BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.38 Cytochrome P450 Genotype-Guided Treatment Strategy

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Related Policies:

2.04.110 - Genetic Testing for Diagnosis and Management of Mental Health Conditions
2.04.19 - Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines
2.04.48 - Genotype-Guided Warfarin Dosing
2.04.51 - Genotype-Guided Tamoxifen Treatment
5.85.018- Cerdelga (Eliglustat)
5.60.012- Xenazine (Tetrabenazine)
5.60.34- Mayzent (Siponimod)

Cytochrome P450 Genotype-Guided Treatment Strategy

Description

Description

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

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, and amitriptyline.

Some CYP450 enzymes are highly polymorphic, resulting in some enzyme variants that have variable metabolic capacities among individuals, and some with little to no impact on activity. Thus, CYP450 enzymes constitute an important group of drug-gene interactions influencing the variability of the effect of some CYP450-metabolized drugs.

Individuals with 2 copies (alleles) of the most common (wild-type) DNA sequence of a particular CYP450 enzyme gene resulting in an active molecule are termed extensive metabolizers (EMs; normal). Poor metabolizers (PMs) lack active enzyme gene alleles, and intermediate metabolizers, who have 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.

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

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

Determining Genetic Variability in Drug Response

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

CYP450 enzyme phenotyping (identifying metabolizer status) can be accomplished by administering a test enzyme substrate to a patient and monitoring parent substrate and metabolite concentrations over time (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 (ie, 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.

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 cytochrome P450 enzymes.

POLICY STATEMENT

Cytochrome P450 (CYP450) genotyping for the purpose of aiding in the choice of clopidogrel versus 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 individuals:

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

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

- With relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, being considered for treatment with siponimod.

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 related 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 (eg, metoprolol);

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- 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 cytochrome P450 (CYP450) related genes (eg, the Genecept Assay), which are discussed in evidence review 2.04.110 (Genetic Testing for Mental Health Conditions).

BENEFIT APPLICATION

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

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.

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 (CLIA). Diagnostic genotyping tests for certain CYP450 enzymes are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA 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. Selected Testing Kits for *CYP450* Genotyping Cleared for Marketing by the Food and Drug Administration

Device Name	Manufacturer	Approval Date
Genomadix Cube CYP2C19 System	Genomadix Inc.	2023
xTAG Cyp2c19 Kit V3	Luminex Molecular Diagnostics (now Diasorin)	2013
Spartan Rx Cyp2c19 Test System	Spartan Bioscience	2013
Verigene Cyp2c19 Nucleic Acid Test (2c19)	Nanosphere	2012
Infiniti Cyp2c19 Assay	AutoG enomics	2010
xTAG Cyp2d6 Kit V3, Model I030c0300 (96)	Luminex Molecular Diagnostics	2010
Invader Ugt1a1 Molecular Assay	Third Wave Technologies (now Hologic)	2005
Roche AmpliChip Cyp450 Test	Roche Molecular Systems	2005

CYP450: cytochrome P450.

Several manufacturers market diagnostic genotyping panel tests for *CYP450* genes, such as the YouScript Panel (Aranscia), 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 (Myriad Genetics). These tests are beyond the scope of this evidence review.

Food and Drug Administration Labeling on *CYP450* Genotyping

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The FDA maintains online compendia of pharmacogenetic associations under 3 categories: 1) pharmacogenetic associations for which the data support therapeutic management recommendations; 2) pharmacogenetic associations for which the data indicate a potential impact on safety or response; and 3) pharmacogenetic associations for which the data demonstrate a potential impact on pharmacokinetic properties only.[1,]

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 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 boxed warning 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.[2,]

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 per day 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.[3,]

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 years 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.[4,]

Siponimod

The FDA has approved siponimod for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults. The recommended maintenance dosage is 2 mg. The recommended maintenance dosage in patients with a *CYP2C9*1/*3* or **2/*3* genotype is 1 mg. Siponimod is contraindicated in patients with a *CYP2C9*3/*3* genotype.[5,]

