Protocol

Cytochrome P450 Genotyping

(20438)

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

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: • Testing for CYP2C19 metabolizer status by *CYP2C19* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With various clinical conditions undergoing or being considered for treatment with a drug metabolized by CYP450 enzyme(s)[a]	Interventions of interest are: • Cytochrome P450 genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related mortality • Treatment-related morbidity

[a] Drugs metabolized by CYP450 enzymes considered here include: selective serotonin reuptake inhibitors, selective norepinephrine and serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, antipsychotic drugs, codeine, efavirenz and other antiretroviral therapies, immunosuppressants for organ transplantation, β-blockers, and anti-tuberculosis drugs

Description

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

Summary of Evidence

The evidence for testing for CYP2C19 metabolizer status by *CYP2C19* genotyping in patients with a need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy includes one randomized controlled trial (RCT) of *CYP2C19* genotype-directed antiplatelet therapy, observational studies, and analyses or RCTs of clopidogrel therapy, and meta-analyses of these studies. Relevant outcomes are morbid events and treatment-related morbidity and mortality. Systematic reviews of observational studies report that genetic variants may be associated with a modest increase in the rate of stent thrombosis and clinical end points. *CYP2C19* genotype has been associated with increased risk of thrombosis in patients with coronary disease or

cardiac interventions being considered as candidates for clopidogrel treatment. This observation is most pronounced for stent thrombosis in patients undergoing percutaneous coronary intervention. The evidence addressing whether the use of *CYP2C19* genotype-directed therapy improves outcomes is limited. One RCT comparing *CYP2C19* genotype-directed antiplatelet therapy reported that patients receiving genotype-directed therapy had higher on-treatment platelet reactivity. However, the effect on clinical end points is not well understood. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for cytochrome P450 genotyping in patients with various clinical conditions undergoing or being considered for treatment with a drug metabolized by CYP450 enzyme(s) includes prospective and retrospective observational studies reporting associations with CYP450 metabolizer status and medication response or adverse effects. Relevant outcomes are symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity and mortality. Most published studies of CYP450 pharmacogenomics are retrospective evaluations of *CYP450* genotype association with intermediate (e.g., circulating drug concentrations) or, less often, final outcomes (e.g., adverse events or efficacy) and are largely small and underpowered or not designed to examine the clinical effects of homozygous variant poor metabolizers and of ultrarapid metabolizers, where the strongest effects, if any, would be seen. The hazards associated with different metabolizer status are therefore uncertain. Decision-making regarding dose or medication selection changes in response to CYP450 metabolizer status is poorly defined, and outcome changes are uncertain. 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 dosing of selective serotonin reuptake inhibitors (SSRIs)
- selection or dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
- selection or dosing of tricyclic antidepressants
- selection or dosing of antipsychotic drugs
- selection or dosage of codeine
- dosing of efavirenz and other antiretroviral therapies for HIV (human immunodeficiency virus) infection
- dosing of immunosuppressants for organ transplantation
- selection of dose of β-blockers (e.g., metoprolol)
- dosing and management of anti-tuberculosis medications.

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

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.

Policy Guidelines

This protocol does not address the use of panels of genetic tests that include 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.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background

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.

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

Pharmacogenomics is the study of 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 polymorphisms (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 effects, and decrease medical costs.

Cytochrome P450 System

The 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, anti-arrhythmics, antidepressants, and morphine derivatives), including many of the most prescribed drugs. CYP2C19 metabolizes several important types of drugs, including proton pump inhibitors, diazepam, propranolol, imipramine, and amitriptyline.

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

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 (IMs), 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 effects 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. In addition, interaction between different metabolizing genes, interaction of 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 inter-individual 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 (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse effects outside that range. However, TDM 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 consequent patient outcomes) is favored when the drug under consideration has a narrow therapeutic dose range (window), 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. Yet, the potential severity of the disease condition may call for immediate and sufficient therapy; genotyping might speed the process of achieving a therapeutic dose and avoiding significant adverse events.

Regulatory Status

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet

the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Laboratories that offer LDTs must be licensed by 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 have been cleared for marketing by (FDA product code: NTI). They include:

- The AmpliChip® (Roche Molecular Systems) was cleared for marketing by FDA in January 2005. The AmpliChip® is a microarray consisting of many DNA sequences complementary to two *CYP450* genes and applied in microscopic quantities at ordered locations on a solid surface (chip). The AmpliChip® tests the DNA from a patient's white blood cells collected in a standard anticoagulated blood sample for 29 polymorphisms and mutations for the *CYP2D6* gene and two polymorphisms for the *CYP2C19* gene. FDA cleared the test "based on results of a study conducted by the manufacturers of hundreds of DNA samples, as well as on a broad range of supporting peer-reviewed literature." According to FDA labeling, "Information about CYP2D6 genotype may be used as an aid to clinicians in determining therapeutic strategy and treatment doses for therapeutics that are metabolized by the CYP2D6 product."
- The xTAG® CYP2D6 Kit (Luminex Molecular Diagnostics, Toronto, ON) was cleared for marketing by FDA in August 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify a panel of nucleotide variants within the polymorphic CYP2D6 gene on chromosome 22.
- The INFINITI CYP2C19 Assay (AutoGenomics, Vista, CA) was cleared for marketing by FDA in October 2010 based on substantial equivalence to the AmpliChip CYP450 test. It is designed to identify variants within the CYP2C19 gene (*2, *3, and *17)
- Verigene CYP2C19 Nucleic Acid Test (Nanosphere, Northbrook, IL), designed to identify variants within the CYP2C19 gene, was cleared for marketing by FDA in November 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The Spartan RX CYP2C19 Test System Spartan Bioscience, Redwood Shores, CA), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles), was cleared for marketing by FDA in August 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The xTAG® CYP2C19 Kit v3 (Luminex Molecular Diagnostics, Toronto, ON), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles) was cleared for marketing by FDA in September 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.

Several manufacturers market panels of diagnostic genotyping tests for CYP450 genes, such as the YouScript Panel (Genelex Corp., Seattle, WA), which includes CYP2D6, CYP2C19, CYP2C9, VKORC1, CYP3A4, and CYP3A5. Other panel tests include both CYP450 genes and other non-CYP450 genes involved in drug metabolism, such as the GeneSight Psychotropic panel (Assurex Health, Mason, OH) and PersonaGene Genetic Panels (AIBioTech, Richmond, VA) these tests are beyond the scope of this protocol.

Related Protocols

Genetic Testing for Mental Health Conditions

Genetic Testing for Tamoxifen Treatment

Genetic Testing for 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 Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment 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.**

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

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