

2.04.38 Cytochrome P450 Genotype-Guided Treatment Strategy

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Policy Statement

Note: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene.

- I. Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered **medically necessary** for individuals with either of the following conditions:
 - A. Gaucher disease being considered for treatment with eliglustat
 - B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day
 - C. With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with siponimod
- II. 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**
- III. 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 (see Policy Guidelines):
 - A. Selection or dosage of codeine
 - B. Dosing of efavirenz and other antiretroviral therapies for HIV infection
 - C. Dosing of immunosuppressants for organ transplantation
 - D. Selection or dosing of β -blockers (e.g., metoprolol)
 - E. Dosing and management of antitubercular medications
- IV. The use of genetic testing panels that include multiple CYP450 variants is considered **investigational**.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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

- 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

The Food and Drug Administration maintains a database of pharmacogenomic biomarkers in drug labeling. See section "Regulatory Status" for details.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals

understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

The following are specific CPT coding for this testing:

- **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)

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)

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

- **81402:** Molecular pathology procedure, Level 3 (e.g., >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 –
 - *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 (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 –
 - *CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1)* (e.g., primary congenital glaucoma), full gene sequence
- **81405:** 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 –
 - *CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1)* (e.g., congenital adrenal hyperplasia), full gene sequence
 - *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 isoform, congenital adrenal hyperplasia), full gene sequence

PLA codes include:

- **0029U:** Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) (Focused Pharmacogenomics Panel)
- **0031U:** CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7) (Cytochrome P450 1A2 Genotype)

PLA codes include:

- **0070U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
- **0071U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
- **0072U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
- **0073U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)
- **0074U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
- **0075U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication)
- **0076U:** CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/multiplication)

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

- N/A

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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Diagnostic genotyping tests for certain CYP450 enzymes are available under the auspices of the Clinical Laboratory Improvement Amendments.

Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 cleared for marketing by the FDA (FDA product code: NTI) are summarized in Table 1.

Table 1. Selected Testing Kits for *CYP450* Genotyping Cleared for Marketing by FDA

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

FDA: Food and Drug Administration.

Several manufacturers market diagnostic genotyping panel tests for *CYP450* genes, such as the YouScript Panel (Genelex Corp.), 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) and PersonaGene Genetic Panels (AlBioTech). These tests are beyond the scope of this evidence review.

FDA Labeling on *CYP450* Genotyping

The 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, the 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. The 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.¹

Tetrabenazine

The 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.²

Codeine

The FDA does not recommend genotyping before prescribing codeine. The 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 who 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.³

Rationale

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 technology improves the net health outcome. Broadly defined, health outcomes are the 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 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 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.

CYP450 Genotype-guided Treatment Strategy

Clinical Context and Therapy Purpose

The purpose of a cytochrome P450 (*CYP450*) 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 *CYP450* genotype-guided strategy change patient management in a way that improves net health outcome?

The following PICO was used to select literature to inform this review.

Populations

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

Review of Evidence**Clopidogrel****Randomized Controlled Trials**

Dual antiplatelet therapy with aspirin and a P2Y₁₂ 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.⁶ 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 P2Y₁₂ 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 smaller effect.⁷ Wang et al (2016) reported post hoc analysis of the

Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events 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 versus aspirin alone was associated with statistical significant reduction in the risk of stroke (6.7% vs. 12.4%; hazard ratio [HR], 0.51; 95% confidence interval [CI], 0.35 to 0.75) but not among those who carried loss of function alleles (9.4% vs. 10.8%; HR, 0.93; 95% CI, 0.69 to 1.26).⁸ 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 an 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.⁹ Among those who received prasugrel and clopidogrel based on genotyping test, 0% and 10%, respectively, exhibited high on-treatment platelet reactivity while 17% patients who received standard treatment with clopidogrel without any genotypes testing exhibited high on-treatment platelet 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 per day for 6 days and subsequently 75 mg per day).¹⁰ 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).

