vs 5.6%, p=0.003; 3.2% vs 7.8%, p=0.012; 4.2% vs 9.4%, p=0.010), respectively. No significant differences in the rates of bleeding were found between the 2 groups (p>0.05).

In 2012, Roberts et al reported on 200 patients randomized to use of a point-of-care test for the CYP2C19*1C to determine treatment or to standard treatment. In the tested group, carriers were given prasugrel 10 mg daily. Noncarriers and all patients in the control group were given clopidogrel 75 mg per day. The primary end point was high on-treatment platelet reactivity. In the group with genotyping, none of the 23 carriers had high on-treatment platelet reactivity; in the group receiving standard treatment, 30% of 23 carriers had high on-treatment platelet reactivity. These trialists concluded that rapid genotyping with subsequent personalized treatment reduced the number of carriers treated who exhibited high on-treatment reactivity. They also noted that alternative approaches using either phenotyping or a combination of phenotyping and genotyping might optimize treatment decision making.

Desai et al (2013) reported results of a study of antiplatelet therapy prescribing behavior for 499 patients with a recent acute coronary syndrome or PCI who underwent CYP2C19 genotyping. Among the 146 (30%) subjects with at least one CYP2C19 reduced-function allele, although
providers were more likely to increase antiplatelet therapy intensification than for noncarriers, only 20% had their clopidogrel dose changed or switched to prasugrel.

An RCT, the POPular Genetics study (NCT01761786), was designed to compare a strategy of antiplatelet therapy directed by CYP2D19 genotype with routine care with prasugrel or ticagrelor in patients undergoing PCI. Initial results (2014) describing the feasibility of CYP2D19 genotyping have been presented in abstract form, but no published study results were identified.

Section Summary: Clinical Utility for Selection and Dosing of Clopidogrel
The clinical utility of genetic testing for CYP450 for selection and dosing of clopidogrel for clinically meaningful outcomes has not been demonstrated. One RCT has shown that rapid genotyping with subsequent personalized treatment reduced the number of carriers treated who exhibit high on-treatment platelet reactivity compared to those managed without genetic testing. Another RCT has shown that treatment of high-risk carriers with prasugrel resulted in a significant reduction in high on-treatment platelet reactivity after 1 month compared to augmented dosing of clopidogrel. The same trial also showed that clopidogrel may be adequate for vast majority of patients who do not possess an at-risk genotype. Another study showed that, in patients with a recent acute coronary syndrome or PCI who underwent CYP2C19 genotyping, providers were more likely to increase antiplatelet therapy intensification for carriers than for noncarriers. A small proportion (20%) of the carriers had their clopidogrel dose changed or switched to prasugrel. More evidence is needed to refine optimal use of testing and to understand the relative merit of management options better.

Dosing of Immunosuppressant for Organ Transplantation
Based on observations that patients with CYP3A5 variants require higher tacrolimus doses to achieve a therapeutic trough concentration (C₀), Thervet et al (2010) conducted an RCT to compare the proportion of tacrolimus-treated renal transplant patients within a targeted C₀ range for 2 tacrolimus dosing strategies—CYP3A5 genotype-informed dosing and standard dosing. The trial included 280 patients, 140 who received standard dosing and 140 who received CYP3A5 genotype-specific dosing. The genotype-directed therapy group was more likely to achieve the trial’s primary outcome (proportion of patients with tacrolimus C₀ in the target range after 6 oral doses) than the control group (43.2% [95% CI, 36% to 51.2%] vs 29.1% [95% CI, 22.8% to 35.5%]; p=0.030), respectively. The genotype-directed therapy group had fewer dose adaptations (281 vs 420; p=0.004). Graft function and survival were similar between groups.

Section Summary: Clinical Utility Dosing of Immunosuppressant for Organ Transplantation
The clinical utility of CYP450 testing for dosing of tacrolimus has not been demonstrated. One RCT demonstrated that the use of a CYP3A5 genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges; no differences in mortality or morbidity or graft survival were reported, which the authors attributed to a patient population at low risk of acute rejection or other clinical events. Additional studies of the clinical utility of CYP3A5 testing–based algorithms in tacrolimus management are needed.

