MEDICAL POLICY

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**4/1/2025**

I. POLICY

CYP2D6 genotyping to determine drug metabolizer status may be considered **medically necessary** for members:

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

CYP2C9 genotyping to determine drug metabolizer status may be considered **medically necessary** for members:

- 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 (Mayzent ®)

CYP2C19 genotyping for the purpose of aiding in the choice of clopidogrel (Plavix®), versus alternative anti-platelet agents may be considered **medically necessary** for select members in high-risk clinical scenarios. (See Policy Guidelines)

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**, aside from determinations in the separate cross-referenced policies:

- Selection or dosing of codeine; **or**
- Dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection; **or**
- Dosing of immunosuppressants for organ transplantation; **or**
- Selection or dosing of β blockers (e.g., metoprolol); **or**
- Dosing and management of antitubercular medications.

There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this testing for these indications.

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

The use of genetic testing panels that include multiple *CYP450* variants is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these testing panels.

Policy Guidelines

This policy does not address the use of genetic panel testing that include tests for genes other than *CYP450*-related genes (e.g., the Genecept Assay), which are discussed in **MP 2.264 Genetic Testing for Mental Health Conditions**.

Clinical guidelines from the American College of Cardiology Foundation/American Heart Association and European Society of Cardiology recommend against routine *CYP2C19* testing. However, these groups have noted that use of *CYP2C19* testing to guide selection of prasugrel or ticagrelor in *CYP2C19* IMs and PMs may be considered in select patients undergoing PCI and with ACS at high risk for poor outcomes (e.g., urgent PCI for an ACS event, elective PCI for unprotected left main disease or last patent coronary artery).

The current evidence does not support a clopidogrel dose escalation strategy based on *CYP2C19* genotype.

Genetics Nomenclature Update

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

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

Table PG1. Nomenclature to Report on variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Associated Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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.

Genetic Counseling

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

Cross-References:

MP 2.218 Pharmacogenomic and Metabolite Markers for Patients with Inflammatory Bowel Disease Treated with Thiopurines
MP 2.264 Genetic Testing for Diagnosis and Management of Mental Health Conditions
MP 2.307 Genotype-Guided Tamoxifen Treatment
MP 2.306 Genotype-Guided Warfarin Dosing

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

Drug Efficacy and Toxicity

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

Drug efficacy and toxicity vary substantially across individuals. Plasma drug levels can vary more than 1000-fold when the same drug dose is administered to two individuals having approximately the same weight. 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. Drug-drug interactions, drug-food interactions, sex, age, disease state (i.e., renal, and hepatic function) and pregnancy can all influence variability in drug responses between patients. However, genetic factors are also likely to play a major role, since the individual response to a given pharmacologic agent is highly reproducible, 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, β-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 one active and one inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than two 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 one 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.

Specific Drugs and Genotyping

Tetrabenazine is the only US Food and Drug Administration (FDA)-approved drug for HD, indicated for the treatment of chorea associated with HD. Per the prescribing information, “before patients are given a daily dose of greater than 50 mg, they should be tested for the *CYP2D6* gene to determine whether they are poor, extensive, or intermediate metabolizers”.

Eliglustat is a glucosylceramide synthase inhibitor used in the treatment of Gaucher disease (GD). Eliglustat is indicated for the long-term treatment of adult individuals with Gaucher disease type 1 (GD1) who are *CYP2D6* normal metabolizers, intermediate metabolizers, or poor metabolizers as detected by an FDA-cleared test. Eliglustat is broken down to inactive metabolites by *CYP2D6* and, to a lesser extent, *CYP3A*. The dosage of eliglustat is based on

the individual's *CYP2D6* metabolizer status. Individuals with normal *CYP2D6* activity are termed normal metabolizers (NM), those with reduced activity are termed intermediate metabolizers (IM), and if activity is absent, poor metabolizers (PM).

Clopidogrel is commonly prescribed to reduce the risk of myocardial infarction (MI) and stroke in patients with acute coronary syndromes (ACS) and/or following percutaneous coronary intervention (PCI). Despite the availability of newer and more potent agents (i.e., prasugrel and ticagrelor), clopidogrel remains the most commonly prescribed antiplatelet drug in North America for ACS and PCI. Clopidogrel is also indicated for patients with a recent MI, recent stroke, or established peripheral arterial disease. *CYP2C19* is the most validated genetic determinant of clopidogrel response.

On the basis of available evidence and the Food and Drug Administration boxed warning, the consensus advice is that *CYP2C19* genotyping for use of clopidogrel should not be used routinely in patients with stable CAD but may be reasonable to consider in specific high-risk clinical scenarios (e.g., left main coronary artery stenting, last patent vessel PCI, complex lesions, 2-stent bifurcation treatment, prior stent thrombosis).

