MEDICAL POLICY

Medical Policy Title	**Pharmacogenetics**
Policy Number	**2.02.30**
Current Effective Date	February 20, 2025
Next Review Date	February 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Cytochrome p450 (CYP450) CYP2D6 genotyping to determine drug metabolizer status is considered **medically necessary** for patients with **EITHER** of the following:

   A. Gaucher type I 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 (refer to pharmacy policy regarding off label uses).

II. CYP450 2C9 (CYP2C9) genotyping to determine drug metabolizer status may be considered **medically necessary** for members being considered for treatment with MAYZENT (Siponimod), with relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.

III. Genotyping or phenotyping for thiopurine methyltransferase (TPMT) mutations is considered **medically appropriate** for **EITHER** of the following criteria:

   A. Prior to initiation of azathioprine (AZA) or 6-mercaptopurine (6-MP) therapy;

   B. When standard dosing of AZA/6-MP fails to produce a therapeutic response.

IV. Genotyping to determine CYP450 genetic polymorphisms for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity is considered **investigational**. This includes, but is not limited to, the following applications:

   A. selection or dosing of selective serotonin reuptake inhibitors (SSRI);

   B. selection or dosing of antipsychotic drugs;

   C. selection and dosing of selective norepinephrine reuptake inhibitors;

   D. selection and dosing of tricyclic antidepressants;

   E. dosing of efavirenz (common component of highly active antiretroviral therapy for human immunodeficiency virus (HIV) infection;

   F. deciding whether to prescribe codeine for nursing mothers;

   G. dosing of immunosuppressant for organ transplantation; or

   H. selection or dose of beta blockers (e.g., metoprolol).

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

VI. CYP450 CYP2C19 genotyping is considered **investigational** for the purpose of aiding in the

choice of clopidogrel (Plavix) versus alternative anti-platelet agents, or in deciding on the optimal dosing for clopidogrel.

VII. Genotyping to determine CYP2C9 and vitamin K epoxide reductase subunit C1 (VKORC1) genetic polymorphisms is considered **investigational** to detect variants that affect response to Coumadin (warfarin).

RELATED POLICIE(S)

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

Pharmacy Policy

09 Clinical Review Prior Authorizations (CRPA) Rx

POLICY GUIDELINE(S)

I. The Health Plan and its employees adhere to all State and Federal laws concerning the confidentiality of genetic testing and the results of genetic testing. All records, findings and results of any genetic test performed on any person shall be deemed confidential and shall not be disclosed without the written informed consent of the person to whom such genetic test relates. This information shall not be released to any person or organization not specifically authorized by the individual subject of the test or in compliance with applicable law.

II. Genetic testing is appropriate only when performed by a qualified laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and offered in a setting with adequately trained health care professionals who are qualified to provide appropriate pre- and post-test counseling.

III. Genetic testing is contract dependent. Coverage only applies to members with a valid contract; coverage is not provided for family members without a valid contract.

IV. Supporting documentation required: The following factors will be considered when determining the medical appropriateness of a genetic test:

   A. There must be reasonable expectation based on family history, pedigree analysis, risk factors, and/or symptomatology that a genetically inherited condition exists. Autosomal recessive disorders may be present without a family history.

   B. The genotypes to be detected by a genetic test must be shown by scientifically valid methods to be associated with the occurrence of the disease, and the analytical and clinical validity of the test must be established.

   C. The clinical utility of the test must be established (e.g., test results will influence decisions concerning disease treatment or prevention).

   D. Genetic testing should be performed for management or treatment of the patient and not only for knowledge purposes. Documentation should demonstrate how test results will impact treatment or medical management.

E. When there is family history or phenotype suggestive of a specific syndrome, results of targeted testing for the mutation associated with the syndrome should be documented prior to any panel testing. If targeted testing has not been performed, rationale as to why panel testing is medically necessary should be documented.

