MEDICAL POLICY

Medical Policy Title	**Pharmacogenetics**
Policy Number	**2.02.30**
Current Effective Date	**February 19, 2026**
Next Review Date	**February 2027**

Our medical policies are guides to evaluate technologies or services for medical necessity. Criteria are established through the assessment of evidence based, peer-reviewed scientific literature, and national professional guidelines. Federal and state law(s), regulatory mandates and the member's subscriber contract language are considered first in the determination of a covered service.
(Link to Product Disclaimer)

POLICY STATEMENT(S)

I. Cytochrome P450 (CYP450) polymorphism genotyping is **medically necessary** to determine drug metabolism for **ANY** of the following indications:

   A. CYP2D6 polymorphism genotyping for **either** of the following:

      1. Gaucher type I disease being considered for treatment with eliglustat; **or**

      2. 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);

   B. CYP2C9 polymorphism genotyping for **any** of the following:

      1. Individuals being considered for treatment with MAYZENT (Siponimod), with relapsing forms of multiple sclerosis, to include:

         a. Clinically isolated syndrome;

         b. Relapsing-remitting disease; **or**

         c. Active secondary progressive disease.

II. Thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) mutation genotyping or phenotyping is **medically appropriate** for **EITHER** of the following criteria:

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

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

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

IV. 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.

V. CYP450 polymorphism genotyping is considered **investigational** for the purpose of aiding in the choice of drug or dose to increase efficacy or avoid toxicity. 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 immunosuppressants for organ transplantation; **or**

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

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

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 expectations 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.

Ultrarapid metabolizers (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.

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. Nudix hydrolase 15 is a protein that is encoded by the NUDT15 gene, the mutation of this gene will cause poor metabolism of thiopurines. Deficiency of NUDT15 is more common in individuals with East Asian ancestry and less common in individuals with European or African ancestry.

SUPPORTIVE LITERATURE

Clopidogrel (Plavix)

Holmes et al (2010) responded 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". 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.

Pereira et al (2020) reported the results of the TAILOR-PCI is a multi-site, open label, prospective, randomized trial which aimed to 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 to 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.

Sharma et al (2024) conducted a systematic meta-analysis 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, among 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 carriers 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 has been treated through enzyme replacement or substrate reduction therapy. Eliglustat tartrate is an orally administered selective inhibitor of glucosylceramide synthase.

Mayzent (Siponimod)

Gardin et al (2019) conducted 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 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

Albers et al (2025) conducted an industry sponsored meta-analysis to investigate the clinical utility of a single weighted multigene pharmacogenomic (PGx) test in adults with major depressive disorder (MDD) who have failed at least one treatment, though prior studies varied in design and test type. To assess the clinical utility, six prospective studies were included, with a total of 3,532 adults with MDD. Compared to unguided care, PGx-guided treatment significantly increased the likelihood of response by 30% and remission by 41% at 8–10 weeks, with no heterogeneity across studies. These findings support the effectiveness of weighted multigene PGx testing in improving treatment outcomes for MDD patients after initial therapy failure. Being that this was an industry sponsored study there is a risk for bias as employees of Myriad Genetics Inc, did receive salary and stock options at the time of the study.

Oslin et al (2022) conducted a 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.

PROFESSIONAL GUIDELINE(S)

Cardiology

- CYP2C19-Clopidogrel
    - The American College of Cardiology Foundation/ America Heart Association (ACCF/AHA): Clopidogrel Clinical Alert: Approaches to the FDA "boxed warning"- insufficient evidence to recommend testing. Holmes et al (2010).
    - The ACCF/AHA/ Society for Cardiovascular Angiography and Interventions (SCAI): 2011 Guideline for Percutaneous Coronary Intervention-Testing is not recommended. Levine GN et al (2011).
    - The ACC/AHA/American College of Emergency Physicians (ACEP)/National Association of EMS Physicians (NAEMSP)/Society for Cardiovascular Angiography & Interventions (SCAI): 2025 Guideline for the Management of Patients with Acute Coronary Syndromes- No recommendations currently. Rao et al (2025).
    - ACC/AHA: Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients with Coronary Artery Disease -Testing is not recommended. Mauri, Smith Jr (2016).
    - ACC: Updated Expert Consensus Statement on Platelet Function and Genetic Testing for Guiding P2Y12 Receptor Inhibitor Treatment in Percutaneous Coronary Intervention- Testing may be considered to escalate treatment. Sibbing et al (2019).
- CYP2C9 or VKORC1-Warfarin
    - The American College of Chest Physicians (ACCP): Pharmacology and Management of Vitamin K Antagonists- Insufficient evidence to recommend testing. Ansell et al (2008)
    - American College of Medical Genetics (ACMG): Pharmacogenetic testing of CYP2C9 and VKORC1 Alleles for Warfarin- Insufficient evidence to recommend testing. Flockhart et al (2008).

Pain and General Medicine

- CYP2D6-codeine, CYP2D6-Tramadol
    - The American Academy of Pain Medicine (AAPM): Rational Urine Drug Monitoring in Patients Receiving Opioids for Chronic Pain: Consensus Recommendations- No recommendations currently. Argoff et al (2018).
    - AAPM: Using Clinical Laboratory Tests to Monitor Drug Therapy in Pain Management Patients- No recommendation. Jannetto, Langman (2018).
    - The National Comprehensive Cancer Network (NCCN): Adult Cancer Pain V1.2026- Testing

may be considered.

