

## Cytochrome p450 Genotyping

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**Policy Number:**

MM.02.004

**Line(s) of Business:**

HMO; PPO; QUEST Integration

**Section:**

Medicine

**Place(s) of Service:**

Laboratory

**Original Effective Date:**

04/01/2011

**Current Effective Date:**

07/27/2018

### I. Description

The cytochrome p450 (CYP450) family is involved in the metabolism of a significant proportion of currently administered drugs, and genetic variants in cytochrome p450 are associated with altered metabolism of many drugs. Genetic testing for cytochrome p450 variants may assist in selecting and dosing drugs that are impacted by these genetic variants.

#### Clonidogrel

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clonidogrel therapy who receive testing for CYP2C19 metabolizer status by CYP2C19 genotyping, the evidence includes 2, randomized controlled trials (RCTs). Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of CYP2C19 genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with on-treatment high platelet reactivity between genotype-guided management or standard treatment with clonidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clonidogrel as well as they did to prasugrel, and physician-directed clonidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI) assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes.

#### Other Drugs

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation,  $\beta$ -blockers, or antitubercular medications who receive CYP450 genotyping, the evidence includes retrospective studies. Relevant outcomes are medication use and treatment-related morbidity. In general, most published CYP450 pharmacogenomic studies for these drugs consist of 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 these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

## II. Criteria/Guidelines

- A. CYP450 genotyping is covered (subject to Limitations and Administrative Guidelines) once per lifetime for the purpose of aiding in the choice of clopidogrel (Plavix) versus alternative anti-platelet agents, or in decisions on the optimal dosing of clopidogrel.
- B. CYP450 genotyping is covered (subject to Limitations and Administrative Guidelines) once per lifetime to determine drug metabolizer status for patients:
  1. With Gaucher disease being considered for treatment with eliglustat; or
  2. With Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day

## III. Limitations

- A. 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 not covered, including but not limited to the following applications:
  1. Selection of dosing of-codeine
  2. Dosing of efavirenz and other antiretroviral therapies for HIV
  3. Dosing of immunosuppressant for organ transplantation
  4. Selection or dose of beta blockers (e.g., metoprolol)
  5. Dosing and management of anti-tubercular medications
- B. CYP450 genotyping for CYP2C19 and CYP2D6 is limited to once per lifetime.
- C. CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, is not covered.
- D. The use of genetic panels that include multiple CYP450 mutations, or other conditions are not covered as they are not know to be effective in improving long term health outcomes.

## IV. Administrative Guidelines

Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

CPT	Description
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
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)

81401	<p>Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) includes:</p> <ul style="list-style-type: none"> <li>• CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6)</li> <li>• CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6)</li> </ul>
81402	<p>Molecular pathology procedure, Level 3 (e.g., &gt;10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) includes:</p> <ul style="list-style-type: none"> <li>• 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)</li> </ul>
81404	<p>Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes:</p> <ul style="list-style-type: none"> <li>• CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (e.g., primary congenital glaucoma), full gene sequence</li> </ul>
81405	<p>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes:</p> <ul style="list-style-type: none"> <li>• CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence</li> <li>• CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence</li> <li>• CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence</li> </ul>
<b>ICD-10 Codes</b>	<b>Description</b>
E75.22	Gaucher disease
G10	Huntington's disease
I20.0	Intermediate coronary syndrome (unstable angina)
I21.01-I22.9	Acute myocardial infarction code range
I24.1	Post-myocardial infarction syndrome (Dressler's syndrome)

I2511.0	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I63.50-I63.549	Occlusion and stenosis of cerebral arteries, resulting in cerebral infarction, code range
I66.01-I66.9	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction, code range
I73	Other peripheral vascular disease

## REGULATORY STATUS

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Some tests are offered as in-house laboratory-developed test services, which do not require FDA approval but which must meet Clinical Laboratory Improvement Act (CLIA) quality standards for high complexity testing.