DESCRIPTION

Drug efficacy and toxicity vary across individuals. Because drugs and doses are typically adjusted, if needed, by trial and error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result. Various factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation (polymorphisms) in genes coding for drug metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways may also have major effects on the efficacy or toxicity of a drug.

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. Certain CYP450 enzyme genes 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 enzyme variants constitute one important group of drug-gene interactions influencing the variability of effect of some CYP450 metabolized drugs.

How an individual metabolizes drugs via the CYP450 pathway can be divided into four groups: poor, intermediate, extensive, and ultrarapid metabolizers. Poor metabolizers (PMs) lack active enzyme gene alleles. Intermediate metabolizers (IMs), who have one active and one inactive enzyme gene allele, may suffer to a lesser degree some of the consequences of poor metabolizers. Individuals with two copies (alleles) of the most common DNA sequence of a particular CYP450 enzyme gene are termed extensive metabolizers (EMs). 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 who are 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 effects and while PMs may not respond.

It is important to realize that many drugs are metabolized to varying degrees by more than one enzyme, either within or outside of the CYP450 superfamily. In addition, interactions between different metabolizing genes, between genes and the environment, and interactions among different non-genetic 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 inter-individual differences in metabolism and consequent efficacy or toxicity.

The FDA added a warning that Mayzent (Siponimod) is contraindicated in patients with a CYP2C9*3/*3 genotype. All patients should be tested before starting treatment for relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, or active

secondary progressive disease. Patients will undergo a genotype test to identify their specific variant of CYP2C9, the principal enzyme that metabolizes Siponimod. This genotype test identifies the appropriate Siponimod maintenance dose. Cytochrome P450 (CYP) 2C9 is the major enzyme responsible for the clearance of Siponimod. Siponimod is eliminated from the systemic circulation due to metabolism and subsequently biliary/fecal excretion.

Genetic variants of CYP2C9 result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and higher risk of serious bleeding. VKORC1 genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses. CYP2C9 and VKORC1 genetic variation accounts for approximately 55% of the variability in warfarin maintenance dose.

It has been proposed that using the results of CYP2C9 and VKORC1 genetic testing to predict a warfarin starting dose that approximates the individual patient's likely maintenance dose may benefit patients by decreasing the risk of serious bleeding events and the time to stable INR. Algorithms have been developed that incorporate, not only genetic variation, but also other significant factors to predict the best starting dose. Based on available evidence, not all patients with one or more genetic variants in CYP2C9 or VKORC1 will have a serious bleeding event; nor will all patients without gene variants avoid a bleeding episode.

The GeneSight Psychotropic test (Myriad Neuroscience), the Genomind PGx test (Genomind,Inc), analyze genes that may affect a patient's response to antidepressant, antipsychotic, or anticonvulsant medications, and to narcotics. The tests include genotyping the pharmacokinetic genes from the CYP450 family and other pharmacodynamic genes related specifically to a system such as the serotonin system. Clinicians use results of the testing to guide therapy, determine response to therapy, and determine risk of adverse events from drug dosage.

This variation in TPMT activity has been related to three distinct TPMT mutations and has permitted the development of TPMT genotyping based on a polymerase chain reaction (PCR). For example, patients with high TPMT activity are found to have two normal (wild-type) alleles for TPMT; those with intermediate activity are heterozygous (e.g., have a mutation on one chromosome), while those with low TPMT activity are homozygous for TPMT mutations (e.g., a mutation is found on both chromosomes). Genetic analysis has been explored as a technique to identify patients at risk for bone marrow suppression; those with intermediate TPMT activity may be initially treated with lower doses of AZA, while those with low TPMT activity may not be good candidates for AZA therapy. Prescribing information for AZA states that prospective TPMT genotyping, or phenotyping may help identify patients who may be at increased risk of developing severe, life-threatening myelotoxicity.

