Cytochrome p450 Genotyping

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I. 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 impacted by these genetic variants.

The evidence for testing for CYP2C19 metabolizer status by CYP2C19 genotyping in patients with need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy includes 1 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 ultra-rapid 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.

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 accumulated that CYP2C19 genotype is not associated with differences in the magnitude of benefit for patients treated with clopidogrel. As a result, genetic testing for selection and dosing of clopidogrel are considered investigational.

The FDA labeling for the orphan drugs eliglustat (for Gaucher disease) and tetrabenazine (for Huntington disease) recommends CYP2D6 genotyping before use. There is limited published evidence about outcome changes associated with genotype-directed therapy for these medications. However, given the FDA labeling and the high variation in drug exposure based on metabolizer status, genotyping of CYP2D6 to determine metabolizer status before the use of these drugs is reasonable and may be considered medically necessary.

Because the clinical utility of genetic testing for individual CYP450 polymorphisms has not demonstrated clinical utility, the use of genetic panel testing for CYP450 polymorphisms is not covered.

This policy 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.

**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 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, beta-blockers, antiarrhythmics, 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 poor metabolizers. 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.

Ultrarapid metabolizers 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 non-genetic
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.

**II. Criteria/Guidelines**
A. CYP450 genotyping is covered (subject to Limitations and Administrative Guidelines) once per lifetime for the purpose of aiding in the choice of clopidogrel (Plavix) versus alternative anti-platelet agents, or in decisions on the optimal dosing of clopidogrel.

B. CYP450 genotyping is covered (subject to Limitations and Administrative Guidelines) once per lifetime to determine drug metabolizer status for patients:
   1. With Gaucher disease being considered for treatment with eliglustat; or
   2. With Huntington disease being considered for treatment with tetrabenazine in a dosage greater than 50 mg per day

**III. Limitations**
A. 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 not covered, including but not limited to the following applications:
   1. Selection or dosing of selective serotonin reuptake inhibitor (SSRI)
   2. Selection or dosing of antipsychotic drugs
   3. Selection of dosing of codeine
4. Selection and dosing of selective norepinephrine reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors
5. Selection and dosing of tricyclic antidepressants
6. Dosing of efavirenz and other antiretroviral therapies for HIV
7. Dosing of immunosuppressant for organ transplantation
8. Selection or dose of beta blockers (e.g., metoprolol)
9. Dosing and management of anti-tuberculosis medications

B. CYP450 genotyping for CYP2C19 is limited to once per lifetime.
C. The use of genetic panels that include multiple CYP450 mutations, or other conditions are not covered as they are not known to be effective in improving long term health outcomes.

IV. Administrative Guidelines
A. Precertification is not required. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

B. Applicable CPT codes:

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<tr>
<th>CPT</th>
<th>Description</th>
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<td>81225</td>
<td>CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19) e.g., drug metabolism, gene analysis, common variants e.g., *2, *3, *4, *8, *17</td>
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<tr>
<td>81227</td>
<td>CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3, *5, *6)</td>
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| 81401| Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) includes:  
  - CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6)  
  - CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (e.g., drug metabolism), common variants (e.g., *2, *3, *4, *5, *6) |
| 81402   | Molecular pathology procedure, Level 3 (e.g., >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD]) includes:  
|         | • CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (e.g., IVS2-13G, P30L, I172N, exon 6 mutation cluster [I235N, V236E, M238K], V281L, L307FfsX6, Q318X, R356W, P453S, G110VfsX21, 30-kb deletion variant) |

| 81404   | Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis) includes:  
|         | • CYP1B1 (cytochrome P450, family 1, subfamily B, polypeptide 1) (e.g., primary congenital glaucoma), full gene sequence |

| 81405   | Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) includes:  
|         | • CYP11B1 (cytochrome P450, family 11, subfamily B, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence  
|         | • CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (e.g., congenital adrenal hyperplasia), full gene sequence  
|         | • CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (e.g., steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence |

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<tr>
<th>ICD-10 Codes</th>
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<td>E75.22</td>
<td>Gaucher disease</td>
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<tr>
<td>G10</td>
<td>Huntington's disease</td>
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<tr>
<td>I20.0</td>
<td>Intermediate coronary syndrome (unstable angina)</td>
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<td>I21.01-I22.9</td>
<td>Acute myocardial infarction code range</td>
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<tr>
<td>I24.1</td>
<td>Post-myocardial infarction syndrome (Dressler’s syndrome)</td>
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<tr>
<td>I2511.0</td>
<td>Atherosclerotic heart disease of native coronary artery with unstable angina pectoris</td>
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<td>I63.50-I63.549</td>
<td>Occlusion and stenosis of cerebral arteries, resulting in cerebral infarction, code range</td>
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<tr>
<td>I66.01-I66.9</td>
<td>Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction, code range</td>
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<td>I73</td>
<td>Other peripheral vascular disease</td>
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**REGULATORY STATUS**

Diagnostic genotyping tests for certain CYP450 enzymes are now available. Some tests are offered as in-house laboratory-developed test services, which do not require FDA approval but which must meet Clinical Laboratory Improvement Act (CLIA) quality standards for high complexity testing.

Several testing kits for CYP450 genotyping have been cleared for marketing by FDA (FDA product code: NTI). These include:

- The AmpliChip (Roche Molecular Systems, Inc.) was cleared for marketing 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) was cleared for marketing 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, Inc., Vista, CA) was cleared for marketing 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, Inc., Northbrook, IL), designed to identify variants within the CYP2C19 gene, was cleared for marketing 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 in August 2013 based on substantial equivalence to the INFINITI CYP2C19 Assay.
- The xTAG CYP2C19 Kit v3 (Luminex Molecular Diagnostics, Toronto), designed to identify variants in the CYP2C19 gene (*2, *3, and *17 alleles) was cleared for marketing 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 Corporation, 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, Inc., Mason, OH); these tests are beyond the scope of this policy.

V. Scientific Background

This policy has been updated periodically with reviews of the medical literature via a search of the MEDLINE database. The most recent review covered the period through October 12, 2015. Validation of genotyping to improve pharmacologic treatment outcomes is a multistep process. In general, major suggested steps in the validation process are as follows:

- Establish the specific genotyping test performance characteristics, i.e., does the test accurately and reproducibly detect the gene markers of interest (analytic validity).
- For each drug of interest, conduct preliminary performance studies in relevant populations or population subsets as appropriate to evaluate the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events; may be retrospective (clinical validity).
- Conduct prospective trial(s) in relevant patient populations to compare the use of genotyping for specific genetic markers to guide prescribing and dosing to standard treatment without genotyping. Determine whether genotyping improves patient outcomes such as therapeutic effect, time to effective dose, and adverse event rate (clinical utility).

Further discussion of the validation process is provided in a 2004 TEC Special Report, Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status, on which this policy is based. The purpose of the Report was to provide background information on cytochrome p450 (CYP450) enzymes; genotyping applications for currently available drugs; examples of companies and products; evaluation of clinical utility; examples and the current state of evidence, regulatory issues, and cost-effectiveness analysis. The Report, along with updated literature, offered the following general observations and conclusions:

- Although a genotyping assay may be designed to determine metabolizer status for a variety of enzymes and need only be performed once per patient to generate results relevant to a variety of drugs, whether or not the information is relevant for a particular drug must be validated for each drug of interest.
- The analytical validity of pharmacogenomic testing is likely to be high but should be evaluated for each marker of interest. A recent publication suggests that the Roche AmpliChip may have a low sensitivity for the CYP2D6 ultrarapid metabolizer genotype.
- Data suggest a strong association between specific variant alleles and increased adverse events related to specific drugs or between specific variant alleles and final doses for specific drugs (clinical validity). Such associations, however, may not explain the majority of inter-individual variability in drug response. For example, although CYP2C9 genotype is an independent predictor of final warfarin dose,
CYP2C9 genotype in combination with other known genetic and nongenetic significant confounders statistically explains up to 60% of the variation in final dose. Whether or not that is sufficient to improve patient outcomes after genotype-directed dosing is, at present, unknown.