RATIONALE

Summary of Evidence

For individuals with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive a cytochrome P450 (CYP) *2C19* guided treatment strategy, the evidence includes systematic reviews, randomized controlled trials (RCTs), and a prospective, nonrandomized clinical trial. Relevant outcomes are overall survival, medication use, and treatment-related morbidity. A meta-analysis including 44 studies to evaluate the effect of CYP2C19 genotype on atherothrombotic events, found that genotype-guided therapy reduced major adverse cardiovascular events (MACE), myocardial infarction, and stent thrombosis in coronary artery disease (CAD), but had no significant impact on bleeding rates. Stroke patients with loss-of-function alleles had higher risks of MACE and recurrent ischemic stroke, while no differences in MACE or major bleeding were observed in peripheral arterial disease patients. This meta-analysis however faced several limitations, including heterogeneity in studies on CAD and cerebrovascular disease, varied follow-up durations, unspecified stroke types in many studies, and the use of cohort studies and post hoc RCT analyses for peripheral arterial disease and cerebrovascular disease, with RCTs only in CAD. Five RCTs have evaluated the role of genetic testing for *CYP2C19* for selecting appropriate antiplatelet treatment and/or amplified dosing of clopidogrel using an intermediate outcome measure of platelet reactivity to predict CYP2C19 metabolic state. One RCT has shown there was no statistical difference in patients with "on-treatment high platelet reactivity" who received genotype-guided management or standard treatment with clopidogrel. The second RCT showed that carriers of loss of function alleles did not respond to augmented clopidogrel as well as they did to prasugrel, while physician-directed clopidogrel was effective for most

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noncarriers. However, routine testing using platelet reactivity as an outcome measure to predict CYP2C19 metabolic state has not been shown to improve health outcomes. The third non-inferiority RCT showed that genotype guided strategy led to outcomes that were at least as good as, if not better than, outcomes with the standard approach of prescribing prasugrel or ticagrelor to all patients. Results of this trial do not inform whether using genotype based strategy for prescribing clopidogrel results in any incremental net health benefit versus standard treatment with clopidogrel. Furthermore, the statistical significant difference observed in favor of genotype guided strategy for bleeding outcome was primarily driven by minor bleeding events. There was no difference in the incidence of major bleeding between the 2 groups. Results of TAILOR-PCI reported no statistically significant difference in a composite end point of cardiovascular death, myocardial infarction, stroke, stent thrombosis, and severe recurrent ischemia among patients with *CYP2C19* loss-of-function alleles who underwent percutaneous coronary intervention (PCI), genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy. In a trial comparing ticagrelor and clopidogrel use in individuals with stroke, results of the CHANCE-2 RCT reported a statistically significant decrease in risk of recurrent stroke in *CYP2C19* loss-of-function carriers taking ticagrelor compared to clopidogrel in the first 90 days after presentation, without an increased risk of significant bleeding. Ticagrelor was associated with a higher number of total bleeding events compared to clopidogrel. These results are limited, however, by the homogenous Han Chinese population, lack of inclusion of those with delayed presentation, receipt of thrombolysis, or cardioembolic stroke, and majority of patients genotyped as intermediate metabolizers, limiting generalizability. A prospective, nonrandomized clinical trial conducted across multiple clinical sites in South Korea to examine the impact of CYP2C19 genotypes on the prognosis of acute ischemic stroke patients treated with clopidogrel, found higher cardiovascular events in LOF allele carriers compared to noncarriers. The study observed no significant differences in major bleeding or all-cause mortality but highlighted limitations such as lack of randomization and short follow-up duration. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents, immunosuppressant therapy for organ transplantation, beta-blockers, or antitubercular medications who receive a CYP450-guided treatment strategy, the evidence includes retrospective studies and underpowered RCTs. 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 that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology Foundation

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.[32,] The recommendations for practice included the following statements:

1. "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...
2. Clinicians must be aware that genetic variability in CYP [cytochrome P450] 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....
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."

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American College of Cardiology, American Heart Association Task Force et al

In 2016, the American College of Cardiology and the American Heart Association (AHA) Task Force in collaboration with other specialty societies issued a guideline on dual antiplatelet therapy (DAPT) in coronary artery disease.[33,]The following recommendation was made on use of genetic testing:

- "To date, no RCT has demonstrated that routine platelet function testing or genetic testing to guide P2Y12 inhibitor therapy improves outcome; thus, the routine use of platelet function and genetic testing is not recommended (Class III: No Benefit)."