SUPPORTIVE LITERATURE

Clopidogrel (Plavix)

The FDA approved a new label for clopidogrel with a "boxed warning" about the diminished effectiveness of the drug in patients with impaired ability to convert the drug into its active form. The boxed warning is based upon the concern that the antiplatelet effect of clopidogrel depends primarily on its activation by the CYP450 system. Patients with decreased CYP2C19 function due to genetic polymorphisms metabolize clopidogrel poorly and have higher rates of cardiovascular events after

acute coronary syndrome (ACS) and percutaneous coronary interventions (PCIs) than patients with normal CYP2C19 function. The warning also notes that tests are available to identify patients with genetic polymorphisms, and that alternative treatment strategies should be considered for PMs of the drug.

In response to the FDA "boxed warning" for clopidogrel use, the American College of Cardiology Foundation (ACCF) Task Force on Clinical Expert Consensus Documents and the American Heart Association (AHA) published the ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning" (2010). The report was developed to help guide practitioners and patients in prescribing pharmacogenomic testing to identify patients with altered clopidogrel metabolism which has been shown to increase patient's risk for a suboptimal clinical response to clopidogrel thus changing their treatment. The report emphasized that the FDA warning originated from a small unpublished crossover trial of 40 healthy patients receiving clopidogrel, which evaluated pharmacokinetic and antiplatelet response. The chief findings were decreased active metabolite exposure and increased platelet aggregation in the poor metabolizers when compared with the other groups. Seven recommendations for practice were put forward. One recommendation was that 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. It has been shown that the genetic variability in CYP causes variable response to clopidogrel however the specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined. Information regarding the predictive value of pharmacogenomic testing is limited currently. The clinical course of most patients treated with clopidogrel without either genetic testing or functional testing is excellent. Genetic testing to determine whether a patient is predisposed to poor clopidogrel metabolism (a PM) may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. Patients believed to be at moderate or high risk for poor outcomes might include, among others, patients undergoing elective high-risk PCI procedures (e.g., treatment of extensive and/or overly complex disease). For patients who experience poor response or adverse effects when taking clopidogrel, other treatment options are available such as using higher loading doses or switching from clopidogrel to prasugrel.

The TAILOR-PCI is a multi-site, open label, prospective, randomized trial wo determine the effect of a genotype-guided oral P2Y12 inhibitor strategy on ischemic outcomes in the CYP2C19 loss-of-function carriers after a percutaneous coronary intervention (PCI). The study consisted of 5302 patients undergoing PCI for acute coronary syndromes (ACS) or stable coronary artery disease (CAD). Patients were enrolled at 40 centers in the US, Canada, South Korea, and Mexico from May 2013 through October 2018; final date of follow-up was October 2019. Patients were randomized to the genotype guided (n = 2652) underwent point-of-care genotyping. CYP2C19 LOF carriers were prescribed ticagrelor and noncarriers clopidogrel. Patients randomized to the conventional group (n = 2650) were prescribed clopidogrel and underwent genotyping after 12 months. The primary end point was a composite of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia at 12 months. A secondary end point was major or minor bleeding at 12 months. The primary analysis was in patients with CYP2C19 LOF variants, and secondary analysis included all randomized patients. The trial had 85% power to detect a minimum hazard ratio of 0.50. It was found that CYP2C19 LOF carriers with ACS and stable CAD undergoing PCI, genotype-guided selection of an oral P2Y12 inhibitor, compared with conventional clopidogrel therapy without point-of-

care genotyping, resulted in no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia based on the prespecified analysis plan and the treatment effect that the study was powered to detect at 12 months (Pereira, 2020).