- Reduced activity in a particular CYP450 enzyme because of genotype may not affect outcomes when other metabolic pathways are available and when other confounders influence drug metabolism. Therefore, prospective studies of clinical utility are important to validate hypotheses generated by associational studies. However, few prospective studies of genotype-directed dosing or drug choice have been conducted and none support genotype-directed decision-making.

- Without prospective evidence defining the effect of genotyping on such outcomes, there are few dosing recommendations based on genotype. In one example, Kirchheiner et al. reviewed CYP2D6 and CYP2C19 polymorphisms and pharmacokinetic data for several antidepressants and antipsychotic drugs to provide dose recommendations. However, these recommendations were largely extrapolated from data on genotype-dependent pharmacokinetics for use in future clinical trials; efficacy of the recommendations in routine clinical use has not been established.

Below are brief synopses of the application and evidence for clinical topic areas of particular interest in the literature.

**Selection and dosing of clopidogrel**

Guidelines from the American Heart Association and the American College of Cardiology recommend the use of dual antiplatelet therapy with aspirin and a P2Y12 inhibitor, such as clopidogrel, prasugrel, or ticagrelor, for the prevention of atherothrombotic events after acute myocardial infarction (MI). However, a substantial number of subsequent ischemic events still occur, which may be at least partly due to interindividual variability in the response to clopidogrel. Clopidogrel is a prodrug which is converted by several CYP450 enzymes, CYP2C19 in particular, to an active metabolite. For this reason, genetic polymorphisms that inactivate the CYP2C19 enzyme are associated with impaired pharmacodynamic response in healthy individuals. Previous studies have shown that persistent high platelet reactivity, despite clopidogrel treatment at standard dosing, is associated with CYP2C19 variants that code for inactive enzymes;15 higher loading and/or maintenance doses decrease reactivity even in initial nonresponders, presumed to be CYP2C19 PMs.16-18 Higher platelet reactivity has also been associated with a higher rate of subsequent thrombotic events. However, the intrinsic variability of platelet monitoring is a known limitation of all tests measuring platelet aggregation, making it difficult to use these tests for treatment modulation.

In 2009, the FDA expanded the pharmacogenetics section of the clopidogrel label to include information on the metabolic impact of polymorphic CYP450 enzymes. However, no dosing or drug selection recommendations were made. In March 2010, the FDA issued a safety communication indicating it was adding a boxed warning to the label of Plavix. This warning includes information to:
• Warn about reduced effectiveness in poor metabolizers of Plavix (patients with CYP2C19 *2/2, *3/3, or *2/3 genotypes)
• Indicate tests are available to identify genetic differences in CYP2C19 function that will help identify poor metabolizers
• Advise healthcare professionals to consider alternative dosing or use of other medications in patients identified as potential poor metabolizers

Observational Studies of CYP2C19 and CYP2C19 & Outcomes for Clopidogrel-Treated Patients

A number of publications have evaluated outcomes in patients treated with clopidogrel according to their CYP2C19 genetic status. These studies showed that patients with genetic variants have worse outcomes than those without genetic variants. These data raised the possibility that the efficacy of clopidogrel was reduced in patients with genetic variants. A summary of some of these studies follows.

Simon et al. and Mega et al. found significant, although modest, increases in risk of subsequent thrombotic events for CYP2C19 variant carriers in unselected patient populations; Collet et al. found a stronger risk in a highly selected population of younger patients with family history.