Selection and Dosing for Eliglustat, Tetrabenazine, Selective Serotonin Reuptake Inhibitors, SNRIs, TCAs, Antipsychotic Drugs, Codeine, Highly Active Antiretroviral Agents, β-Blockers, and Antitubercular Medications
In general, most published CYP450 pharmacogenomic studies for eliglustat, tetrabenazine, SSRIs, SNRIs, TCAs, antipsychotic drugs, codeine, highly active antiretroviral agents, β-blockers, and antitubercular medications, if available, are retrospective evaluations of CYP450 genotype associations, reporting intermediate outcomes (e.g., circulating drug concentrations) or less often, final outcomes (e.g., adverse events or efficacy). Many of the studies are small and underpowered. Clinical utility depends on whether the use of CYP450 genotyping improves on existing clinical decision making process to guide dose or drug selection, which will then translate into improvement in patient outcomes. However, in many of these cases, the
association between genetic variants and phenotypes has not been conclusively established or, when established, are not clinically meaningful. Although establishing improved outcomes compared to existing clinical practices could be demonstrated with clinical trials, the expected difference in outcomes would probably be so small that the trial sample size would be impractically large. No studies identified evaluated whether a testing strategy for CYP450 variant improves health outcomes for these drugs.

**Summary of Evidence**

For individuals with need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence includes multiple systematic reviews, secondary analyses of a randomized controlled trial (RCT) and multiple observational studies. Relevant outcomes are test accuracy and validity, change in disease status, morbidity events, and treatment-related mortality and morbidity. Multiple observational studies have reported that genetic variants associated with CYP2C19 may be associated with a modest increase in the rate of stent thrombosis and increased incidence of adverse clinical events. However, 2 large meta-analysis that included patients treated with and without percutaneous coronary intervention showed conflicting results of the impact of CYP2C19 variants on clinical outcomes. The evidence addressing whether the use of CYP2C19 genotype-directed therapy improves clinically meaningful outcomes is limited. RCTs have shown that rapid genotyping with subsequent personalized treatment reduces the number of carriers who exhibit high on-treatment platelet reactivity compared to those managed without genetic testing. A prospective cohort study reported that, in patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent CYP2C19 genotyping, providers were more likely to increase intensity of antiplatelet therapy for carriers than for noncarriers. A randomized, prospective study comparing the clinical utility of genetic testing versus standard clinical management is required to understand the relative merit of management options better. Given the association between CYP2C19 metabolizer status and risk of stent thrombosis in patients undergoing cardiac interventions, genotype may be used to consider treatment alternatives (e.g., higher doses of clopidogrel or alternative drug choices). The U.S. Food and Drug Administration (FDA) created a black box warning indicating testing should be considered. Clinical input from academic medical centers and specialty societies was mixed concerning the benefit of genetic testing, but there was not consensus that the medically necessary determination be changed. However, since clinical input was obtained and the black box labeling was created, additional evidence has suggested that CYP2C19 genotype is not associated with differences in the magnitude of benefit for patients treated with clopidogrel. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with Gaucher disease type 1 who are undergoing or being considered for treatment with eliglustat who receive testing for CYP2D6 metabolizer status by CYP2D6 genotyping, the evidence includes subgroup analysis of clinical trial data submitted to the FDA by the manufacturer as part of regulatory submission. Relevant outcomes are test accuracy and validity, morbidity events, medication use, and treatment-related morbidity. Eliglustat tartrate is primarily metabolized by the CYP2D6 enzyme. The FDA review reported that, at doses as high of 200 mg twice daily, the exposure in ultrarapid metabolizers (UMs) was about 57% and about 82% lower than the exposures for extensive metabolizers and intermediate metabolizers at 100 mg twice daily, respectively. Based on this high variation in drug exposure based on metabolizer status, the FDA label requirement for genotyping of CYP2D6 to determine metabolizer status before the use of eliglustat may be clinically reasonable and UM be excluded from being prescribed eliglustat because these patients may not achieve adequate concentrations for therapeutic effect. Although there is no published evidence about outcome changes associated with genotype-directed therapy for this medication, there are changes in management that are likely to occur with differences in genotypes that may be associated with improved health outcomes. The evidence is sufficient to determine the effects of the technology on health outcomes.
For individuals with Huntington disease who are undergoing or being considered for treatment with tetrabenazine who receive testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence consists of a single cohort study. Relevant outcomes are test accuracy and validity, morbid events, medication use, and treatment-related morbidity. The FDA labeling for the orphan drug tetrabenazine for Huntington disease recommends CYP2D6 genotyping before use. There is limited published evidence about outcome changes associated with genotype-directed therapy for this medication. One cohort study has reported that patients categorized as UMs by a CYP450 genotype test require a high dose of tetrabenazine compared to those who are not. However, this finding was based in a sample of 127 patients of whom only 2 were categorized as UMs. Therefore, these findings must be reproduced in a larger cohort. The evidence is insufficient to determine the effects of the technology on health outcomes.