- CYP2C9-NSAIDs
  - The American College of Critical Care Medicine/Society of Critical Care Medicine (ACCM/SCCM): Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU-No recommendations currently. Devlin et al (2018)
- HLA-B*58:01-Allopurinol
  - The American College of Rheumatology: Guideline for the Management of Gout- Testing prior to starting allopurinol is conditionally recommended for patients of Southeast Asian descent and African American patients. FitzGerald et al (2020).
- CYP2C19–Proton Pump Inhibitors
  - The American College of Gastroenterology (ACG): Guidelines for the Diagnosis and Management of Gastroesophageal Reflux Disease- Testing is not recommended. Katz et al (2022).

Infectious Disease

- HLA-B*57:01-Abacavir
  - The Department of Health and Human Services (DHHS)**:** Use of Antiretroviral Agents in Adults and Adolescents with HIV- Testing is recommended. updated 2024 Sep 12
  - DHHS: Use of Antiretroviral Agents in Pediatric HIV Infection- Testing is recommended. updated 2025 Sep 30.
  - The Infectious Diseases Society of America (IDSA): Primary Care Guidance for Persons with HIV- Testing is recommended. Thompson et al (2021).
- CYP2B6-Efavirenz
  - The DHHS: Use of Antiretroviral Agents in Pediatric HIV Infection (2022)- Recommends testing in pediatric HIV infected patients less than 3 years old. updated 2025 Sep 30.
- NAT2-Isoniazid
  - No recommendations currently.
- CYP2C19-Voriconazole
  - No recommendations currently.

Psychiatry and Neurology

- CYP2C19-Antidepressants, CYP2D6- Antidepresseants (Including tricyclic and serotonin reuptake inhibitors.)
  - The American Academy of Child and Adolescent Psychiatry (AACAP): Clinical Use of Pharmacogenetic Tests in Prescribing Psychotropic Medications for Children and Adolescents (2020)- Does not recommend testing when prescribing psychotropic medications for children

and adolescents.

- CYP2D6-Antipsychotics (Including risperidone, aripiprazole, and brexpiprazole.)
  - The AACAP: Clinical Use of Pharmacogenetic Tests in Prescribing Psychotropic Medications for Children and Adolescents (2020)- Does not recommend testing when prescribing psychotropic medications for children and adolescents.
- CYP2D6-Atomoxetine or Stimulants
  - The American Academy of Pediatrics (AAP): Clinical Guidelines for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents- Does not recommend testing. Wolraich et al (2019)
- HLA-B*15:02-carbamazepine, HLA-B*15:02- Oxcarbazepine, HLA-B*15:02-Phenytoin;

  HLA-A*31:01-Carbamazepine, HLA-A*31:01- Oxcarbazepine, HLA-A*31:01-Phenytoin
  - The American Epilepsy Society- do not mention HLA testing.

<u>Oncology</u>

- TPMT-thiopurines, NUDT15-Thiopurinesc (Including 6-mercaptopurine and 6-thioguanine.)
  - NCCN: Pediatric Acute Lymphoblastic Leukemia V1.2026- There is sufficient data to support testing to help guide decisions regarding drug dosing.
  - NCCN: Adult Acute Lymphoblastic Leukemia V2.2025- Testing should be considered, especially for patients of East Asian descent.
- DPYD-Fluoropyrimidines (Including 5-fluorouracil and capecitabine.)
  - NCCN: Colon Cancer V5.2025- Testing may be considered prior to the initiation of chemotherapies.
- UGT1A1-Irinotecan
  - NCCN: Colon Cancer V5.2025- Testing may be considered prior to the initiation of chemotherapies.
  - NCCN: Rectal Cancer V4.2025- Guidelines for the use of testing in clinical practice have not been established.
- CYP2D6-Tamoxifen
  - NCCN: Breast Cancer V1.2026- Testing is not recommended.
- G6PD-Rasburicase
  - NCCN: B Cell Lymphoma V1.2026- Testing is required prior to use of rasburicase.
  - NCCN: T Cell Lymphoma V1.2026- No recommendations currently mentioned.
  - NCCN: Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma V2.2026- No recommendations currently mentioned.
  - NCCN: Pediatric Aggressive Mature B Cell Lymphomas V2.2025- Testing is required prior to

use of rasburicase.

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".

FDA labeling for Eliglustat tartrate 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.

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.

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)

Code	Description
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
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)

Code	Description
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	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)
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)

Code	Description
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,)
0286U (E/I)	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)

Code	Description
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)
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)

Code	Description
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
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 (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 (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
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
0516U (E/I)	Drug metabolism, whole blood, pharmacogenomic genotyping of 40 genes and CYP2D6 copy number variant analysis, reported as metabolizer status
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

Code	Description
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
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

HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
E75.22	Gaucher disease
G10	Huntington’s disease
G35.A-G35.D	Multiple sclerosis (code range)
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)
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)

Code	Description
Z86.71	Personal history of venous thrombosis and embolism
Z86.72	Personal history of thrombophlebitis

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Pharmacogenomic Testing for Warfarin Response (NCD 90.1) [accessed 2025 Dec 15]

Molecular Pathology Procedures (LCD L35000) [accessed 2025 Dec 15]

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, 02/19/26	
Date	**Summary of Changes**
02/19/26	• Annual review; policy intent unchanged.
02/20/25	• Policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
12/20/07	• Original effective date of policy.