In a systematic meta-analysis conducted by Sharma et al. in 2024, they set out to systematically analyze the current evidence regarding the association of CYP2C19 variants with coronary artery disease (CAD) and a meta-analysis to a investigate the association between loss of function (LoF) CYP2C19 modifications and CAD. It was determined that 87 studies were pertinent, with 52,542 patients in all, within those patients 21,747 were on CYP2C19 LoF carrier whereas remaining 30,795 were in CYP2C19 LoF non carrier group. Although the heterogeneity among the studies was quite high (63%), primary analysis showed CYP2C19 LoF allele carrier was at increased risk compared to CYP2C19 LoF allele non carrier. A sub-group analysis for the Asian population was performed to evaluate the effect of Clopidogrel use and CYP2C19 LoF carrier versus CYP2C19 LoF non carrier on the outcome with coronary artery events. A total of 26,214 patients were included in the analysis. The heterogeneity among the studies was quite high (62%), the pooled ratio was 1.95 which indicates signification association and showed CYP2C19 LoF allele carrier were at increased risk as compared to the non-carriers. The results suggest that CYP2C19 LoF alleles may be involved in the variability of response to clopidogrel and may raise the risk of CAD events in specific groups such as the Asian population, or at particular doses.

Gaucher Disease is a rare autosomal recessive lipid storage disease in which deficiency or absence of the enzyme β-glucocerebrosidase leads to lysosomal accumulation of the glycosphingolipid glucosylceramide. Untreated, this accumulation can lead to a range of effects, including anemia and thrombocytopenia, splenomegaly, bone disease, pulmonary fibrosis, and central nervous system involvement. Gaucher disease has been treated through enzyme replacement or substrate reduction therapy. Eliglustat tartrate is an orally administered selective inhibitor of glucosylceramide synthase. It received FDA approval in 2014; and, in three phase III clinical trials, has been found to lead to improvements in hematologic metrics and organomegaly. Eliglustat tartrate is metabolized by CYP2D6 and CYP3A. FDA labeling requires that patients be selected based on CYP2D6 metabolizer status as determined by genotype, with recommendations based on genotype about dosage and concomitant use of CYP2D6 and CYP3A inhibitors.

Huntington's Disease is an autosomal dominant genetic neurodegenerative disorder characterized by progressive cognitive and motor dysfunction, including chorea. In 2008, the FDA approved tetrabenazine as an orphan drug for the treatment of chorea in Huntington's Disease based on RCT evidence of improved chorea symptoms in ambulatory patients with Huntington's Disease. FDA labeling for tetrabenazine includes recommendations for genotyping for CYP2D6 for patients who are being considered for doses above 50 mg per day. The labeling states: "Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM)." Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg. Maximum daily dose in EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg.

Mayzent (Siponimod)

In a study conducted by Gardin et al. (2019), a drug–drug interaction (DDI) study was conducted

with a CYP2C9 inhibitor to evaluate the effect of CYP2C9 inhibition on siponimod pharmacokinetics. In the absence of any strong CYP2C9 inhibitor, fluconazole was selected as it is one of the most potent CYP2C9 inhibitors used in clinical practice. Fluconazole is a moderate CYP2C9 and CYP3A inhibitor and is recommended in regulatory guidance as a prototype inhibitor to assess potential DDI by CYP2C9 inhibition. This supports the development of clinical recommendations for siponimod coadministration with CYP2C9/CYP3A inhibitors. Study A, in vivo effects of the steady-state CYP2C9 enzyme inhibitor, fluconazole, on the pharmacokinetics and safety/tolerability of a single oral dose of siponimod 4 mg in healthy adult subjects; and Study B, the pharmacokinetics and safety/tolerability of a single dose and 3-day dosing of siponimod in healthy subjects with polymorphic variants of CYP2C9. In study A, coadministration with fluconazole produced a twofold increase in mean area under the curve (AUC) versus siponimod alone (from 1110 to 2160 h*ng/mL), and an increase in maximum plasma concentration (Cmax; from 31.2 to 34.0 ng/mL) and elimination half-life (T½; from 40.6 to 61.6 h). In Study B, the area under the curve of siponimod were approximately two to fourfold greater in subjects with the CYP2C9*2/*3 and CYP2C9*3/*3 genotypes, with a minor increase in Cmax versus the CYP2C9*1/*1 genotype. The mean T½ was prolonged in the CYP2C9*2/*3 (51 h) and CYP2C9*3/*3 (126 h) genotypes versus the CYP2C9*1/*1 (28 h) genotype. Siponimod did not result in increased adverse events in healthy subjects in both studies. Changes in siponimod pharmacokinetics, when co-administered with fluconazole at steady-state and in subjects with different CYP2C9 genotypes, indicate that the reduced CYP2C9 enzymatic activity does not affect the absorption phase of siponimod but prolongs the elimination phase. These results confirm the relevance of CYP2C9 activity on siponimod metabolism in humans.

