Protocol

Cytochrome P450 Genotyping

(20438)

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

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: • Test accuracy • Test validity • Change in disease status • Morbid events • Medication use • Treatment-related mortality • Treatment-related morbidity
Individuals: • With Gaucher disease type 1 who are undergoing or being considered for treatment with eliglustat	Interventions of interest are: • Testing for *CYP2D6* metabolizer status by *CYP2D6* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Medication use • Treatment-related morbidity
Individuals: • With Huntington disease who are undergoing or being considered for treatment with tetrabenazine	Interventions of interest are: • Testing for *CYP2D6* metabolizer status by *CYP2D6* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with selective serotonin reuptake inhibitors	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are undergoing or being considered for treatment with serotonin-norepinephrine reuptake inhibitors	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with tricyclic antidepressants	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with antipsy-chotic drugs	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with codeine	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related mortality • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with highly active antiretroviral agents	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with immuno-suppressant therapy for organ transplantation	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related mortality • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are undergoing or being considered for treatment with β-blockers	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • Medication use • Treatment-related morbidity
Individuals: • Who are undergoing or being considered for treatment with antitubercular medications	Interventions of interest are: • *CYP450* genotyping	Comparators of interest are: • Clinical management without genotyping	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status • Morbid events • 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

For individuals with need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy who receive testing for *CYP2C19* metabolizer status by *CYP2C19* genotyping, the evidence incudes multiple systematic reviews, secondary analyses of a randomized controlled trial (RCT) and multiple observational studies. Relevant outcomes are test accuracy and validity, change in disease status, morbid events, and treatment-related mortality and morbidity. Multiple observational studies have reported that genetic variants associated with *CYP2C19* may be associated with a modest increase in the rate of stent thrombosis and increased incidence of adverse clinical events. However, two large meta-analysis that included patients treated with and without percutaneous coronary intervention showed conflicting results of the impact of *CYP2C19* variants on clinical outcomes. The evidence addressing whether the use of *CYP2C19* genotype-directed therapy improves clinically meaningful outcomes is limited. RCTs have shown that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment platelet reactivity compared to those managed without genetic testing. A prospective cohort study reported that, in patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent *CYP2C19* genotyping, providers were more likely to increase intensity of antiplatelet therapy for carriers than for noncarriers. A randomized, prospective study comparing the clinical utility of genetic testing versus standard clinical management is required to understand the relative merit of management options better. Given the association between *CYP2C19* metabolizer status and risk of stent thrombosis in patients undergoing cardiac interventions, genotype may be used to consider treatment alternatives (e.g., higher doses of clopidogrel or alternative drug choices). The U.S. Food and Drug Administration (FDA) created a black box warning indicating testing should be considered. Clinical input from academic medical centers and specialty societies was mixed concerning the benefit of genetic testing, but there was not consensus that the medically necessary determination be changed. However, since clinical input was obtained and the black box labeling was created, additional evidence has suggested that

CYP2C19 genotype is not associated with differences in the magnitude of benefit for patients treated with clopidogrel. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with Gaucher disease type 1 who are undergoing or being considered for treatment with eliglustat who receive testing for *CYP2D6* metabolizer status by *CYP2D6* genotyping, the evidence includes subgroup analysis of clinical trial data submitted to FDA by the manufacturer as part of regulatory submission. Relevant outcomes are test accuracy and validity, morbid events, medication use, and treatment-related morbidity. Eliglustat tartrate is primarily metabolized by the CYP2D6 enzyme. FDA review reported that, at doses as high of 200 mg twice daily, the exposure in ultrarapid metabolizers (UMs) was about 57% and about 82% lower than the exposures for extensive metabolizers and intermediate metabolizers at 100 mg twice daily, respectively. Based on this high variation in drug exposure based on metabolizer status, the FDA label requirement for genotyping of *CYP2D6* to determine metabolizer status before the use of eliglustat may be clinically reasonable and UMs be excluded from being prescribed eliglustat because these patients may not achieve adequate concentrations for therapeutic effect. Although there is no published evidence about outcome changes associated with genotype-directed therapy for this medication, there are changes in management that are likely to occur with differences in genotypes that may be associated with improved health outcomes. The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals with Huntington disease who are undergoing or being considered for treatment with tetrabenazine who receive testing for *CYP2C19* metabolizer status by *CYP2C19* genotyping, the evidence consists of a single cohort study. Relevant outcomes are test accuracy and validity, morbid events, medication use, and treatment-related morbidity. The FDA labeling for the orphan drug tetrabenazine for Huntington disease recommends *CYP2D6* genotyping before use. There is limited published evidence about outcome changes associated with genotype-directed therapy for this medication. One cohort study has reported that patients categorized as UMs by a *CYP450* genotype test require a high dose of tetrabenazine compared to those who are not. However, this finding was based in a sample of 127 patients of whom only two were categorized as UMs. Therefore, these findings must be reproduced in a larger cohort. The evidence is insufficient to determine the effects of the technology on health outcomes.

Although the evidence is limited on the use of *CYP2C19* genotyping in patients undergoing or being considered for treatment with tetrabenazine, given the FDA labeling and the potential for high variation in drug exposure based on metabolizer status, genotyping of *CYP2D6* to determine metabolizer status before use of tetrabenazine may be clinically reasonable. *CYP2C19* may be considered medically necessary in patients with Huntington disease being considered for treatment with tetrabenazine at a dosage greater than 50 mg per day.