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

Device Name	Manufacturer	Approval Date
xTAG Cyp2d6 Kit V3	Luminex Molecular Diagnostics	2017
xTAG Cyp2c19 Kit V3	Luminex Molecular Diagnostics	2013
Spartan Rx Cyp2c19 Test System	Spartan Bioscience	2013
xTAG Cyp2d6 Kit V3 (Including Tdas Cyp2d)	Luminex Molecular Diagnostics	2013
Verigene Cyp2c19 Nucleic Acid Test (2c19)	Nanosphere	2012
Infiniti Cyp2c19 Assay	Autogenomics	2010
xTAG Cyp2d6 Kit V3, Model I030c0300 (96)	Luminex Molecular Diagnostics	2010
Invader Ugt1a1 Molecular Assay	Third Wave Technologies	2005
Roche AmpliChip Cyp450 Test	Roche Molecular Systems	2005

Several manufacturers market panels of diagnostic genotyping tests for CYP450 genes, such as the YouScript Panel (Genelex Corporation, Seattle, WA), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4 and CYP3A5. Other panel tests include both CYP450 genes and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health, Inc., Mason, OH); these tests are beyond the scope of this policy.

## V. Scientific Background

### Genetics Nomenclature Update

The Human Genome Variation Society 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). The Society's nomenclature is recommended by the Human Variome Project, the HUMAN Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to 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**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

### 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.

Multiple 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 studies 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 events, 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,  $\beta$ -blockers, antiarrhythmics, antidepressants, 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 the 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 (EMs; 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.

Ultrarapid 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. Also, the interaction between different metabolizing genes, the 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 for drugs with a very narrow therapeutic range and/or potentially serious adverse events outside that range. However, therapeutic drug monitoring 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) may be 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. 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.

### **Regulatory Status**

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Some tests are offered as in-house laboratory-developed test services, which do not require FDA approval but which must meet Clinical Laboratory Improvement Act (CLIA) quality standards for high complexity testing.

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

<b>Device Name</b>	<b>Manufacturer</b>
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xTAG Cyp2c19 Kit V3	Luminex Molecular Diagnostics
Spartan Rx Cyp2c19 Test System	Spartan Bioscience

xTAG Cyp2d6 Kit V3 (Including Tdas Cyp2d)	Luminex Molecular Diagnostics
Verigene Cyp2c19 Nucleic Acid Test (2c19)	Nanosphere
Infiniti Cyp2c19 Assay	Autogenomics
xTAG Cyp2d6 Kit V3, Model I030c0300 (96)	Luminex Molecular Diagnostics
Invader Ugt1a1 Molecular Assay	Third Wave Technologies
Roche AmpliChip Cyp450 Test	Roche Molecular Systems

Several manufacturers market panels of diagnostic genotyping tests for CYP450 genes, such as the YouScript Panel (Genelex Corporation, Seattle, WA), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4 and CYP3A5. Other panel tests include both CYP450 genes and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health, Inc., Mason, OH); these tests are beyond the scope of this policy.

### **FDA Labeling on CYP450 Genotyping**

FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, FDA has given clear and specific directives on either use of a specific dose (e.g., eliglustat, tetrabenazine) or when a drug may not be used at all (e.g., codeine) and therefore evidence in such cases is not reviewed in the Rationale section.

#### **Eliglustat**

The FDA has approved eliglustat for treatment of adults with Gaucher disease type 1 who are CYP2D6 EMs, intermediate metabolizers, or PMs as detected by an FDA-cleared test. Further, the label acknowledges the limitation of use among UMs because they may not achieve adequate concentrations and a specific dosage was not recommended for patients with indeterminate CYP2D6 metabolizer's status. Further, the label states that the dosing strategy should be 84 mg orally, twice daily for CYP2D6 EMs or intermediate metabolizers and 84 mg orally, once daily for CYP2D6 PMs. FDA has included a black box to warn about the reduced effectiveness in PMs and to advise healthcare professionals to consider alternative dosing or to use of other medications in patients identified as potential PMs.<sup>1</sup>

#### **Tetrabenazine**

FDA has approved tetrabenazine for the treatment of chorea associated with Huntington disease. According to the label, patients requiring doses above 50 mg/d should be genotyped for the drug-metabolizing enzyme CYP2D6 to determine if the patient is a PM or EM. For patients categorized as PMs using an FDA-approved test, the maximum daily dose should not exceed 50 mg, with a maximum single dose of 25 mg.<sup>2</sup>

#### **Codeine**

FDA does not recommend genotyping before prescribing codeine. FDA has contraindicated codeine for treating pain or cough in children under 12 years of age and codeine is not recommended for use in adolescents ages 12 to 18 that are obese or have conditions such as obstructive sleep apnea or severe lung disease. There is an additional warning to mothers not to breastfeed when taking codeine.