Claassens et al (2019)¹¹ reported on the results of the CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment (POPular Genetics) trial. In this non-inferiority trial, patients with acute coronary syndrome were randomly assigned to receive standard treatment (prasugrel or ticagrelor) or genotype-guided treatment (clopidogrel in those without *CYP2C19* loss-of-function variants; standard treatment otherwise). Results of the primary combined endpoint met the P value for non-inferiority. Thus, one can conclude that a genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. However, the trial results do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, there was no difference in the incidence of PLATO major bleeding between the genotype-guided group and the standard-treatment group (2.3% in both groups; HR, 0.97; 95% CI, 0.58 to 1.63). The statistically significant difference observed in the primary bleeding outcome was primarily driven by PLATO minor bleeding events in the genotype-guided group versus standard-treatment group (7.6% vs. 10.5%; HR, 0.72; 95% CI, 0.55 to 0.94).

Pereira et al (2021) reported the results of the open-label randomized TAILOR-PCI trial of 5302 patients undergoing PCI for acute coronary syndromes or stable coronary artery disease.¹² The genotype-guided group underwent point-of-care genotyping for detection of *CYP2C19* carriers and were prescribed ticagrelor (prasugrel was recommended as an alternative for patients who did not tolerate ticagrelor) and noncarriers were prescribed clopidogrel. Patients randomized to the conventional group were prescribed clopidogrel and underwent genotyping after 12 months. Among 5302 patients randomized (median age, 62 years; 25% women), 94% completed

the trial. Of 1849 *CYP2C19* carriers, 764 of 903 (85%) assigned to genotype-guided therapy received ticagrelor, and 932 of 946 (99%) assigned to conventional therapy received clopidogrel. The primary end point (a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months) occurred in 35 of 903 *CYP2C19* carriers (4.0%) in the genotype-guided therapy group and 54 of 946 (5.9%) in the conventional therapy group at 12 months (HR, 0.66; 95% CI, 0.43 to 1.02; $p=.06$). None of the 11 prespecified secondary end points showed significant differences, including major or minor bleeding in *CYP2C19* carriers in the genotype-guided group (1.9%) versus the conventional therapy group (1.6%) at 12 months (HR, 1.22; 95% CI, 0.60 to 2.51; $p=.58$). Among all randomized patients, the primary end point occurred in 113 of 2641 (4.4%) in the genotype-guided group and 135 of 2635 (5.3%) in the conventional group (HR, 0.84; 95% CI, 0.65 to 1.07; $p=.16$). The trial failed to meet the pre-specified end point and the authors contend that the trial was underpowered to detect an effect size less than the 50% relative risk after a revised sample calculation. Despite the occurrence of 89 ischemic events observed in this trial, which exceeded the 76 events anticipated to provide adequate power, the observed relative risk reduction was 34% instead of the estimated 50%, hence a borderline p value of .056 was observed. Further, the authors also comment that the potential benefit of genotype-guided oral P2Y12 inhibitor therapy may be important early after PCI rather than 12 months after PCI. A post-hoc analysis of the data from the trial showed that a nearly 80% reduction in the rate of adverse events occurred in the first three months of treatment among patients who received genetically guided therapy compared with those who did not.

Table 3. Summary of Key Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
So et al (2016)¹⁰; RAPID STEMI	Canada	1	2011-2012	18-75 y who had PCI for STEMI who received POC testing for <i>CYP2C19</i> *2, <i>AB</i> <i>CB1</i> TT, and <i>CYP2C19</i> *17 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)⁹; 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</i> *2 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
Claassens et al (2019)¹¹; POPular Genetics	Europe	10	2011-2018	21 y or older with signs and symptoms of STEMI undergoing PCI (n=2488)	Genotype-guided group: Individuals received clopidogrel (non-carriers) or prasugrel/ticagrelor (carriers) for one year	Prasugrel/ticagrelor or for one year
Pereira et al (2021)¹²; TAILOR PCI	US, Canada, South Korea, and Mexico	40	2013-2018	Adult undergoing PCI for ACS or stable CAD (n=5302).	Genotype-guided therapy group using POC genotyping. <i>CYP2C19</i> carriers were prescribed ticagrelor for maintenance therapy, and noncarriers or those with inconclusive results were prescribed clopidogrel. Prasugrel	Conventional therapy group without prospective genotyping. All were prescribed clopidogrel according to drug label (n=2650 randomized; n=2635 eligible for

