Introduction

Metabolism is the term for how the body processes substances. Just as the body processes (metabolizes) foods, it also metabolizes medications. One gene in particular, cytochrome P450 (also called CYP450), is known to be involved in processing a large number of drugs. Certain changes, called mutations, may affect how well or poorly a drug is metabolized. Medical studies have shown that genetic testing for certain CYP450 gene mutations is helpful in determining how a person would metabolize some drugs. For example, drugs like clopidogrel for heart disease, eliglustat for Gaucher disease, and tetrabenazine for Huntington disease. However, reliable and large studies have not yet shown that this type of genetic testing is useful for other drugs. This policy describes when CYP450 genetic testing is covered.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
### Policy Coverage Criteria

**Test** | **Medical Necessity**  
--- | ---  
CYP450 genotyping (including CYP2C19 and CYP2D6 genes) | CYP450 genotyping for the CYP2C19 gene may be considered medically necessary for the following indication:  
- To aid in the choice of clopidogrel (Plavix®) versus alternative anti-platelet agents  
**OR**  
- To determine optimal dosing for clopidogrel  

CYP2D6 genotyping to determine drug metabolizer status may be considered medically necessary for the following indications:  
- Patient with Gaucher disease considering treatment with eliglustat (Cerdelga™)  
**OR**  
- Patient with Huntington disease considering treatment with tetrabenazine (Xenazine®) in a dosage greater than 50 mg per day  

| Test | Investigational  
--- | ---  
CYP450 genotyping (including CYP2C19 and CYP2D6 genes) | CYP450 genotyping (including CYP2C19 and CYP2D6 genes) to determine drug choice or dose for all other drugs not listed in the Medical Necessity section above is considered investigational, unless noted otherwise in a separate policy (see Related Medical Policies).  

The use of genetic testing panels that include multiple CYP450 variants/mutations/polymorphisms is considered investigational.  

**Note:**  
Multigene testing panels that include CYP450 and other non CYP450 genes are addressed in other policies. (See Related Medical Policies)  
This policy only addresses individual genetic tests for CYP450 (including CYP2C19, and CYP2D6 genes).
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Coding</td>
</tr>
<tr>
<td>0028U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, copy number variants, common variants with reflex to targeted sequence analysis (new code effective 1/1/18)</td>
</tr>
<tr>
<td>0029U</td>
<td>Drug metabolism (adverse drug reactions and drug response), targeted sequence analysis (ie, CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, SLCO1B1, VKORC1 and rs12777823) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>0031U</td>
<td>CYP1A2 (cytochrome P450 family 1, subfamily A, member 2) (eg, drug metabolism) gene analysis, common variants (ie, *1F, *1K, *6, *7) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>0069U</td>
<td>Oncology (colorectal), microrna, rt-pcr expression profiling of mir-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score</td>
</tr>
<tr>
<td>0071U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, full gene sequence (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0072U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D6-2D7 hybrid gene) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0073U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, CYP2D7-2D6 hybrid gene) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0074U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, non-duplicated gene when duplication/multiplication is trans) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>0075U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 5' gene duplication/multiplication) (List separately in addition to code for primary procedure)</td>
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<tr>
<td>0076U</td>
<td>CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism) gene analysis, targeted sequence analysis (ie, 3' gene duplication/multiplication) (List separately in addition to code for primary procedure)</td>
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<tr>
<td>81225</td>
<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) (eg, drug analysis)</td>
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</table>

Page | 3 of 17
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81230</td>
<td>CYP3A4 (cytochrome P450 family 3 subfamily A member 4) (eg, drug metabolism), gene analysis, common variant(s) (eg, *2, *22) (new code effective 1/1/18)</td>
</tr>
<tr>
<td>81402</td>
<td>Molecular pathology procedure, Level 3 (eg, &gt;10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) includes: CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (eg, congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (eg, IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N,V236E, M238K], V281L, L307FsX6, Q318X, R356W, P453S, G110VfsX21, 30-kb deletion variant)</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes: CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (eg, primary congenital glaucoma), full gene sequence</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes: CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (eg, congenital adrenal hyperplasia), full gene sequence CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (eg, congenital adrenal hyperplasia), full gene sequence CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (eg, steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence</td>
</tr>
</tbody>
</table>

**Note:** The CPT genetic modifier that is specific to CYP2 genes is: -9B CYP2 genes, commonly called cytochrome p450 (drug metabolism)

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Related Information

Definition of Terms

**Cytochrome P450**: This refers to a family of 60 different enzymes involved in drug and toxin metabolism.

**Genotype testing**: This is a type of testing used to determine the DNA sequence in genes.

**Metabolize**: This is a term that refers to breaking down a molecule into smaller units. If a drug is metabolized, it is no longer clinically active.

**Polymorphisms**: This is a genetic variation between individuals resulting in differences in form or gene expression, in this case differing activity of various enzymes.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated</td>
<td>Disease-associated change in the DNA sequence</td>
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</table>
### Definition

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td>variant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

### Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

### Evidence Review
Description

The cytochrome P450 (CYP450) family is involved in the metabolism of many currently administered drugs, and genetic variants in cytochrome P450 are associated with altered metabolism of many drugs. Testing for cytochrome P450 variants may assist in selecting and dosing drugs affected by these genetic variants.