#### **Rationale**

This evidence review was created in April 2005 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through April 9, 2018.

The primary goal of pharmacogenomics testing and personalized medicine is to achieve better clinical outcomes in compared with the standard of care. Drug response varies greatly between individuals, and genetic factors are known to play a role. However, in most cases, the genetic variation only explains a modest portion of the variance in the individual response because clinical outcomes are also affected by a

wide variety of factors including alternate pathways of metabolism and patient- and disease-related factors that may affect absorption, distribution, and elimination of the drug. Therefore, assessment of clinical utility cannot be made by a chain of evidence from clinical validity data alone. In such cases, evidence evaluation requires studies that directly demonstrate that the pharmacogenomic test alters clinical outcomes; it is not sufficient to demonstrate that the test predicts a disorder or a phenotype.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **P450 Genotype-Guided Treatment Strategy**

#### **Clinical Context and Therapy Purpose**

The purpose of a P450 genotype-guided strategy is to tailor selection and dosing of drugs based on 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 question addressed in this evidence review is: Does P450 genotype-guided strategy change patient management in a way that improves net health outcome?

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, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotic drugs, codeine, efavirenz and other antiretroviral therapies for HIV infection, immunosuppressants for organ transplantation,  $\beta$ -blockers (e.g., metoprolol), and antitubercular medications.

#### **Interventions**

Commercial tests for individual genes or gene 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 following practice is currently being used: standard clinical management without genetic testing.

#### **Outcomes**

Specific outcomes of interest are listed in Table 2.

**Table 2. Outcomes of Interest for Individuals with Altered Drug Metabolism**

Drug	Outcomes
Clopidogrel	<ul style="list-style-type: none"> <li>• Initial and maintenance dose selection</li> <li>• Decrease in platelet reactivity</li> <li>• Myocardial infarction, cardiovascular or all-cause death, revascularization, fatal/nonfatal cerebrovascular accident, aortic event</li> </ul>
Highly active antiretroviral agents	<ul style="list-style-type: none"> <li>• Dose selection</li> <li>• Avoidance of treatment failure</li> <li>• Avoidance or reduction of adverse events</li> </ul>
Immunosuppressant therapy for organ transplantation	<ul style="list-style-type: none"> <li>• Dose selection</li> <li>• Avoidance of organ failure</li> <li>• Avoidance or reduction of adverse events</li> </ul>
$\beta$ -blocker(s)	<ul style="list-style-type: none"> <li>• Dose selection</li> <li>• Superior control of blood pressure</li> <li>• Avoidance or reduction of adverse events due to overtreatment</li> </ul>
Antitubercular medications	<ul style="list-style-type: none"> <li>• Dose selection</li> <li>• Avoidance or reduction of hepatotoxicity due to overtreatment</li> </ul>

**Timing**

Outcomes in the first 3 months are relevant because the interest is in whether P450 genotype-guided strategy reduces adverse events or avoids treatment failure.

**Setting**

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

**Clopidogrel**

Dual antiplatelet therapy with aspirin and a P2Y<sub>12</sub> inhibitor (clopidogrel, prasugrel, ticagrelor) is the standard of care for the prevention of subsequent atherothrombotic events such as stent thrombosis or recurrent acute coronary syndrome in patients who undergo a percutaneous intervention or who have an acute coronary syndrome.

Clopidogrel is a prodrug that is converted to its active form by several CYP450 enzymes (particularly CYP2C19). Individuals with genetic variants that inactivate the CYP2C19 enzyme are associated with lack of response to clopidogrel. There are several variants of CYP2C19 but the 2 most frequent variants associated with loss of function alleles are CYP2C19\*2 and CYP2C19\*3. It is hypothesized that such individuals may benefit from other drugs such as prasugrel or ticagrelor or a higher dose of clopidogrel. Approximately 30% of whites and blacks and 65% of Asians carry a nonfunctional CYP2C19 gene variant.<sup>4</sup> While CYP2C19 is the major enzyme involved in the generation of clopidogrel active metabolite, the variability in clinical response seen with clopidogrel may also result from other factors such as variable absorption, accelerated platelet turnover, reduced CYP3A metabolic activity, increased adenosine diphosphate exposure, or upregulation of P2Y<sub>12</sub> pathways, drug-drug interactions, comorbidities (e.g., diabetes, obesity), and medication adherence.

