Cytochrome P450 Genotype-Guided Treatment Strategy

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.

OBJECTIVE

The objective of this evidence review is to evaluate whether testing for cytochrome P450 variants improves the net health outcome by influencing the selection and dosing of drugs metabolized by CYP450 enzymes.

POLICY STATEMENT

CYP450 genotyping for the purpose of aiding in the choice of clopidogrel vs alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, is considered investigational.

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

- With Gaucher disease being considered for treatment with eliglustat; OR
- With Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day.
CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for the following drugs is considered investigational, aside from determinations in the separate policies noted above:

- selection or dosage of codeine
- dosing of efavirenz and other antiretroviral therapies for HIV infection
- dosing of immunosuppressants for organ transplantation
- selection or dosing of β-blockers (e.g., metoprolol)
- dosing and management of antitubercular medications.

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

**POLICY GUIDELINES**

This policy does not address the use of genetic panel tests for genes other than CYP450-related genes (e.g., the Genecept Assay), which are discussed in evidence review 2.04.110: Genetic Testing for Mental Health Conditions

**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. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). 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 PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</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>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
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<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>
</tbody>
</table>

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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.

BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Diagnostic genotyping tests for certain CYP450 enzymes are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Several testing kits for CYP450 genotyping cleared for marketing by the FDA (FDA product code: NTI) are summarized in Table 1.

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

<table>
<thead>
<tr>
<th>Device Name</th>
<th>Manufacturer</th>
<th>Approval Date</th>
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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>
</tr>
<tr>
<td>Spartan Rx Cyp2c19 Test System</td>
<td>Spartan Bioscience</td>
<td>2013</td>
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FDA: Food and Drug Administration.

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

## FDA Labeling on CYP450 Genotyping

The FDA has included pharmacogenomics information in the physician prescribing information (drug labels) of multiple drugs. In most cases, this information is general and lacks specific directives for clinical decision making. In the following examples, the FDA has given clear and specific directives on either use of a specific dose (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.

### Eliglustat

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

### Tetrabenazine

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

### Codeine

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

**RATIONALE**

### 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. The 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.

#### Other Drugs

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, b-blockers, or antitubercular medications who receive a CYP2C19-guided treatment strategy, the evidence includes retrospective studies. The 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.

### SUPPLEMENTAL INFORMATION

#### 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 the selection and dosing of clopidogrel was published in 2010. The recommendations for practice included the following statements:

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

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

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

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

5. "The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time...."

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6. There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

**U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations for cytochrome P450 have been identified.

**Medicare National Coverage**

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

**REFERENCES**


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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

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<th>Date</th>
<th>Action</th>
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<tr>
<td>December 2011</td>
<td>New policy</td>
<td>Policy updated with literature search, references updated, wording of medically necessary statement clarified for clopidogrel. Investigational statements added for selective norepinephrine reuptake inhibitors and tricyclic antidepressants</td>
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<tr>
<td>December 2012</td>
<td>Replace policy</td>
<td>Policy updated with literature review, references 79, 82, and 87 added. Investigational statement added for dosing of antituberculosis.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 9, 2018; several references deleted/added/ or revised. Medically necessary statements for CYP2B6 genotyping for patients being considered for eliglustat or tetrabenazine therapy added; “for all drugs” statement removed from investigational statement; medical necessary statement for CYP2C19 genotyping for patients receiving clopidogrel therapy changed to investigational. Four criteria removed from the third investigational statement; the intent of statements otherwise unchanged. Policy title changed to “Cytochrome P450 Genotype Guided Treatment Strategy”. Information on pharmacologic treatments used to treat mental health disorders were removed from this policy and added to policy 2.04.110.</td>
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<tr>
<td>September 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through April 3, 2019; references added. Policy statements unchanged.</td>
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