Background

**Drug Efficacy and Toxicity**

Drug efficacy and toxicity vary substantially between individuals. Because drugs and doses are typically adjusted, if needed, by trial-and-error, clinical consequences may include a prolonged time to optimal therapy. In some cases, serious adverse events may result.

Multiple factors may influence the variability of drug effects, including age, liver function, concomitant diseases, nutrition, smoking, and drug-drug interactions. Inherited (germline) DNA sequence variation in genes coding for drug-metabolizing enzymes, drug receptors, drug transporters, and molecules involved in signal transduction pathways also may have major effects on the activity of those molecules and thus on the efficacy or toxicity of a drug.

Pharmacogenomics studies how an individual's genetic inheritance affects the body's response to drugs. It may be possible to predict therapeutic failures or severe adverse drug reactions in individual patients by testing for important DNA variants (genotyping) in genes related to the metabolic pathway (pharmacokinetics) or signal transduction pathway (pharmacodynamics) of the drug. Potentially, test results could be used to optimize drug choice and/or dose for more effective therapy, avoid serious adverse events, and decrease medical costs.

**Cytochrome P450 System**

The cytochrome P450 (CYP450) family is a major subset of all drug-metabolizing enzymes; several CYP450 enzymes are involved in the metabolism of a significant proportion of currently administered drugs. CYP2D6 metabolizes approximately 25% of all clinically used medications (eg, 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, amitriptyline, and clopidogrel.
Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of the effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 1 active and 1 inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than 2 alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs administered an active drug may not reach therapeutic concentrations at usual recommended doses of active drugs, while PMs may suffer more adverse events at usual doses due to reduced metabolism and increased concentrations. Conversely, for administered prodrugs that must be converted by CYP450 enzymes into active metabolites, UMs may suffer adverse events, and PMs may not respond.

Many drugs are metabolized to varying degrees by more than 1 enzyme, either within or outside of the CYP450 superfamily. Also, the interaction between different metabolizing genes, the interaction between genes and environment, and interactions among different nongenetic factors also influence CYP450-specific metabolizing functions. Thus, identification of a variant in a single gene in the metabolic pathway may be insufficient in all but a small proportion of drugs to explain interindividual differences in metabolism and consequent efficacy or toxicity.

**Determining Genetic Variability In Drug Response**

Genetically determined variability in drug response has been traditionally addressed using a trial-and-error approach to prescribing and dosing, along with therapeutic drug monitoring for drugs with a very narrow therapeutic range and/or potentially serious adverse events outside that range. However, therapeutic drug monitoring is not available for all drugs of interest, and a cautious trial-and-error approach can lengthen the time to achieving an effective dose.

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (eg, 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. FDA has required the package insert for clopidogrel carry a black box warning concerning possible worse outcomes with clopidogrel treatment in patients with genetic variants. The FDA warning suggests changes in doses or changes in drug.

**Summary of Evidence**

**Clopidogrel**

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a CYP2C19-guided treatment strategy, the evidence includes 2 RCTs. Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The 2 RCTs evaluated the impact of CYP2C19 genotyping using an intermediate outcome measure (platelet reactivity). One RCT showed no statistical difference between patients with on-treatment high platelet reactivity between genotype-guided management or standard treatment with clopidogrel. The second RCT showed carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, and physician-directed clopidogrel was effective for most noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. Results of an ongoing RCT (TAILOR-PCI), assessing outcomes in 5270 patients randomized to genotype-based antiplatelet therapy approach or standard care, are expected in 2020 and likely to address this gap. The evidence is insufficient to determine the effects of the technology on health outcomes. Despite this lack of evidence, FDA labeling recommends cytochrome p450 genetic testing for selection and dosing of clopidogrel (Plavix(R)) therefore, the plan covers the test when ordered by a provider.
**Other Drugs**

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, β-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 (eg, circulating drug concentrations) or less often, final outcomes (eg, adverse events or efficacy). Many of these studies are small, underpowered and hypothesis generating. Prospective intervention studies, including RCTs documenting the clinical usefulness of CYP450 genotyping to improve existing clinical decision making to guide dose or drug selection, which may then translate into improvement in patient outcomes, were not identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 3 below.

**Table 3. Summary of Key Trials**

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

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.
Clinical Input From Physician Specialty Societies And Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. Opinions on use of genotype testing of patients being considered for clopidogrel treatment were mixed, with 5 suggesting the test be considered investigational and 3 suggesting it be considered medically necessary.

Practice Guidelines and Position Statements

A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010.21 The recommendations for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.

- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.

- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined...

- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, is both important additional considerations.

- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time...
There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

U.S. Preventive Services Task Force Recommendations

No U.S. Preventive Services Task Force recommendations for cytochrome p450 have been identified.

Medicare National Coverage Decisions

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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 FDA (FDA product code: NTI) are summarized in Table 4.