Multiple observational studies in patients undergoing percutaneous coronary intervention (PCI) have reported associations between the presence of loss of function alleles and lower levels of active clopidogrel metabolites, high platelet reactivity, and increased risk of adverse cardiovascular events. However, evidence of publication bias has been reported in these studies where smaller studies have reported larger benefits than larger studies which have reported no effect or a smaller effect.<sup>5</sup> Wang et al

(2016) reported post hoc analysis of the CHANCE trial conducted in China; it randomized patients with a transient ischemic attack or minor stroke to clopidogrel plus aspirin or aspirin alone. In a subgroup analysis of patients who did not have the loss of function alleles, clopidogrel plus aspirin vs aspirin alone was associated with statistical significant reduction in the risk of stroke (6.7% vs 12.4%; hazard ratio, 0.51; 95% confidence interval, 0.35 to 0.75) but not among those who carried loss of function alleles (9.4% vs 10.8%; hazard ratio, 0.93; 95% confidence interval, 0.69 to 1.26).<sup>6</sup> Results of this analysis have contributed to the formulation of the hypothesis of a differential effect of clopidogrel in patients with and without loss of function alleles.

Trials are important to validate such hypotheses. However, only a few trials of genotype-directed dosing or drug choice have been conducted; they are summarized in Tables 3 and 4 and discussed next. It is important to note that these trials use “high on-treatment platelet reactivity” as the outcome measure. Patients who exhibit “high on-treatment platelet reactivity” are referred to as being nonresponsive, hyporesponsive, or resistant to clopidogrel in the published literature.

Roberts et al (2012) reported on the results of RCT that allocated patients undergoing PCI for acute coronary syndrome or stable angina to genotype-guided management to select for treatment with prasugrel (carriers) or clopidogrel (noncarriers) or to standard treatment with clopidogrel.<sup>7</sup> Among those who received prasugrel and clopidogrel based on genotyping test, 0% and 10%, respectively, exhibited high on-treatment reactivity while 17% patients who received standard treatment with clopidogrel without any genotypes testing exhibited high on-treatment reactivity. This difference was not statistically significant. So et al (2016) reported on the results of an RCT that randomized ST-elevation myocardial infarction patients who were carriers of *CYP2C19\*2*, *ABCB1* TT, and *CYP2C19\*17* alleles to prasugrel 10 mg daily or an augmented dosing strategy of clopidogrel (150 mg/d for 6 days and subsequently 75 mg/d).<sup>8</sup> Results showed that (1) carriers did not respond to augmented clopidogrel as well as they did to prasugrel (24% patients with high platelet reactivity vs 0%) and (2) among noncarriers, physician-directed clopidogrel was effective for most patients (95% did not have high platelet reactivity).

**Table 3. Summary of Key RCT Characteristics**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
So et al (2016) <sup>8</sup> ; RAPID STEMI	Canada	1	2011-2012	18-75 y who had PCI for STEMI who received POC testing for <i>CYP2C19*2</i> , <i>ABCB1</i> TT, and <i>CYP2C19*17</i> alleles (N=102)	Carriers randomized to prasugrel 10 mg/d (n=30) or augmented clopidogrel (150 mg/d for 6 d and then 75 mg/d) (n=29)	Noncarriers given clopidogrel with dosing as per treating physician (n=43)
Roberts et al (2012) <sup>7</sup> ; RAPID GENE	Canada	1	2010-2011	18-75 y undergoing PCI for acute coronary syndrome or stable angina (n=200)	POC testing for <i>CYP2C19*2</i> allele (n=102). Of these, 23 carriers were given prasugrel 10 mg/d, and 74 noncarriers were given clopidogrel 75 mg/d	No genetic testing and clopidogrel 75 mg/d

PCI: percutaneous coronary intervention; POC: point of care; RCT: randomized controlled trial ; STEMI: ST-elevation myocardial infarction.