Antidepressant Therapy

Oslin et al. (2022) in this randomized clinical trial, the PRIME Care (PRecision Medicine In MEntal Health Care) (PRIME Care), 1944 patients with major depressive disorder (MDD) were studied to see if providing pharmacogenomic testing for drug-gene interactions affect selection of antidepressant medication and response of depressive symptoms. Participants were enrolled from 22 Department of Veterans Affairs medical centers from July 2017 through February2021, with follow-up ending November 2021. Eligible patients were those with MDD who were initiating or switching treatment with a single antidepressant. Exclusion criteria included an active substance use disorder, mania, psychosis, or concurrent treatment with a specified list of medications. The coprimary outcomes were the proportion of prescriptions with a predicted drug-gene inter- action written in the 30 days after randomization and remission of depressive symptoms as measured by the Patient Health Questionnaire-9 (PHQ-9) (remission was defined as PHQ-9 ≤ 5). Remission was analyzed as a repeated measure across 24 weeks by blinded raters. Remission rates over 24 weeks were higher among patients whose care was guided by pharmacogenomic testing than those in usual care but were not significantly higher at week 24 when 130 patients in the pharmacogenomic-guided group and 126 patients in the usual care group were in remission. Among patients with MDD, provision of pharmacogenomic testing for drug-gene interactions reduced prescription of medications with predicted drug-gene interactions compared with usual care. Provision of test results had small nonpersistent effects on symptom remission.

Brown et al. (2022) conducted a comprehensive meta-analysis that synthesized the findings of prospective RCTs and open-label trials investigating the efficacy of pharmacogenomic guided testing in achieving remission of depressive symptoms. The meta-analysis revealed a favorable rate of

remission among individuals who received therapy guided by pharmacogenomics compared to those receiving standard of care treatment for depression. The analysis included a total of 13 trials, consisting of 10 RCTs and 3 open-label studies published through July 2022. Six of these included studies utilized the GeneSight test for guiding pharmacogenomic therapy. The analysis encompassed a sample of 4,767 individuals across these 13 trials, all studies exclusively enrolled individuals diagnosed with major depressive disorder. Most trials (69%) measured their primary endpoint at 8 weeks after baseline, although the range extended to 24 weeks. Notably, all studies included pharmacogenomic assessments of the cytochrome P450 (CYP)-C19 and CYP2D6 genes, although other genes tested varied across studies. Although the authors found an increased likelihood of remission among individuals with depression who received pharmacogenomic guided therapy, the heterogeneity in study methodology, such as the variations in the genetic variants tested, poses challenges in making recommendations for a specific testing strategy.

Thiopurine Methyltransferase (TPMT)

TMPT activity results in increased likelihood of myelotoxicity, a serious side-effect of AZA treatment. In addition, the data suggest that knowledge of TPMT activity is helpful in selecting the initial dose of drug. Thus, one-time testing is considered medically necessary.

