

Protocol

Cytochrome P450 Genotype-Guided Treatment Strategy

(20438)

Medical Benefit		Effective Date: 06/01/19	Next Review Date: 03/21
Preauthorization	No	Review Dates: 09/09, 09/10, 07/11, 07/12, 03/13, 03/14, 03/15, 03/16, 03/17, 03/18, 03/19, 03/20	

Preauthorization is not required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy	Interventions of interest are: • CYP2C19-guided treatment strategy	Comparators of interest are: • Clinically guided management	Relevant outcomes include: • Overall survival • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with highly active antiretroviral agents	Interventions of interest are: • CYP450-guided treatment strategy	Comparators of interest are: • Clinically guided management	Relevant outcomes include: • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with immunosuppressant therapy for organ transplantation	Interventions of interest are: • CYP450-guided treatment strategy	Comparators of interest are: • Clinically guided management	Relevant outcomes include: • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with beta-blockers	Interventions of interest are: • CYP450-guided treatment strategy	Comparators of interest are: • Clinically guided management	Relevant outcomes include: • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with antitubercular medications	Interventions of interest are: • CYP450-guided treatment strategy	Comparators of interest are: • Clinically guided management	Relevant outcomes include: • Medication use • Treatment-related morbidity

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.

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 two randomized controlled trials (RCTs). Relevant outcomes are overall survival, medication use, and treatment-related morbidity. The two 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 non carriers. 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 5,270 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, 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 (e.g., circulating drug concentrations) or less often, final outcomes (e.g., 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.

POLICY

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 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 policy statements noted above:

- selection or dosage of codeine
- dosing of efavirenz and other antiretroviral therapies for human immunodeficiency virus infection

- dosing of immunosuppressants for organ transplantation
- selection or dosing of β -blockers (e.g., metoprolol)
- dosing and management of anti-tubercular medications.

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

POLICY GUIDELINES

This protocol 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 the Genetic Testing for Mental Health Conditions Protocol.

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

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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.

MEDICARE ADVANTAGE

CYP2C19 genotyping may be **medically necessary** once per lifetime to identify individuals:

- Who are poor metabolizers of clopidogrel, so that alternative treatment or treatment strategies can be considered.
- Who are poor metabolizers of clopidogrel with acute coronary syndrome or who are undergoing percutaneous coronary intervention.

For Medicare Advantage the following genetic tests are unlikely to impact therapeutic decision-making in the clinical management of the patient and are considered **not medically necessary**:

- CYP1B1
- CYP21A2
- CYP2C9
- CYP3A4
- CYP3A5

BACKGROUND

DRUG EFFICACY AND TOXICITY

Drug efficacy and toxicity vary substantially 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.

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 (e.g., 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 two 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 one active and one inactive enzyme gene allele, may experience to a lesser degree some of the consequences of PMs. Ultrarapid metabolizers (UMs) are individuals with more than two alleles of an active enzyme gene. There is pronounced ethnic variability in the population distribution of metabolizer types for a given CYP enzyme.

UMs 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 (e.g., 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.

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

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

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 protocol.

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 (e.g., eliglustat, tetrabenazine) or when a drug may not be used at all (e.g., 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.³

RELATED PROTOCOLS

Genetic Testing for Diagnosis and Management of Mental Health Conditions

Genotype-Guided Tamoxifen Treatment

Genotype-Guided Warfarin Dose

Pharmacogenomic and Metabolite Markers for Patients Treated With Thiopurines

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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24. National Government Services, Inc. (Primary Geographic Jurisdiction 06 & K - Illinois, Minnesota, Wisconsin, Connecticut, New York - Entire State, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont) Local Coverage Article: Billing and Coding: Molecular Pathology Procedures (A56199), Revision Effective Date 10/15/2019.