Shuldiner et al. demonstrated platelet response to clopidogrel was highly heritable in a population of 429 healthy Amish patients matching genotype results for P450 (CYP) 2C19*2 variant with platelet aggregometry. It was estimated that the *2 genotype could be used to predict 12% of variation in platelet aggregation measures. This compared to an estimate of 22% using age, BMI and lipid levels. The effect of the *2 genotype was subsequently evaluated by these investigators in a more heterogeneous population of 227 patients treated with percutaneous intervention. The relation between genotype and platelet aggregation was replicated. Patients with *2 genotypes were found to have an increased cardiovascular (CV) ischemic event or death rate during 1 year of follow-up (hazard ratio 2.42). Sibbing et al. recently reported that in a study of 2,485 patients pretreated with clopidogrel as part of coronary stent placement, those carrying *2 mutations had an increased 30 days likelihood of stent thrombosis (hazard ratio 3.81).

Sibbing et al., in a study that included 1524 subjects, reported that the presence of the CYP2C19*17 allele appears to result in decreased platelet aggregation when compared with wild- type homozygotes, with an increased 30-day risk of bleeding but no change in the occurrence of stent thrombosis. Tiroch et al., in a study of 928 patients with acute MI, found that patients treated with continuous clopidogrel therapy exhibited improved outcomes (the need for target lesion revascularization and major adverse cardiovascular events) in carriers of increased function alleles CYP2C19*17).

CYP2C19 Status and Response to Clopidogrel in RCTs

More direct information on whether the efficacy of clopidogrel is reduced in patients with genetic variants can be obtained by genotyping both the treatment and control groups in
RCTs to determine whether patients with genetic variants have the same response to treatment relative to placebo. In one such study, Pare et al. retrospectively genotyped 5,059 patients from 2 large randomized trials (the Clopidogrel in Unstable Angina to Prevent Recurrent Events or “CURE” trial and the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events or “Active” trial) that showed clopidogrel reducing the rate of cardiovascular events when compared to placebo in patients with acute coronary syndromes and atrial fibrillation. Genotyping was performed for *2, *3, and *17 of the CYP2C19 allele. These investigators observed that the efficacy and safety of clopidogrel as compared with placebo was not affected by CYP2C19 loss of function alleles. Even when data were restricted to evaluation of patients homozygous for loss of function, no increased risk of cardiovascular events was observed. Although the reason for these divergent findings remains unclear, it was noted that in the populations studied, use of stents was substantially less than in previous reports (19% of patients with acute coronary syndromes and only 14.5% in patients with atrial fibrillation).

**Systematic Reviews and Meta-Analyses**

Studies on the association between CYP2C19 genotype and clopidogrel response have been summarized in a number of systematic reviews and meta-analyses, some of which have come to opposing conclusions.

In 2015, Osnabrugge et al reported a systematic review of 11 meta-analyses that summarized studies evaluating the associations between CYP2C19 genetic status and outcomes in clopidogrel- treated patients. The 11 meta-analyses included a total of 30 primary studies, but not all studies were included in all meta-analyses. Among the 30 primary studies, there were 23 cohort studies and 7 post hoc analyses of RCTs. Eight out of 11 meta-analyses on clinical end points reported a statistically significant association between CYP2C19 genotype and outcomes, with mean effect sizes ranging from 1.26 to 1.96. Five of these 8 concluded that there was an association between CYP2C19 genotype and the clinical end point, 2 inferred that there was a possible association, and 1 concluded that the association was not proven because of publication bias. For the outcome of stent thrombosis, all 11 meta-analyses reported a statistically significant association between CYP2C19 genotype and stent thrombosis, with mean effect sizes ranging from 1.77 to 3.82.

Examples of some of the available systematic reviews on the association between CYP2C19 genotype and clopidogrel response follow.