**Table 4. Summary of Key RCT Results**

Study; Trial	High Platelet Reactivity <sup>a</sup>
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So et al (2016) <sup>8</sup> ; RAPID STEMI	102
Carriers	
Prasugrel	0% <sup>d</sup>
Augmented clopidogrel	24% <sup>d</sup>
Noncarriers	
Clopidogrel as per treating physician	5% <sup>d</sup>
p	0.0046 <sup>b</sup> ; 0.507 <sup>c</sup>
Roberts et al (2012) <sup>7</sup> ; RAPID GENE	187
Genotype-guided management	
Prasugrel 10 mg/d	0%
Clopidogrel 75 mg/d	10%
Entire cohort	10%
Standard clinical management	
Clopidogrel 75 mg/d	17% <sup>e</sup>
p	NS

<sup>a</sup> P2Y12 reaction unit >234 (a measure of high on-treatment platelet reactivity).

<sup>b</sup> Prasugrel vs augmented clopidogrel.

<sup>c</sup> Prasugrel vs physician-directed clopidogrel.

<sup>d</sup> At 30 days.

<sup>e</sup> At 1 week.

The purpose of the gaps tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of the evidence supporting the position statement. The studies were, in general, well-designed and -conducted, the major limitation being the use of platelet activity, which is an intermediate outcome measure, and lack of reporting on health endpoints over a longer follow-up.

Platelet reactivity during treatment is an intermediate end point that has been shown to have a limited value in guiding therapeutic decisions based on results of the large ARTIC RCT.<sup>9,10</sup> Briefly, the ARCTIC trial randomized 2440 patients scheduled for coronary stenting to platelet-function monitoring or no monitoring. Platelet-function testing was performed in the monitored group both before and 14 to 30 days after PCI. Multiple therapeutic changes, including an additional loading dose of clopidogrel (at a dose  $\geq 600$  mg) or a loading dose of prasugrel (at a dose of 60 mg) before the procedure, followed by a daily maintenance dose of clopidogrel 150 mg or prasugrel 10 mg, were made according to a predefined protocol. There was no difference in the rate of the primary composite end point (death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) at 1 year between the monitoring (34.6%) and no monitoring groups (31.1%). In the absence of results from well-performed randomized trials designed to evaluate this issue, performing routine genetic testing or ex vivo tests of platelet reactivity to predict CYP2C19 metabolic state and identify PMs has not been shown to improve health clinical outcomes. TAILOR-PCI (NCT01742117) is a large ongoing RCT that will randomize 5270 patients undergoing PCI to clopidogrel without prospective genotyping guidance or a prospective CYP2C19 genotype-based antiplatelet therapy approach (ticagrelor 90 mg bid in CYP2C19\*2 or CYP2C19\*3 reduced function allele patients, clopidogrel 75 mg once daily in non-CYP2C19\*2 or -CYP2C19\*3 patients). The trial is expected to be completed in March 2020.

**Table 5. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
So et al (2016) <sup>8</sup> ; RAPID STEMI				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms not reported	1, 2. Outcomes assessed at 1 mo
Roberts et al (2012) <sup>7</sup> ; RAPID GENE				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms no reported	1, 2. Outcomes assessed at 1 wk

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 6. Study Design and Conduct Gaps**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Power <sup>d</sup>	Statistical <sup>f</sup>
So et al (2016) <sup>6</sup> ; RAPID STEMI						
Roberts et al (2012); RAPID GENE <sup>7</sup>	3. Allocation concealment unclear					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> Statistical key: 1. Intervention is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Intervention is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

### Section Summary: Clopidogrel

Two RCTs have evaluated the role of genetic testing for CYP2C19 for selecting appropriate antiplatelet treatment and/or amplified dosing of clopidogrel using an intermediate outcome measure of platelet reactivity to predict CYP2C19 metabolic state. One RCT has shown there was no statistical difference in patients with “on-treatment high platelet reactivity” who received genotype-guided management or standard treatment with clopidogrel. The second RCT showed that carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, while physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap.