Study; Trial	Countries	Sites	Dates	Participants	Interventions
					was recommended as an alternative for patients who did not tolerate ticagrelor (n=2653 randomized; n=2641 eligible for analysis; n=903 CYP2C19 carriers identified and included in primary analysis).

PCI; Percutaneous coronary intervention; POC; point of care; STEMI; ST-elevation myocardial infarction
 POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an Individualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an Individualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

Table 4. Summary of Key Randomized Controlled Trial Results

Study; Trial	Outcome
	High Platelet Reactivity^a
So et al (2016) ¹⁰ ; RAPID STEMI	102
Carriers	
Prasugrel	0% ^d
Augmented clopidogrel	24% ^d
Noncarriers	
Clopidogrel as per treating physician	5% ^d
p	.0046 ^b ; .507 ^c
Roberts et al (2012) ⁹ ; 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% ^e
p	NS
Claassens et al (2019) ¹¹ ; POPular Genetics	Primary Combined Outcome ^f
Genotype-guided management (n=1242)	63 (5.1%)
Standard-treatment group (n=1246)	73 (5.9%)
Absolute difference (95% CI); p	0.7 (-2.0 to 0.7); <.001 for noninferiority
	Primary Bleeding Outcome ^g
Genotype-guided management (n=1242)	122 (9.8%)
Standard-treatment group (n=1246)	156 (12.5%)
Hazard ratio (95% CI); p	0.78 (0.61 to 0.98); .04
Pereira et al (2021) ¹² ; TAILOR PC	Primary Combined Outcome ^h
Genotype-guided management (n=903)	35 (4%)
Conventional therapy (n=946)	54 (5.9%)
Difference in 12-month event rates, % (95% CI)	-1.8 (-3.9 to 0.1)
Hazard ratio (95% CI) ; p	0.66 (0.43 to 1.02) ;.06
	Secondary Combined Outcome ⁱ
Genotype-guided management (n=903)	16 (1.9%)
Conventional therapy (n=946)	14 (1.6%)
Difference in 12-month event rates, % (95% CI)	0.3 (-0.9 to 1.6)
Hazard ratio (95% CI) ; p	1.22 (0.60 to 2.51) ;.58

POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an Individualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an Individualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

CI: confidence interval; NS: not significant.

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

^b Prasugrel vs. augmented clopidogrel.

^c Prasugrel vs. physician-directed clopidogrel.

^d At 30 days.

^e At 1 week.

^f Death from any cause, myocardial infarction, definite stent thrombosis, stroke, or major bleeding as defined by Platelet Inhibition and Patient Outcomes (PLATO) criteria at 12 months

^g PLATO major bleeding (coronary artery bypass graft [CABG]-related and non-CABG-related) or minor bleeding at 12 months (primary bleeding outcome)

^h Cardiovascular death, myocardial infarction, stroke, severe recurrent ischemia, stent thrombosis

Major or minor bleeding as defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria. The purpose of the limitation tables (see Tables 5 and 6) is to display notable limitations 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 endpoint that has been shown to have a limited value in guiding therapeutic decisions based on results of the large Assessment by a Double Randomization of a Conventional Antiplatelet Strategy Versus a Monitoring-Guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption Versus Continuation One Year After Stenting (ARCTIC) RCT.^{13,14} 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 ≥ 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 endpoint (death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization) at 1 year between the monitoring (34.6%) and no monitoring groups (31.1%). Further, an adequately powered TAILOR-PCI RCT reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent PCI, genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. Limitations of this trial included the possibility of being underpowered when sample size calculations were revised, some patients not receiving designated antiplatelet therapy and the open-label nature of the trial. However, the adjudication of all events was blinded.