Bauer et al performed extensive searches of MEDLINE, EMBASE, and the Cochrane Library for relevant peer-reviewed reports of observational studies and clinical trials on genotyping. Out of 4203 reports in their initial search, they identified 15 studies for detailed analysis. They reported that on comparison of carriers of at least one reduced function allele of CYP2C19 with non-carriers; the unadjusted odds ratios of major adverse events were higher in 3 studies, lower in 1, and not significantly different in 8. For stent thrombosis the OR associated with reduced function allele carrier status was reduced in 4 studies but showed no significant difference in 5. No studies showed a significant positive or negative impact on outcomes as a result of CYP2C19*17 testing.

Holmes et al. identified 32 studies including 42,106 participants. Twenty-one studies
included patients with acute coronary syndromes, and 8 studies included patients with stable coronary heart disease—the latter is usually associated with coronary stent placement. While the authors observed a decrease in the measurable concentration of clopidogrel metabolite in patients with a loss-of-function gene on 75 mg of clopidogrel, they were unable to show that this resulted in a clinically meaningful change in outcomes. Of particular note was the observation that when studies were stratified by numbers of outcome events, there was a clear trend toward the null in larger studies, consistent with small-study bias. The strongest data supporting use of testing was to predict stent thrombosis with a risk ratio of 1.75 (confidence interval [CI]: 1.50 to 2.03) for fixed effects and 1.88 (CI: 1.46 to 2.41) for random effects modeling. But again a trend toward the null was observed in larger studies. Assuming an event risk of 18 per 1,000 in the control group, they calculated that this corresponded to an absolute increase of 14 stent thromboses per 1,000 patients. Holmes et al. noted a trade-off between decreased risk of bleeding with loss of function that in part appeared to mitigate increased susceptibility to thrombosis. They cautioned that efforts to personalize treatment in the loss of function setting should be considered carefully because efforts to improve efficacy might be offset by risks of harms such as bleeding.

Mao et al conducted a systematic review and meta-analysis of studies assessing the effect of CYP2C19 polymorphisms on clinical outcomes in patients with coronary artery disease treated with clopidogrel. The authors included 21 studies involving 23,035 patients, including prospective cohort studies and post-hoc analyses of RCTs involving patients with coronary artery disease. Carriers (N=6868) of the CYP2C19 variant allele had a higher risk of adverse clinical events than the 14,429 non-carriers (OR=1.50; 95% CI, 1.21 to 1.87; p<0.000). Patients with a loss-of-function CYP2C19 allele had a higher risk of MI (OR=1.62; 95% CI, 1.35 to 1.95; p<0.000) and a higher risk of in-stent thrombosis, among those who underwent stent implantation (OR=2.08; 95% CI, 1.67 to 2.60; p<0.000).

In an older meta-analysis, Mega et al. performed a meta-analysis of 9 studies (n=9,685 patients) comparing CYP2C19 genotype to clinical outcomes in patients treated with clopidogrel. Most patients (91.3%) had undergone percutaneous coronary interventions, and 54.5% had an acute coronary syndrome. They observed a significantly increased risk of cardiovascular death, MI, stroke, or stent thrombosis in patients with 1 and 2 reduced function CYP2C19 alleles as compared with non-carriers.

**Outcomes from CYP2C19 Genotype Directed Therapy**

Roberts et al. reported on 200 patients randomized to compare use of a point-of-care test for the CYP2C19*C to determine treatment versus standard treatment. In the tested group, carriers were given 10 mg of prasugrel daily. Non-carriers and all patients in the control group were given 75 mg of clopidogrel per day. The primary endpoint was high on-treatment platelet reactivity. In the group with genotyping, none of the 23 carriers had high on-treatment platelet reactivity; in the group receiving standard treatment 30% of 23 carriers had high on-treatment platelet reactivity. These authors concluded that rapid genotyping with subsequent personalized treatment reduces the number of carriers treated who exhibit high on-treatment reactivity. The authors do note that alternative approaches using either phenotyping or a combination of both phenotyping and genotyping might optimize treatment decision making.
Desai et al reported results of a study of antiplatelet therapy prescribing behavior for antiplatelet therapy for 499 patients with a recent acute coronary syndrome or percutaneous coronary intervention who underwent CYP2C19 genotyping. Among the 146 subjects (30%) with at least 1 CYP2C19 reduced function allele, although providers were more likely to increase antiplatelet therapy intensification than for noncarriers, only 20% had their clopidogrel dose changed or were switched to prasugrel.