Multiple sclerosis is a chronic inflammatory neurological disease, and siponimod (Mayzent) is the first oral treatment option for adult patients with secondary progressive multiple sclerosis. The EMA reported the potential long-term safety implications in CYP2C9 poor metabolizer patients treated with this drug. The *CYP2C9* genotype has a significant impact on siponimod metabolism.

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. 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.

Tacrolimus is the mainstay immunosuppressant drug used after solid organ and hematopoietic stem cell transplantation. Individuals who express CYP3A5 (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus as compared with those who are CYP3A5 nonexpressers (poor metabolizers), possibly delaying achievement of target blood concentrations. At present, there is no definitive evidence to indicate that genotype-guided dosing for tacrolimus affects long-term clinical outcomes. However, there is strong evidence to support its effect on achieving target trough whole blood concentrations, which is routine clinical practice for most centers.

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. 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 (AIBioTech). 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.

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.

Siponimod
The FDA has approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a *CYP2C9*1/*3* or **2/*3* genotype is 1 mg. Siponimod is contraindicated in patients with a *CYP2C9*3/*3* genotype. The prescribing information recommends that before initiating siponimod, test patients for CYP2C9 genotype and dose accordingly.

Clopidogrel
In 2010, the US Food and Drug Administration (FDA) issued a black box warning against the use of clopidogrel in patients who are poor metabolizers, noted the availability of *CYP2C19* genetic testing to identify such patients, and suggested treatment with alternative P2Y12 inhibitors.

Codeine
The FDA does not recommend genotyping before prescribing codeine. The FDA has contraindicated codeine for treating pain or a 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.

IV. RATIONALE

TOP

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 randomized controlled trials (RCTs) and several meta-analyses. Relevant outcomes are overall

survival, medication use, and treatment-related morbidity. Several 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.

Another 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.

A non-inferiority RCT 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 statistically 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.

A single center observational study concluded that implementing *CYP2C19* genotype–guided dual anti-platelet therapy is feasible and sustainable in a real-world setting but challenging to maintain at a consistently high level of fidelity. The higher risk of major adverse cardiovascular or cerebrovascular associated with clopidogrel use in *CYP2C19* LOF allele carriers suggests that use of genotype-guided DAPT in practice may improve clinical outcomes.

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.

Large meta-analyses have shown that clopidogrel-treated patients undergoing PCI who are *CYP2C19* intermediate metabolizers have an increased risk for major adverse cardiovascular events. Randomized clinical trial and real-world implementation data in the setting of ACS and PCI support use of a genotype-guided strategy to reduce ischemic events without significantly increasing major bleeding; however, the effectiveness and safety of a genotype-guided approach remains less clear in the setting of neurovascular disease and cardiovascular indications outside the setting of ACS or PCI. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Studies have reported that increasing clopidogrel loading and/or maintenance dose is an alternative strategy to improve inhibition of platelet reactivity among CYP2C19 IMs, and to a lesser degree in PMs. However, early dose escalation studies typically only doubled the

clopidogrel maintenance dose to 150 mg/day in *CYP2C19* no function allele carriers, which has proven to be inadequate based on more rigorous recent studies demonstrating that even higher doses (225 mg/day) are required to achieve platelet inhibition among *CYP2C19* IMs at a level comparable to standard dose clopidogrel (75 mg/day) in NMs. However, a dose of 300 mg/day may be required in *CYP2C19* IMs with diabetes, and doses as high as 300 mg/day in *CYP2C19* PMs do not appear to result in a comparable degree of platelet inhibition. A meta-analysis showed significantly increased risk of MACE in CYP2C19 IMs and PMs treated with higher doses of clopidogrel compared to non-carriers of no function alleles treated with standard doses of clopidogrel (RR 1.68, 95% CI 1.19–2.37). Therefore, the current evidence does not support a clopidogrel dose escalation strategy based on *CYP2C19* genotype. There is insufficient evidence to determine that the technology results in an improvement in the net health outcome.

Other Drugs

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, b-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.

An increased early discontinuation rate with efavirenz has been reported in retrospective cohort studies evaluating multiple *CYP450* variants including *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. The current evidence documenting the usefulness of *CYP450* variant genotyping to prospectively guide antiretroviral medications and assess its impact on clinical outcomes is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

TOP

GENOTYPE refers to the pair of genes present for a particular characteristic or protein.

POLYMORPHISM refers to the state or quality of existing or occurring in several different forms.