Although the evidence is limited on the use of CYP2C19 genotyping in patients undergoing or being considered for treatment with tetrabenazine, given the FDA labeling and the potential for high variation in drug exposure based on metabolizer status, genotyping of CYP2D6 to determine metabolizer status before use of tetrabenazine may be clinically reasonable. CYP2C19 may be considered medically necessary in patients with Huntington disease being considered for treatment with tetrabenazine at a dosage greater than 50 mg per day.

For individuals who are undergoing or being considered for treatment with selective serotonin reuptake inhibitors who receive CYP450 genotyping, the evidence includes 1 systematic review and multiple retrospective and prospective studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple retrospective and prospective studies have evaluated the association between selective serotonin reuptake inhibitors and CYP450 variants and reported conflicting results. Based on a systematic review of the evidence, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group concluded that the evidence was insufficient to support a recommendation for or against use of CYP450 testing in adults beginning selective serotonin reuptake inhibitor treatment for nonpsychotic depression. At present, the clinical utility of CYP450 testing is also poorly defined. It is not known if CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with serotonin-norepinephrine reuptake inhibitors who receive CYP450 genotyping, the evidence includes post hoc reanalysis of several RCTs. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Post hoc reanalysis of data from multiple RCTs has correlated treatment response to venlafaxine with genetic status. However, the clinical utility of CYP450 testing is poorly defined. It is not known if CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with tricyclic antidepressants who receive CYP450 genotyping, the evidence includes multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. These studies have shown that poor metabolizers have high serum concentrations of tricyclic antidepressants drugs and extensive metabolizers have low serum concentrations. However, the observed differences are unlikely to have clinically important effects. At present, the clinical utility of CYP450 testing is poorly defined. It is not known whether CYP450 genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who are undergoing or being considered for treatment with antipsychotic drugs who receive CYP450 genotyping, the evidence includes 1 systematic review and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Observational studies have suggested that individuals with genetic variants in the CYP450 gene may be at increased risk for adverse events from antipsychotic drugs, particularly the extrapyramidal effects such as tardive dyskinesia. However, a large systematic review and meta-analysis of 47 studies found no convincing evidence of an association between test results and either drug efficacy or toxicity. When seen, adverse event differences (an association, e.g., with tardive dyskinesia) were considered too small to be clinically meaningful. At present, the clinical utility of CYP2D6 testing is poorly defined. It is not known whether CYP450 genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with codeine who receive CYP450 genotyping, the evidence includes few case reports. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related mortality and morbidity. Enhanced CYP2D6 enzymatic activity is associated with risk of accelerated codeine metabolism to high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post tonsillectomy. In addition, the American Academy of Pediatrics has recommended that codeine should never be used in children under 12. There is limited evidence on the clinical validity of testing for CYP450 genotype. At present, the clinical utility of CYP2D6 testing is poorly defined. It is not known whether CYP450 genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents who receive CYP450 genotyping, the evidence includes multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple small and large observational studies have shown associations between CYP450 variants and higher drug levels, central nervous system adverse events, and treatment discontinuation. At present, the clinical utility of CYP450 testing is also defined. It is not known whether CYP450 genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with immunosuppressant therapy for organ transplantation who receive CYP450 genotyping, the evidence includes multiple systematic reviews and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related mortality and morbidity. Multiple observational studies, including a large systematic review, have shown that individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus compared with those who do not (poor metabolizers), possibly delaying achievement of target blood concentrations. The evidence addressing whether the use of CYP450 genotype-directed therapy improves clinically meaningful outcomes is limited. One RCT has demonstrated that the use of a CYP450 genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges; no differences in morbidity or mortality or graft survival were reported. Additional studies of the clinical utility of CYP450...
genetic testing–based algorithms in tacrolimus management are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with β-blockers who receive CYP450 genotyping, the evidence includes multiple retrospective cohort studies and reanalysis of a RCT. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple large cohort studies and reanalysis of data from an RCT has suggested that CYP450 variants may be associated with impaired metabolism to β-blocker treatment, resulting in higher blood levels causing adverse events such as bradycardia. However, other studies, notably with smaller samples have refuted such associations. At present, the clinical utility of CYP2B6 testing is poorly defined. It is not known whether CYP450 genotype–guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with antitubercular medications who receive CYP450 genotyping, the evidence includes 2 meta-analysis. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Two meta-analyses have reported that patients with CYP450 variants had an increased risk of liver toxicity with antitubercular medication. At present, the clinical utility of CYP450 testing is poorly defined. It is not known whether CYP450 genotype–guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information
Clinical Input from Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 4 physician specialty societies and 4 academic medical centers in 2012. Opinions on use of genotyping for testing in patients being considered for clopidogrel treatment were mixed, with 5 suggesting the test be considered investigational and 3 suggesting it be considered medically necessary.