PROFESSIONAL GUIDELINE(S)

The 2010 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) Clopidogrel clinical alert discussing the approaches to the FDA "Boxed Warning". The final recommendations for practice are as follows:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined (eg, the importance of CYP2C19*2 versus *3 or *4 for a specific patient), and the frequency of genetic variability differs among ethnic groups.
- 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, are both important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients. Genetic testing to determine if a patient is predisposed to poor clopidogrel metabolism ("poor metabolizers") may be considered before starting clopidogrel therapy in patients believed to be at moderate or high risk for poor outcomes. This might include, among others, patients undergoing elective high-risk PCI procedures (e.g., treatment of extensive and/or very complex disease). If such testing identifies a potential poor metabolizer, other therapies, particularly prasugrel for coronary patients, should be considered.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Committee on IBD published consensus recommendations on the role of TMPT and thiopurine metabolite testing in pediatric IBD (2013) and recommend TPMT testing before initiation of thiopurines. For individuals who are homozygous recessive or have extremely low TPMT activity, the use of thiopurines should be avoided, because of the risk of leucopenia. In addition, individuals on thiopurines should have routine monitoring of blood counts to evaluate for leucopenia, regardless of TPMT testing results. Metabolite testing may be performed to determine adherence to thiopurine activity or to guide dosing changes in patients with active disease. Routine and repeat metabolite testing have little or no role in patients who are responding well to medication and taking an acceptable dose of thiopurines.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) 2022 update of the Guideline for CYP2C19 Genotype and Clopidogrel Therapy makes recommendations of dosing or use of clopidogrel in patients based on their CYP2C19 alleles.

- CYP2C19 likely poor metabolizers are considered individuals carrying one decreased function alleles and one no function alleles (*2/*9, *3/*9).
    - It is recommended to avoid clopidogrel if possible. As for patients that are considered likely intermediate and intermediate metabolizers, they recommend avoiding standard dose (75mg) of clopidogrel if possible.
- CYP2C19 poor metabolizers are considered individuals carrying two no function alleles (*2/*2, *3/*3, *2/*3).
    - It is recommended to avoid clopidogrel if possible. As for patients that are considered likely intermediate and intermediate metabolizers, they recommend avoiding standard dose (75mg) of clopidogrel if possible.
- CYP2C19 likely intermediate metabolizer are considered individuals an individual carrying one normal function allele and one decreased function allele or one increased function allele and one decreased function allele or two decreased function alleles (*1/*9, *9/*17, *9/*9).
    - Avoid standard dose clopidogrel (75mg) if possible.
- CYP2C19 intermediate metabolizer are considered individuals an individual carrying one normal function allele and one no function allele or one increased function allele and one no function allele (*1/*2, *1/*3, *2/*17, *3/*17).
    - Avoid standard dose clopidogrel (75mg) if possible.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) announced the approval of updated labeling for Coumadin, to include information on genetic testing for gene variants that may help "personalize" the starting dose for each patient and reduce the number of serious bleeding events.

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 FDA issued a "boxed warning" Individuals with decreased CYP2C19 function because of genetic polymorphisms metabolize clopidogrel poorly and have higher rates of cardiovascular events after acute coronary syndrome (ACS) and percutaneous coronary interventions (PCIs) than patients with normal CYP2C19 function. The warning also notes that tests are available to identify patients with genetic polymorphisms, and that alternative treatment strategies should be considered in poor metabolizers of the drug".

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
81225 (E/I)	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 (E/I)	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)
81230 (E/I)	CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *22)
81231 (E/I)	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)
81335	TPMT (Thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
81355 (E/I)	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (e.g., warfarin metabolism), gene analysis, common variant(s) (e.g., -1639G>A, c.173+1000C>T)
81418 (E/I)	Drug metabolism (e.g., pharmacogenomics) genomic sequence analysis panel, must include testing of at least 6 genes, including CYP2C19, CYP2D6, and CYP2D6 duplication/deletion analysis