Table 5. Study Relevance Limitations

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
So et al (2016) ¹⁰ ; 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) ⁹ ; RAPID GENE				2. Platelet activity is an intermediate outcome measure 3. CONSORT harms no reported	1, 2. Outcomes assessed at 1wk

Study	Population ^a	Intervention ^b	Comparator ^c	Outcomes ^d	Follow-Up ^e
Claassens et al (2019);¹¹; POPular Genetics	2. Clinical context is unclear	2. Not standard or optimal			
Pereira et al (2021)¹²; TAILOR PC		2. Version used unclear (some patients not receiving designated antiplatelet therapy)			

POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

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

^a 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.

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

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

^d 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.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation ^a	Blinding ^b	Selective Reporting ^d	Data Completeness ^e	Power ^d	Statistical ^f
So et al (2016)¹⁰; RAPID STEMI						
Roberts et al (2012)⁹; RAPID GENE	3. Allocation concealment unclear					
Claassens et al (2019);¹¹; POPular Genetics		1. Not blinded to treatment assignment;				
Pereira et al (2021)¹²; TAILOR PC		1. Not blinded to treatment assignment				

POPular Genetics: Cost-effectiveness of CYP2C19 Genotype Guided Treatment With Antiplatelet Drugs in Patients With ST-segment-elevation Myocardial Infarction Undergoing Immediate PCI With Stent Implantation: Optimization of Treatment; RAPID GENE: ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy Based on GENetic Evaluation; RAPID STEMI: ReAssessment of Anti-Platelet Therapy Using an InDividualized Strategy in Patients With ST-segment Elevation Myocardial Infarction.

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

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

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

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d 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).

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

^f 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

Four 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. The third non-inferiority RCT compared showed that genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. Results of this trial do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, the statistical significant difference observed in favor of genotype guided strategy for bleeding outcome was primarily driven by minor bleeding events. There was no difference in the incidence of major bleeding between the 2 groups. Results of TAILOR-PCI reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent PCI, genotype-guided selection of an oral P2Y₁₂ inhibitor compared with conventional clopidogrel therapy.

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.¹⁵ 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* poor metabolizers have markedly reduced adverse events while maintaining viral immunosuppression at substantially lower doses.^{16,17} An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple *CYP450* variants including *CYP2B6*.^{18,19} *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.²⁰ 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 (poor metabolizers) 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 includes RCTs by Thervet et al (2010)²¹, and Min et al (2018).²² Both RCTs compared the impact of *CYP3A5* genotype-informed dosing with standard dosing strategies on tacrolimus drug levels. The trials were not powered to assess any clinical

outcomes such as graft function or survival, which otherwise were similar between groups in Thervet et al (2010).²¹

b-Blockers

Several reports have indicated that lipophilic b-blockers (e.g., metoprolol), used in treating hypertension, may exhibit impaired elimination in patients with *CYP2D6* variants.^{23,24} 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.²⁵ 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, b-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

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 3 RCTs. Relevant outcomes are overall survival, medication use, and treatment-related morbidity. Four 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. The third non-inferiority RCT compared showed that genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. Results of this trial do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, the statistical significant difference observed in favor of genotype guided strategy for bleeding outcome was primarily driven by minor bleeding events. There was no difference in the incidence of major bleeding between the 2 groups. Results of TAILOR-PCI reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent PCI, genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. A meta-analysis that included 7 RCTs (15,949 patients) comparing clopidogrel versus alternative (prasugrel or ticagrelor) demonstrated that ticagrelor or prasugrel compared with clopidogrel significantly reduced ischemic events in *CYP2C19* carriers but not in noncarrier patients with coronary artery disease after PCI. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 that the technology results in an improvement in the net health outcome.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation

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 2010.²⁶ 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

No relevant ongoing or unpublished studies that might influence this review were identified.