American Heart Association

In 2024, the AHA, following a review of key clinical trials and meta-analyses, released a scientific statement concerning CYP2C19 genetic testing in relation to P2Y12 inhibitor therapy ((clopidogrel, prasugrel, ticagrelor).[11,] Below are the essential points from this AHA scientific statement:

1. There is significant variability in the efficacy and safety of oral P2Y12 inhibitors, which are used to prevent ischemic outcomes in common diseases such as coronary and peripheral arterial disease and stroke.
2. Clopidogrel, a prodrug, is the most used oral P2Y12 inhibitor and is activated primarily after being metabolized by a highly polymorphic hepatic cytochrome CYP2C219 enzyme.
3. Loss-of-function genetic variants in *CYP2C219* are common, can result in decreased active metabolite levels and increased on-treatment platelet aggregation, and are associated with increased ischemic events on clopidogrel therapy. Such patients can be identified by *CYP2C19* genetic testing and can be treated with alternative therapy.
4. Conversely, universal use of potent oral P2Y12 inhibitors such as ticagrelor or prasugrel, which are not dependent on CYP2C19 for activation, has been recommended but can result in increased bleeding.
5. Recent clinical trials and meta-analyses have suggested that a precision medicine approach in which loss-of-function carriers are prescribed ticagrelor or prasugrel and noncarriers are prescribed clopidogrel may reduce ischemic events without increasing bleeding risk.
6. The evidence appears to support *CYP2C19* genetic testing before oral P2Y12 inhibitors are prescribed in patients with acute coronary syndromes (ACS) or percutaneous coronary intervention (PCI).
7. Clinical implementation of such genetic testing will depend on multiple factors: rapid availability of results or adoption of the concept of performing preemptive genetic testing, provision of easy-to-understand results with therapeutic recommendations, and seamless integration in the electronic health record.
8. The 2016 American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guideline on dual antiplatelet therapy (DAPT) in coronary artery disease (CAD) does not recommend the routine use of genetic testing (see above).
9. The 2017 European Society of Cardiology focused update on DAPT in CAD similarly does not recommend routine genetic testing except in specific situations such as for patients with recurrent adverse events if the results of testing may change therapy.
10. Given the pharmacokinetic, pharmacodynamic, clinical trial data (with mixed results) and recent meta-analyses findings, *CYP2C19* genetic testing before prescription of clopidogrel or ticagrelor/prasugrel in patients with ACS or PCI may be beneficial but needs more real-world high-quality validation data.

U.S. Preventive Services Task Force Recommendations

No **U.S. Preventive Services Task Force** recommendations for cytochrome P450 testing 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.

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With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation. Sep 06 2016; 134(10): e123-55. PMID 27026020

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

Date	Action	Description
December 2011	New policy	
December 2012	Replace policy	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
March 2014	Replace policy	Policy updated with literature review, references 79, 82, and 87 added. Investigational statement added for dosing of antituberculosis.
June 2015	Replace policy	Policy updated with literature review. References 33, 35, 42- 44, 49, 74, 79, 95-97 and 101-102 added. Investigational statement added for the use of panel tests of CYP450 mutations. Wording changes made for clarity and consistency to the list of investigational uses.
September 2018	Replace policy	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.
September 2019	Replace policy	Policy updated with literature review through April 3, 2019; references added. Policy statements unchanged.
September 2020	Replace policy	Policy updated with literature review through May 1, 2020; references added. Policy statements unchanged.
September 2021	Replace Policy	Policy updated with literature review through April 28, 2021; references added. Policy statements unchanged.
September 2022	Replace Policy	Policy updated with literature review through April 25, 2022; no references added. Policy statements changed. CYP2D6 genotyping to determine drug metabolizer status may be considered medically necessary for patients being considered for treatment with siponimod. Minor editorial refinements also made to policy statements.
September 2023	Replace policy	Policy updated with literature review through April 25, 2023; references added. Minor editorial refinements to policy statements; intent unchanged.
September 2024	Replace policy	Policy updated with literature review through April 22, 2024; reference added. Policy statements unchanged.
September 2025	Replace policy	Policy updated with literature review through May 1, 2025; references added. Policy statements unchanged.

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