Code	Description
81479	Unlisted molecular pathology procedure
81599	Unlisted multianalyte assay with algorithmic analysis
84433	Thiopurine S-methyltransferase (TPMT)
0029U (E/I)	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, Mayo Clinic, Mayo Clinic)
0030U (E/I)	Drug metabolism (warfarin drug response), targeted sequence analysis (i.e., CYP2C9, CYP4F2, VKORC1, rs12777823) (Warfarin Response Genotype, Mayo Clinic, Mayo Clinic)
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15) (e.g., thiopurine metabolism), gene analysis, common variants (i.e., TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5) (Thiopurine Methyltransferase (TPMT) and Nudix Hydrolase (NUDT15) Genotyping, Mayo Clinic)
0070U (E/I)	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) (CYP2D6 Common Variants and Copy Number, Mayo Clinic, Mayo Clinic, Laboratory Developed Test)
0071U (E/I)	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) (CYP2D6 Full Gene Sequencing, Mayo Clinic, Laboratory Developed Test)
0072U (E/I)	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure) (CYP2D6-2D7 Hybrid Gene Targeted Sequence Analysis, Mayo Clinic, Laboratory Developed Test)

Code	Description
0073U (E/I)	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) (CYP2D7-2D6 Hybrid Gene Targeted Sequence Analysis, Mayo Clinic, Laboratory Developed Test)
0074U (E/I)	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) (List separately in addition to code for primary procedure) (CYP2D6 trans-duplication/multiplication non-duplicated gene targeted sequence analysis, Mayo Clinic, Laboratory Developed Test)
0075U (E/I)	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 5' gene duplication/multiplication) (List separately in addition to code for primary procedure) (CYP2D6 5’ gene duplication/multiplication targeted sequence analysis, Mayo Clinic, Laboratory Developed Test)
0076U (E/I)	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (e.g., drug metabolism) gene analysis, targeted sequence analysis (i.e., 3' gene duplication/multiplication) (List separately in addition to code for primary procedure) (CYP2D6 3’ gene duplication/multiplication targeted sequence analysis, Mayo Clinic, Laboratory Developed Test)
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants (NT (NUDT15 and TPMT) genotyping panel, RPRD Diagnostics)
0173U (E/I)	Psychiatry (i.e., depression, anxiety), genomic analysis panel, includes variant analysis of 14 genes (Psych HealthPGx Panel, RPRD Diagnostics)
0175U (E/I)	Psychiatry (e.g., depression, anxiety), genomic analysis panel, variant analysis of 15 genes (Genomind Professional PGx Express™ CORE, Genomind, Inc,)

Code	Description
0286U	CEP72 (centrosomal protein, 72-KDa), NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants (CNT (CEP72, TPMT and NUDT15) genotyping panel, RPRD Diagnostics)
0345U (E/I)	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (GeneSight Psychotropic, Assurex Health, Inc, Myriad Genetics, Inc)
0347U (E/I)	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 16 gene report, with variant analysis and reported phenotypes (RightMed PGx16 Test, OneOme, OneOme, LLC)
0348U (E/I)	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 25 gene report, with variant analysis and reported phenotypes (RightMed Comprehensive Test Exclude F2 and F5, OneOme, OneOme, LLC)
0349U (E/I)	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes and impacted gene-drug interaction (RightMed Comprehensive Test, OneOme, OneOme, LLC)
0350U (E/I)	Drug metabolism or processing (multiple conditions), whole blood or buccal specimen, DNA analysis, 27 gene report, with variant analysis and reported phenotypes (RightMed Gene Report, OneOme, OneOme, LLC)
0392U (E/I)	Drug Metabolism (depression, anxiety, attention deficit hyperactivity disorder [ADHD], gene-drug interactions, variant analysis of 16 genes, including deletion/duplication of CYP2D6, reported as impact of gene-drug interaction for each drug (Medication Management Neuropsychiatric Panel, RCA Laboratory Services LLC d/b/a GENETWORx, GENETWORx)