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health

benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Investigational; therefore, not covered:

Procedure Codes								
0031U	0070U	0071U	0072U	0073U	0074U	0075U	0076U	0392U
0434U	0438U	0461U	0516U	0533U	81230	81231	81418	

Covered when medically necessary:

Procedure Codes								
81226	81227							

ICD-10-CM Diagnosis Codes	Description
E75.22	Gaucher disease
E75.27	Pelizaeus-Merzbacher disease
G10	Huntington's disease
G35	Multiple sclerosis
G36.9	Acute disseminated demyelination, unspecified
G37.8	Other specified demyelinating diseases of the central nervous system
G37.9	Demyelinating disease of central nervous system, unspecified

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

Covered when medically necessary for a diagnosis from Table 2

Procedure Codes								
81225								

Table 2

ICD-10-CM Diagnosis Codes	Description
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.81	Angina pectoris with coronary microvascular dysfunction
I20.89	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21.01	ST elevation (STEMI) myocardial infarction involving the left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I21.A1	Myocardial infection type 2
I21.A9	Other myocardial infarction type
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of the anterior wall
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of the inferior wall
I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris
I25.2	Old myocardial infarction

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

ICD-10-CM Diagnosis Codes	Description
I25.700	Atherosclerosis of coronary artery bypass graft(s), unspecified with unstable angina pectoris
I25.701	Atherosclerosis of coronary artery bypass graft(s), unspecified, with angina pectoris with documented spasm
I25.708	Atherosclerosis of coronary artery bypass graft(s), unspecified, with other forms of angina pectoris
I25.709	Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris
I25.710	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris
I25.711	Atherosclerosis of autologous vein coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.718	Atherosclerosis of autologous vein coronary artery bypass graft(s) with other forms of angina pectoris
I25.719	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris
I25.720	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.721	Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.728	Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris
I25.729	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unspecified angina pectoris
I25.730	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris
I25.731	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.738	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with other forms of angina pectoris
I25.739	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unspecified angina pectoris
I25.750	Atherosclerosis of native coronary artery of transplanted heart with unstable angina
I25.751	Atherosclerosis of native coronary artery of transplanted heart with angina pectoris with documented spasm
I25.758	Atherosclerosis of native coronary artery of transplanted heart with other forms of angina pectoris
I25.759	Atherosclerosis of native coronary artery of transplanted heart with unspecified angina pectoris
I25.760	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina

ICD-10-CM Diagnosis Codes	Description
I25.761	Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris with documented spasm
I25.768	Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris
I25.769	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I25.791	Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.798	Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris
I25.799	Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris
I25.810	Atherosclerosis of coronary artery bypass graft(s) without angina pectoris
I25.811	Atherosclerosis of native coronary artery of transplanted heart without angina pectoris
I25.812	Atherosclerosis of bypass graft of coronary artery of transplanted heart without angina pectoris
I25.82	Chronic total occlusion of coronary artery
I25.83	Coronary atherosclerosis due to lipid rich plaque
I25.84	Coronary atherosclerosis due to calcified coronary lesion
I25.89	Other forms of chronic ischemic heart disease
I25.9	Chronic ischemia heart disease, unspecified

IX. REFERENCES

TOP

1. *Genzyme. Highlights of Prescribing Information: Cerdelga (eliglustat). 2014*
2. *Food and Drug Administration. Highlights of Prescribing Information: Xenazine (tetrabenazine). 2015*
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*
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. *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*
8. *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*
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, Loriot 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. *Min S, Papaz T, Lafreniere-Roula M, et al. A randomized clinical trial of age and genotype-guided tacrolimus dosing after pediatric solid organ transplantation. Pediatr Transplant. Nov 2018; 22(7): e13285. PMID 30178515*
19. *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*