### Selection and Dosing of Other Drugs

#### Antiretroviral Agents

Efavirenz is a widely used non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for patients with HIV infection. However, unpredictable interindividual variability in efficacy and toxicity remain important limitations associated with its use. Forty percent to 70% of patients have reported adverse central nervous system events. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse events.<sup>11</sup> Efavirenz is primarily metabolized by the CYP2B6 enzyme, and inactivating variants such as CYP2B6\*6 are associated with higher efavirenz exposure, although plasma levels appear not to correlate with adverse events. On the other hand, CYP2B6 PMs have markedly reduced adverse events while maintaining viral immunosuppression at substantially lower doses.<sup>12,13</sup> An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple CYP450 variants including CYP2B6.<sup>14,15</sup> CYP2B6 G516T and T983C single nucleotide variants were reported by Ciccacci et al (2013) to be associated with susceptibility to Stevens-Johnson syndrome in a case-control study of 27 patients who received nevirapine-containing antiretroviral treatment.<sup>16</sup> The current

evidence documenting the usefulness of CYP450 variant genotyping to prospectively guide antiretroviral medications and assess its impact on clinical outcomes is lacking.

### **Immunosuppressants for Therapy for Organ Transplantation**

Tacrolimus is the mainstay immunosuppressant drug and multiple studies have shown that individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus, possibly delaying achievement of target blood concentrations compared with those who are CYP3A5 nonexpressers (PMs) in whom drug levels may be elevated and possibly result in nephrotoxicity. The current evidence demonstrating the impact of CYP3A5 genotyping to guide tacrolimus dosing and its impact on clinical outcomes is a limited RCT by Thervet et al (2010).<sup>17</sup> This RCT compared the impact of CYP3A5 genotype-informed dosing with standard dosing strategies on tacrolimus drug levels. The trial was not powered to assess any clinical outcomes such as graft function or survival, which otherwise were similar between groups.

### **βeta-Blockers**

Several reports have indicated that lipophilic β-blockers (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with CYP2D6 variants.<sup>18,19</sup> The current evidence documenting the usefulness of CYP2D6 genotyping to prospectively guide antitubercular medications and assess its impact on clinical outcomes is lacking.

### **Antitubercular Medications**

A number of studies, summarized in a systematic review by Wang et al (2016), have reported an association between CYP2E1 status and the risk of liver toxicity from antitubercular medications.<sup>20</sup> The current evidence documenting the usefulness of CYP2E1 genotyping to prospectively guide antitubercular medications and assess its impact on clinical outcomes is lacking.

### **Section Summary: Selection and Dosing of Other Drugs**

In general, most published CYP450 pharmacogenomic studies for highly active antiretroviral agents, β-blockers, and antitubercular medications 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 these studies are small, underpowered, and hypothesis generating. Prospective intervention studies, including RCTs documenting clinical usefulness of CYP450 genotyping to improve existing clinical decision-making to guide dose or drug selection, which will then translate into improvement in patient outcomes, were not identified.

## **SUMMARY OF EVIDENCE**

### **Clopidogrel**

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a *CYP2C19*-guided treatment strategy, the evidence includes 2 RCTs. Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of *CYP2C19* genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with on-treatment high platelet reactivity between genotype-guided management or standard treatment with clopidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, and physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict *CYP2C19* metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes.

## Other Drugs

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation,  $\beta$ -blockers, or antitubercular medications who receive a *CYP2C19*-guided treatment strategy, the evidence includes retrospective studies. Relevant outcomes are medication use and treatment-related morbidity. In general, most published *CYP450* pharmacogenomic studies for these drugs consist of 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 these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of *CYP450* genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. 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, input was received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. Opinions on use of genotype testing of 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 the selection and dosing of clopidogrel was published in 2010.<sup>21</sup> 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. In the absence of a national coverage determination, 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 7.

**Table 7. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
NCT01761786	Cost-effectiveness of Genotype Guided Treatment With Antiplatelet Drugs in STEMI Patients: Optimization of Treatment (POPular Genetics)	2700	April 2019
NCT01742117 <sup>a</sup>	Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention (TAILOR-PCI)	5270	Mar 2020