For individuals who are undergoing or being considered for treatment with selective serotonin reuptake inhibitors who receive *CYP450* genotyping, the evidence includes one systematic review and multiple retrospective and prospective studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple retrospective and prospective studies have evaluated the association between selective serotonin reuptake inhibitors and *CYP450* variants and reported conflicting results. Based on a systematic review of the evidence, Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group concluded that the evidence was insufficient to support a recommendation for or against use of *CYP450* testing in adults beginning selective serotonin reuptake inhibitor treatment for nonpsychotic depression. At present, the clinical utility of *CYP450* testing is also poorly defined. It is not known if *CYP450* genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with serotonin-norepinephrine reuptake inhibitors who receive *CYP450* genotyping, the evidence includes post hoc reanalysis of several RCTs. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use,

and treatment-related morbidity. Post hoc reanalysis of data from multiple RCTs has correlated treatment response to venlafaxine with genetic status. However, the clinical utility of *CYP450* testing is poorly defined. It is not known if *CYP450* genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with tricyclic antidepressants who receive *CYP450* genotyping, the evidence includes multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. These studies have shown that poor metabolizers have high serum concentrations of tricyclic antidepressants drugs and extensive metabolizers have low serum concentrations. However, the observed differences are unlikely to have clinically important effects. At present, the clinical utility of *CYP450* testing is poorly defined. It is not known whether *CYP450* genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with antipsychotic drugs who receive *CYP450* genotyping, the evidence includes one systematic review and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Observational studies have suggested that individuals with genetic variants in the *CYP450* gene may be at increased risk for adverse events from antipsychotic drugs, particularly the extrapyramidal effects such as tardive dyskinesia. However, a large systematic review and meta-analysis of 47 studies found no convincing evidence of an association between test results and either drug efficacy or toxicity. When seen, adverse event differences (an association, e.g., with tardive dyskinesia) were considered too small to be clinically meaningful. At present, the clinical utility of *CYP2D6* testing is poorly defined. It is not known whether *CYP450* genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with codeine who receive *CYP450* genotyping, the evidence includes few case reports. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related mortality and morbidity. Enhanced CYP2D6 enzymatic activity is associated with risk of accelerated codeine metabolism to high levels of circulating morphine in rapid metabolizers, which is thought to have contributed to deaths in infants of nursing mothers prescribed codeine and in pediatric patients post tonsillectomy. In addition, the American Academy of Pediatrics has recommended that codeine should never be used in children under 12. There is limited evidence on the clinical validity of testing for *CYP450* genotype. At present, the clinical utility of *CYP2D6* testing is poorly defined. It is not known whether *CYP450* genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with highly active antiretroviral agents who receive *CYP450* genotyping, the evidence includes multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple small and large observational studies have shown associations between *CYP450* variants and higher drug levels, central nervous system adverse events, and treatment discontinuation. At present, the clinical utility of *CYP450* testing is also defined. It is not known whether *CYP450* genotyping-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with immunosuppressant therapy for organ transplantation who receive *CYP450* genotyping, the evidence includes multiple systematic reviews and multiple observational studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related mortality and morbidity. Multiple observational studies, including a large systematic review, have shown that individuals who express *CYP3A5* (extensive and intermediate metabolizers) generally have decreased dose-adjusted trough concentrations of tacrolimus compared with those who do not (poor metabolizers), possibly delaying achievement of target blood concentrations. The evidence addressing whether the use of *CYP450* genotype-directed therapy improves clinically meaningful outcomes is limited. One RCT has demonstrated that the use of a *CYP450* genotype-directed algorithm was associated with improvements in the proportion of patients with target tacrolimus concentration ranges; no differences in morbidity or mortality or graft survival were reported. Additional studies of the clinical utility of *CYP450* genetic testing-based algorithms in tacrolimus management are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with β-blockers who receive *CYP450* genotyping, the evidence includes multiple retrospective cohort studies and reanalysis of a RCT. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Multiple large cohort studies and reanalysis of data from an RCT has suggested that *CYP450* variants may be associated with impaired metabolism to β-blocker treatment, resulting in higher blood levels causing adverse events such as bradycardia. However, other studies, notably with smaller samples have refuted such associations. At present, the clinical utility of *CYP2B6* testing is poorly defined. It is not known whether *CYP450* genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who are undergoing or being considered for treatment with antitubercular medications who receive *CYP450* genotyping, the evidence includes two metaanalysis. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, medication use, and treatment-related morbidity. Two meta-analyses have reported that patients with *CYP450* variants had an increased risk of liver toxicity with antitubercular medication. At present, the clinical utility of *CYP450* testing is poorly defined. It is not known whether *CYP450* genotype-guided clinical management improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate compared to standard clinical management without genotyping. 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

- 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 human immunodeficiency virus infection
- dosing of immunosuppressants for organ transplantation
- selection of dose of β-blockers (e.g., metoprolol)
- dosing and management of anti-tubercular medications.

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

Policy Guidelines

This protocol does not address the use of genetic panel testing 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).

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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

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.

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.

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.

Different 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 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 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 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, antiarrhythmics, antidepressants, and 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 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 (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. In addition, interaction between different metabolizing genes, 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 (TDM) for drugs with a very narrow therapeutic range and/or potential serious adverse events 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 patient outcomes) is 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. Yet, 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Diagnostic genotyping tests for certain CYP450 enzymes are now available. 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 the FDA (FDA product code: NTI). They include:

- AmpliChip® (Roche Molecular Systems) was cleared for marketing by FDA in January 2005. 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 DNA from a patient's white blood cells collected in a standard anticoagulated blood sample for 29 variants for the *CYP2D6* gene and two variants for the *CYP2C19* gene. FDA cleared the test "based on results of a study conducted by the manufacturer 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. The xTAG® kit 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. INFINITI 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 diagnostic genotyping panel 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* 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

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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.**

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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