Practice Guidelines and Position Statements
A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010. The recommendations for practice included the following statements:

1. Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient...
2. Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
3. The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined....
4. Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of
the specific test, as well as the issue of reimbursement, is both important additional considerations.

5. The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time....

6. There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for cytochrome P450 have been identified.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

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<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>Effects and Cost-Effectiveness of Pharmacogenetic Screening Among Elderly Starters With Antidepressants: A Pragmatic Randomized Controlled Trial</td>
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<td>NCT01878513</td>
<td>Prospective Cytochrome P450 Genotyping and Clinical Outcomes in Patients With Psychosis</td>
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<td>Mar 2019</td>
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<td>NCT01742117&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI)</td>
<td>5270</td>
<td>Mar 2020</td>
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NCT: national clinical trial.
<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

Appendix

Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.38

<table>
<thead>
<tr>
<th>Category</th>
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<td>1. Testing of an affected individual's germline to benefit the individual</td>
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<tr>
<td>1a. Diagnostic</td>
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<tr>
<td>1b. Prognostic</td>
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<tr>
<td>1c. Therapeutic</td>
<td>X</td>
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<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
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<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
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<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
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<tr>
<td>4. Testing of an affected individual's germline to benefit family members</td>
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<tr>
<td>5. Reproductive testing</td>
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<tr>
<td>5a. Carrier testing: preconception</td>
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<tr>
<td>5b. Carrier testing: prenatal</td>
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<tr>
<td>5c. In utero testing: aneuploidy</td>
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<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
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<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
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</tbody>
</table>
References


55. Macaluso M, Preskorn SH. CYP 2D6 PM status and antidepressant response to nortriptyline and venlafaxine: is it more than just drug metabolism? J Clin Psychopharmacol. Apr 2011;31(2):143-145. PMID 21346604


78. King J, Aberg J A. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS. Sep 12 2008;22(14):1709-1717. PMID 18753940


110. So DY, Wells GA, McPherson R, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with STElevation...
myocardial infarction: the RAPID STEMI study. Pharmacogenomics J. Feb 2016;16(1):71-78. PMID 25850030

**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Reason for performing test
  - Signs/symptoms/test results related to reason for genetic testing
  - How test result will impact clinical decision making
  - Diagnosis being considered for treatment

- Physician order for genetic test
  - Name and description of genetic test
  - Name of laboratory that performed the test
  - Any available evidence supporting the clinical validity/utility of the specific test
  - CPT codes billed for the particular genetic test

**Post Service**

- Laboratory report including: specific name and test requested

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.
<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0028U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis <strong>(Code effective 1/1/2018)</strong></td>
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<td>0029U</td>
<td>Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) <strong>(Code effective 1/1/2018)</strong></td>
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<td>0031U</td>
<td>CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7) <strong>(Code effective 1/1/2018)</strong></td>
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<td>81225</td>
<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *8, *17)</td>
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<td>81227</td>
<td>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)</td>
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<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variant(s) (e.g., *2, *22) <strong>(Code effective 1/1/2018)</strong></td>
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<td>CYP3A5 (cytochrome P450 family 3 subfamily A member 5) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *7) <strong>(Code effective 1/1/2018)</strong></td>
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<td>81402</td>
<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 3</td>
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<td>81404</td>
<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 5</td>
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<td>81405</td>
<td>MOLECULAR PATHOLOGY PROCEDURE LEVEL 6</td>
</tr>
</tbody>
</table>

**Policy History**

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
</table>
| 10/01/2010     | New policy Combined the following BSC policies:  
• Cytochrome p450 Genotyping  
• Genetic Testing for Initial Warfarin Dose with BCBSA Medical Policy adoption | Medical Policy Committee |
| 03/12/2012     | Coding Update | Administrative Review |
| 02/22/2013     | Coding Update | Administrative Review |
| 04/04/2014     | Policy revision with position change Coding Update | Medical Policy Committee |
| 05/29/2015     | Coding update | Administrative Review |
| 03/01/2016     | Policy title change from Pharmacogenomics Policy revision with position change effective 5/1/2016 | Medical Policy Committee |
### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.