## VI. References

1. Genzyme. Highlights of Prescribing Information: Cerdelga (eliglustat). 2014; [http://www.cerdelga.com/pdf/cerdelga\\_prescribing\\_information.pdf](http://www.cerdelga.com/pdf/cerdelga_prescribing_information.pdf). Accessed May 24, 2018.
2. Food and Drug Administration. Highlights of Prescribing Information: Xenazine (tetra benazine). 2015; [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2015/021894s010lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/021894s010lbl.pdf). Accessed May 24, 2018.
3. FDA statement from Douglas Throckmorton, M.D., deputy center director for regulatory programs, Center for Drug Evaluation and Research, on new warnings about the use of codeine and tramadol in children & nursing mothers. 2017; <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm553285.htm> Accessed May 24, 2018.
4. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for CYP2C19 genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther.* Sep 2013;94(3):317-323. PMID 23698643
5. Holmes MV, Perel P, Shah T, et al. CYP2C19 genotype, clopidogrel metabolism, platelet function, and cardiovascular events: a systematic review and meta-analysis. *JAMA.* Dec 28 2011;306(24):2704-2714. PMID 22203539
6. Wang Y, Zhao X, Lin J, et al. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA.* Jul 5 2016;316(1):70-78. PMID 27348249
7. Roberts JD, Wells GA, Le May MR, et al. Point-of-care genetic testing for personalisation of antiplatelet treatment (RAPID GENE): a prospective, randomised, proof-of-concept trial. *Lancet.* May 5 2012;379(9827):1705-1711. PMID 22464343
8. So DY, Wells GA, McPherson R, et al. A prospective randomized evaluation of a pharmacogenomic approach to antiplatelet therapy among patients with ST-elevation myocardial infarction: the RAPID STEMI study. *Pharmacogenomics J.* Feb 2016;16(1):71-78. PMID 25850030
9. Collet JP, Cuisset T, Range G, et al. Bedside monitoring to adjust antiplatelet therapy for coronary stenting. *N Engl J Med.* Nov 29 2012;367(22):2100-2109. PMID 23121439

10. Montalescot G, Range G, Silvain J, et al. High on-treatment platelet reactivity as a risk factor for secondary prevention after coronary stent revascularization: A landmark analysis of the ARCTIC study. *Circulation*. May 27 2014;129(21):2136-2143. PMID 24718568
11. King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. *AIDS*. Sep 12 2008;22(14):1709-1717. PMID 18753940
12. Torno MS, Witt MD, Saitoh A, et al. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. *Pharmacotherapy*. Jun 2008;28(6):782-787. PMID 18503405
13. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 \*6 and \*26. *Clin Infect Dis*. Nov 1 2007;45(9):1230-1237. PMID 17918089
14. Wyen C, Hendra H, Siccardi M, et al. Cytochrome P450 2B6 (CYP2B6) and constitutive androstane receptor (CAR) polymorphisms are associated with early discontinuation of efavirenz-containing regimens. *J Antimicrob Chemother*. Sep 2011;66(9):2092-2098. PMID 21715435
15. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *J Infect Dis*. Jan 15 2011;203(2):246-257. PMID 21288825
16. Ciccacci C, Di Fusco D, Marazzi MC, et al. Association between CYP2B6 polymorphisms and Nevirapine-induced SJS/TEN: a pharmacogenetics study. *Eur J Clin Pharmacol*. Nov 2013;69(11):1909-1916. PMID 23774940
17. Thervet E, Lorient MA, Barbier S, et al. Optimization of initial tacrolimus dose using pharmacogenetic testing. *Clin Pharmacol Ther*. Jun 2010;87(6):721-726. PMID 20393454
18. Bijl MJ, Visser LE, van Schaik RH, et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta-blocker users. *Clin Pharmacol Ther*. Jan 2009;85(1):45-50. PMID 18784654
19. Yuan H, Huang Z, Yang G, et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. *J Int Med Res*. Nov-Dec 2008;36(6):1354-1362. PMID 19094446
20. Wang FJ, Wang Y, Niu T, et al. Update meta-analysis of the CYP2E1 RsaI/PstI and DraI polymorphisms and risk of antituberculosis drug-induced hepatotoxicity: evidence from 26 studies. *J Clin Pharm Ther*. Jun 2016;41(3):334-340. PMID 27062377
21. Holmes DR, Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *J Am Coll Cardiol*. Jul 20 2010;56(4):321-341. PMID 20633831.
22. BCBSA Medical Policy Reference Manual. Cytochrome p450 Genotyping #2.04.38. Last reviewed June 2018.