20. *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*
21. *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*
22. *Holmes DR, Jr., Dehmer GJ, Kaul S, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA.2010 Jul 20;56(4):321-41. PMID 20633831*
23. *Claassens DMF, Vos GJA, Bergmeijer TO, et al. A Genotype-Guided Strategy for Oral P2Y 12 Inhibitors in Primary PCI. N Engl J Med. Oct 24, 2019; 381(17): 1621-1631. PMID 31479209*
24. *Pereira NL, Farkouh ME, So D, et al. Effect of Genotype-Guided Oral P2Y12 Inhibitor Selection vs Conventional Clopidogrel Therapy on Ischemic Outcomes After Percutaneous Coronary Intervention: The TAILOR-PCI Randomized Clinical Trial. JAMA. Aug 25, 2020; 324(8): 761-771. PMID 32840598*
25. *Prescribing Label: Mayzent (siponimod) tablets, for oral use. 2019*
26. *Tantisira, Kelan MD, Overview of Pharmacogenomics.. Raby A, Benjamin MD (Eds), In: UpToDate. Literature review through July 2024. Updated July 5, 2024.*
27. *Highlights of Prescribing Information: Plavix, Revised 2009.*
28. *Lee CR, Luzum JA, Sangkuhl K, et al. Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2C19 Genotype and Clopidogrel Therapy: 2022 Update [published online ahead of print, 2022 Jan 16]. Clin Pharmacol Ther. 2022;10.1002/cpt.2526. doi:10.1002/cpt.2526*
29. *Xando Díaz-Villamarín, Raquel Piñar-Morales, Francisco Javier Barrero-Hernández, Alba Antúnez-Rodríguez, José Cabeza-Barrera, Rocío Morón-Romero, Pharmacogenetics of siponimod: A systematic review, Biomedicine & Pharmacotherapy, Volume 153, 2022, 113536, ISSN 0753-3322*
30. *Sibbing D, Aradi D, Alexopoulos D, et al. Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding $P2Y_{12}$ Receptor Inhibitor Treatment in Percutaneous Coronary Intervention. JACC Cardiovasc Interv. 2019;12(16):1521-1537. doi:10.1016/j.jcin.2019.03.034*
31. *Frank S. Tetrabenazine: the first approved drug for the treatment of chorea in US patients with Huntington disease. Neuropsychiatr Dis Treat. 2010;6:657-665. Published 2010 Oct 5.*
32. *Mulder TAM, van Eerden RAG, de With M, et al. CYP3A4∗22 Genotyping in Clinical Practice: Ready for Implementation?. Front Genet. 2021;12:711943. Published 2021 Jul 8. doi:10.3389/fgene.2021.711943 PMID 34306041*
33. *Desta Z, Gammal RS, Gong L, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for CYP2B6 and Efavirenz-Containing Antiretroviral Therapy. Clin Pharmacol Ther. 2019;106(4):726-733.*
34. *Pratt VM, Cavallari LH, Fulmer ML, et al. CYP3A4 and CYP3A5 Genotyping Recommendations: A Joint Consensus Recommendation of the Association for Molecular Pathology, Clinical Pharmacogenetics Implementation Consortium, College of American Pathologists, Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association, European Society for Pharmacogenomics and Personalized*

Therapy, and Pharmacogenomics Knowledgebase [published online ahead of print, 2023 Jul 6]. J Mol Diagn. 2023; S1525-1578(23)00136-8.

35. *Birdwell, K.; Decker, B.; Barbarino, J.; Peterson, J.; Stein, C.; Sadee, W.; Wang, D.; Vinks, A.; He, Y.; Swen, J.; et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for CYP3A5 Genotype and Tacrolimus Dosing. Clin. Pharmacol. Ther. 2015, 98, 19–24. PMID 25801146*
36. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.38, Cytochrome P450 Genotype-Guided Treatment Strategy. July 2024*

X. POLICY HISTORY

TOP

MP 2.234	**04/18/2020 Consensus Review.** Policy statement unchanged. Background and references updated. Coding reviewed.
	10/28/2021 Consensus Review. No change to policy statement. FEP language updated. Rationale and References updated.
	09/14/2022 Minor Review. Updated policy statement to include MN criteria for siponimod. Genotype testing for Plavix updated from INV to MN. Major update to background and rationale. Literature review, ref updated. Coding changes 81225 and 81227 now MN. Additional ICD10 added for new indications.
	12/01/2022 Administrative Update. New Code 81418 Effective 01/01/2023
	03/16/2023 Administrative Update. New Code 0380U Effective 04/01/2023
	06/13/2023 Administrative Update. New Code 0392U Effective 07/01/2023
	08/03/2023 Consensus Review. Policy statement unchanged, background and references updated. Coding reviewed.
	08/28/2023 Administrative Update. New ICD10 codes, effective 10/01/2023.
	12/13/2023 Administrative Update. New CPT codes 0434U, 0438U added as INV, effective 01/01/2024.
	01/18/2024 Administrative Update. Clinical benefit added.
	06/11/2024 Administrative Update. New code 0461U added, effective 07/01/2024.
	08/30/2024 Consensus Review. No change to policy stance. Updated references.
	09/25/2024 Administrative Update. New code 0516U added, effective 10/01/2024.
	12/10/2024 Administrative Update. Deleted procedure code 0380U, effective 01/01/2025
	03/13/2025 Administrative Update. New code, 0533U effective 04/01/2025.

Top

POLICY TITLE	CYTOCHROME P450 GENOTYPE GUIDED TREATMENT STRATEGY
POLICY NUMBER	MP 2.234

and Keystone Health Plan® Central. Independent licensees of the Blue Cross BlueShield Association. Communications issued by Capital Blue Cross in its capacity as administrator of programs and provider relations for all companies.