Table 4. Testing Kits for CYP450 Genotyping Cleared for Marketing by FDA

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

FDA: Food and Drug Administration.

Several manufacturers market diagnostic genotyping panel tests for CYP450 genes, such as the YouScript Panel (Genelex Corporation), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4 and CYP3A5. Other panel test include both CYP450 and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health) And PersonaGene Genetic Panels (AlBioTech). These tests are beyond the scope of this policy.

**FDA Labeling on CYP450 Genotyping**

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

**Clopidogrel**

FDA has required the package insert for clopidogrel carry a black box warning concerning possible worse outcomes with clopidogrel treatment in patients with genetic variants. The FDA warning suggests changes in doses or changes in drug.
Eliglustat

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

Tetrabenazine

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

Codeine

FDA does not recommend genotyping before prescribing codeine. FDA has contraindicated codeine for treating pain or cough in children under 12 years of age and codeine is not recommended for use in adolescents ages 12 to 18 who are obese or have conditions such as obstructive sleep apnea or severe lung disease. There is an additional warning to mothers not to breastfeed when taking codeine.3

References


History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
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<tr>
<td>03/08/16</td>
<td>New policy, replaces 12.04.38.</td>
</tr>
<tr>
<td>05/04/16</td>
<td>Update Related Policies. 12.04.92 was deleted and replaced with 12.04.520.</td>
</tr>
<tr>
<td>06/01/16</td>
<td>Update Related Policies. Removed 12.04.67 as it was deleted; information moved to 2.04.509.</td>
</tr>
<tr>
<td>02/10/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
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<tr>
<td>04/14/17</td>
<td>Updated Related Policies; removed 12.04.520 as it was archived. Minor formatting update.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Annual review. Policy approved on July 25, 2017. Selection or Dosing of Tetrabenazine and Eliglustat were added to the Evidence Review section. No changes to policy statement.</td>
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<tr>
<td>01/23/18</td>
<td>Coding update. added CPT codes 81230 and 81231 (new codes effective 1/1/18).</td>
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<tr>
<td>10/01/18</td>
<td>Annual Review, approved September 20, 2018. Policy updated with literature review through April 2018; several references and subsections of Rationale section were deleted and section was revised. Policy statement unchanged. Policy title changed from “CYP450 Genotyping to Determine Drug Metabolizer Status” to “Cytochrome P450 Genotype Guided Treatment Strategy”. Added CPT codes 0069U, 0070U, 0071U, 0072U, 0073U, 0074U, 0075U, and 0076U.</td>
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</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromoo (Cushite):

Deutsche (German):

Illoko (Illiano):
Daytoy a Pakdaak ket naglaan iti Napateeg nga Impormasion. Daytoy a pakdaak mabalin nga adda ket naglaan iti napateeg nga impormasion maijangeep iti apliksayyon weny coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a pelta iti daytoy a pakdaak. Mabalin nga adda rumbenga a aramidennyo nga addang sakbay dagiti partikular a naijtuda nga adda ailaw tapo napagatalnaydeo ti coverage ti salun-ayto weny tulong kadagit gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasasao nga awan iti bayadaydo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Japanese (Japanese): この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている情報が必ずしも現実的な日付をご確認ください。健康保険の提供やサポートを維持するためには、特定の期限にまでに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。


Lao (Lao): ບໍລິສັດການຢູ່ການຂອງທ່ານໄດ້ຮັບຂໍ້ມູນນີ້ Premera Blue Cross. ບໍລິສັດຈະ ຢ່າງຕ້ອງການໃຫ້ຮັບຂໍ້ມູນນີ້ຢູ່ການຂອງທ່ານມີຄວາມຄຸ້ມຄອງເຖິງການຂອງທ່ານຜ່ານ. ບໍລິສັດຈະຂໍ້ມູນນີ້ຕ້ອງທ່ານຈະມີຄວາມຊ່ວຍເຫຼືການການນີ້ຢູ່ການຂອງທ່ານ. 800-722-1471 (TTY: 800-842-5357)

Punjabi (Punjabi): ਅਜਾਈਬਾਦਾਂ ਤੋਂ ਪ੍ਰਾਪਤ ਸੰਭਾਲਾਂ ਅਨੁਸਾਰ ਸੰਭਾਲਾਂ ਦੀ ਸਥਿਤੀ ਪ੍ਰਕਾਸ਼ਤ ਕਰਨ ਲਈ Premera Blue Cross। ਸੰਭਾਲਾਂ ਦੀ ਸਥਿਤੀ ਪ੍ਰਕਾਸ਼ਤ ਕਰਨ ਦੀ ਲਈ Premera Blue Cross ਦਾ ਸੰਬੰਧ ਹੈ। ਸੰਬੰਧ ਤੌਰ ਤੇ ਸੰਬੰਧ ਦੀ ਸਥਿਤੀ। 800-722-1471 (TTY: 800-842-5357)


Spanish (Spanish): Este Aviso contiene información importante. Es posible que deba tomar alguna medida antes de determinadas fechas. Si desea recibir más información, llame al 800-722-1471 (TTY: 800-842-5357).