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Documentation for Clinical Review

Please provide the following documentation:

- 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 including but not limited to specific drugs being considered for treatment
 - Diagnosis being considered for treatment
 - Name and description of genetic test
 - Name of laboratory that performed the test
 - CPT codes billed for the particular genetic test

Post Service (in addition to the above, please include the following):

- 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.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
	0029U	Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (i.e., CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823)
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7)
	0070U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, common and select rare variants (i.e., *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *xN)
	0071U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)
	0072U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene)
	0073U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure))
	0074U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., non-duplicated gene when duplication/multiplication is trans)
	0075U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication)
	0076U	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/ multiplication)
	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)

Type	Code	Description
	81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
	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)
	81402	Molecular Pathology Procedure Level 3
	81404	Molecular Pathology Procedure Level 5
	81405	Molecular Pathology Procedure Level 6
HCPCS	None	

Policy History

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

Effective Date	Action
10/01/2010	New policy Combined the following BSC policies: <ul style="list-style-type: none"> Cytochrome p450 Genotyping Genetic Testing for Initial Warfarin Dose with BCBSA Medical Policy adoption
03/12/2012	Coding Update
02/22/2013	Coding Update
04/04/2014	Policy revision with position change Coding Update
05/29/2015	Coding update
03/01/2016	Policy title change from Pharmacogenomics Policy revision with position change effective 5/1/2016
05/01/2016	Policy revision with position change
08/01/2017	Policy revision without position change
02/01/2018	Coding update
05/01/2018	Coding update
08/01/2018	Policy title change from Cytochrome p450 Genotyping Policy revision without position change
10/01/2018	Coding update
08/01/2019	Policy revision without position change
03/01/2020	Coding update
08/01/2020	Annual review. No change to policy statement. Literature review updated.
08/01/2021	Annual review. No change to policy statement. Literature review updated.
08/01/2022	Annual review. Policy statement, guidelines and literature updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of

services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.

Appendix A

POLICY STATEMENT	
BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
<p>Cytochrome P450 Genotype-Guided Treatment Strategy 2.04.38</p> <p>Policy Statement: Note: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene.</p> <p>Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered medically necessary for patients with either of the following conditions:</p> <ul style="list-style-type: none"> A. Gaucher disease being considered for treatment with eliglustat B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day <p>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.</p> <p>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 (see Policy Guidelines):</p> <ul style="list-style-type: none"> A. Selection or dosage of codeine B. Dosing of efavirenz and other antiretroviral therapies for HIV infection C. Dosing of immunosuppressants for organ transplantation D. Selection or dosing of β-blockers (e.g., metoprolol) E. Dosing and management of antitubercular medications 	<p>Cytochrome P450 Genotype-Guided Treatment Strategy 2.04.38</p> <p>Policy Statement: Note: Cytochrome P450 is a family of proteins (enzymes) including several genes (CYPs). The letters that follow CYP indicate a subfamily of gene.</p> <ul style="list-style-type: none"> I. Cytochrome P450 2D6 (CYP2D6) genotyping to determine drug metabolizer status may be considered medically necessary for individuals with either of the following conditions: <ul style="list-style-type: none"> A. Gaucher disease being considered for treatment with eliglustat B. Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day C. With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with siponimod II. 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. III. 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 (see Policy Guidelines): <ul style="list-style-type: none"> A. Selection or dosage of codeine B. Dosing of efavirenz and other antiretroviral therapies for HIV infection C. Dosing of immunosuppressants for organ transplantation D. Selection or dosing of β-blockers (e.g., metoprolol) E. Dosing and management of antitubercular medications

POLICY STATEMENT

BEFORE Red font: Verbiage removed	AFTER Blue font: Verbiage Changes/Additions
The use of genetic testing panels that include multiple CYP450 variants is considered investigational .	IV. The use of genetic testing panels that include multiple CYP450 variants is considered investigational .