Code	Description
0411U (E/I)	Psychiatry (e.g., depression, anxiety, attention deficit hyperactivity disorder [ADHD]), genomic analysis panel, variant analysis of 15 genes, including deletion/duplication analysis of CYP2D6 (IDgenetix®, Castle Biosciences, Inc, Castle Biosciences, Inc)
0419U (E/I)	Neuropsychiatry (e.g., depression, anxiety), genomic sequence analysis panel, variant analysis of 13 genes, saliva or buccal swab, report of each gene phenotype (Tempus nP, Tempus Labs, Inc, Tempus Labs, Inc)
0423U (E/I)	Psychiatry (e.g., depression, anxiety), genomic analysis panel, including variant analysis of 26 genes, buccal swab, report including metabolizer status and risk of drug toxicity by condition (Guardant360 Response, Guardant Health, Inc)
0434U (E/I)	Drug metabolism (adverse drug reactions and drug response), genomic analysis panel, variant analysis of 25 genes with reported phenotypes (RightMed® Gene Test Exclude F2 and F5, OneOme® LLC)
0438U (E/I)	Drug metabolism (adverse drug reactions and drug response), buccal specimen, gene-drug interactions, variant analysis of 33 genes, including deletion/duplication analysis of CYP2D6, including reported phenotypes and impacted gene-drug interactions (Effective 01/01/24)
0460U (E/I)	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes (Effective 07/01/24) (RightMed® Oncology Medication Report, OneOme® LLC)
0461U (E/I)	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes (Effective 07/01/24) (RightMed® Oncology Medication Report, OneOme® LLC)
0476U (E/I)	Drug metabolism, psychiatry (e.g., major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis and reported phenotypes (Effective 10/01/24)

Code	Description
0477U (E/I)	Drug metabolism, psychiatry (e.g., major depressive disorder, general anxiety disorder, attention deficit hyperactivity disorder [ADHD], schizophrenia), whole blood, buccal swab, and pharmacogenomic genotyping of 14 genes and CYP2D6 copy number variant analysis, including impacted gene drug interactions and reported phenotypes (Effective 10/01/24)
0516U (E/I)	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status (Effective 10/01/24)
0517U (E/I)	Therapeutic drug monitoring, 80 or more psychoactive drugs or substances, LC MS/MS, plasma, qualitative and quantitative therapeutic minimally and maximally effective dose of prescribed and non-prescribed medications (Effective 10/01/24)
0518U (E/I)	Therapeutic drug monitoring, 90 or more pain and mental health drugs or substances, LC MS/MS, plasma, qualitative and quantitative therapeutic minimally effective range of prescribed and nonprescribed medications (Effective 10/01/24)
0533U (E/I)	Drug metabolism (adverse drug reactions and drug response), genotyping of 16 genes (ie, ABCG2, CYP2B6, CYP2C9, CYP2C19, CYP2C, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, GGCX, NUDT15, SLCO1B1, TPMT, UGT1A1, VKORC1), reported as metabolizer status and transporter function (Effective 04/01/25)

HCPCS Codes

Code	Description
None	

ICD10 Codes

Code	Description
E75.22	Gaucher disease
G10	Huntington's disease
I20.0	Unstable angina
I21.01-I21.09	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction (code range)
I25.110-I25.799	Chronic ischemic heart disease (code range)

Code	Description
I63.40-I63.9	Cerebral infarction (code range)
I66.01-I66.9	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction (code range)
I73.9	Peripheral vascular disease, unspecified
K50.00-K50.919	Crohn's disease (code range)
K51.00-K51.919	Ulcerative colitis (code range)

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Pharmacogenomic Testing for Warfarin Response (NCD 90.1) [accessed 2024 Dec 12]

Molecular Pathology Procedures (LCD L35000) [accessed 2024 Dec 12]

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.
- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION

Committee Approval Dates	
12/18/08, 12/17/09, 02/17/11, 12/15/11, 12/20/12, 12/19/13, 12/18/14, 02/18/16, 02/16/17, 01/18/18, 02/21/19, 02/20/20, 01/21/21, 01/20/22, 01/19/23, 02/22/24, 02/20/25	
Date	**Summary of Changes**
02/20/25	• Policy intent unchanged
01/01/25	• Summary of changes tracking implemented.
12/20/07	• Original effective date of policy