An RCT, the POPular Genetics study (NCT01761786), was designed to compare a strategy of antiplatelet therapy directed by CYP2D19 genotype with routine care with prasugrel or ticagrelor in patients undergoing percutaneous coronary intervention. Initial results describing the feasibility of CYP2D19 genotyping have been presented in abstract form, but no published study results were identified.

Section Summary: Selection and Dosing of Clopidogrel
Individuals with genetic variants of cytochrome p450 have a decreased ability to metabolize clopidogrel, but the impact on clinically meaningful outcomes is uncertain. Some observational studies have reported increased rates of cardiovascular events in patients with genetic variants, but others have not. Systematic reviews of observational studies report that genetic variants may be associated with a modest increase in the rate of stent thrombosis and clinical endpoints. However, the evidence addressing whether the use of CYP2C19 genotype-directed therapy improves outcomes is limited. While genotyping appears in some studies to be helpful in identifying patients at higher risk of treatment failure and may be very useful in selected patients, more information is needed to refine optimal use of testing and to better understand the relative merit of management options.

The FDA has required the package insert for clopidogrel carry a black box warning concerning possible worse outcomes with clopidogrel treatment in patients with genetic variants. The FDA warning suggests changes in doses or changes in drug.

Selection or Dosing of Eliglustat
Gaucher disease is a rare autosomal recessive lipid storage disease in which deficiency or absence of the enzyme β-glucocerebrosidase leads to lysosomal accumulation of the glycosphingolipid glucosylceramide. Untreated, this accumulation can lead to a range of effects, including anemia and thrombocytopenia, splenomegaly, bone disease, pulmonary fibrosis, and central nervous system involvement. Gaucher disease has been treated through enzyme replacement, for which 3 drugs have FDA approval as orphan drugs (imiglucerase, velaglucerase alfa, and taliglucerase alfa) or substrate reduction therapy, for which 2 drugs have FDA approval as orphan drugs (miglustat and eliglustat tartrate). Eliglustat tartrate is an orally administered selective inhibitor of glucosylceramide synthase that received FDA approval in 2014 and has been found in 3 phase 3 clinical trials to lead to improvements in hematologic metrics and organomegaly.

Eliglustat tartrate is metabolized by CYP2D6 and CYP3A. FDA labeling requires that patients be selected on the basis of CYP2D6 metabolizer status as determined by genotype, with recommendations based on genotype about dosage and concomitant use of CYP2D6 and CYP3A inhibitors.
Selection or Dosing of Tetrabenazine
Huntington disease is an autosomal dominant genetic neurodegenerative disorder characterized by progressive cognitive and motor dysfunction, including chorea. In 2008, FDA approved tetrabenazine, a centrally acting vesicular monoamine transporter inhibitor, as an orphan drug for the treatment of chorea in Huntington disease, based on evidence from an RCT of improved chorea symptoms in ambulatory patients with Huntington disease. Tetrabenazine’s primary metabolites are metabolized mainly by CYP2D6. FDA labeling for tetrabenazine includes recommendations for genotyping for CYP2D6 in patients who are being considered for doses above 50 mg per day. The labeling states: “Patients requiring doses above 50 mg per day should be genotyped for the drug metabolizing enzyme CYP2D6 to determine if the patient is a poor metabolizer (PM) or an extensive metabolizer (EM). Maximum daily dose in PMs: 50 mg with a maximum single dose of 25 mg. Maximum daily dose in EMs and intermediate metabolizers (IMs): 100 mg with a maximum single dose of 37.5 mg.

Selection or dosing of SSRI
CYP2D6 and CYP2C19 are primary CYP450 enzymes involved in the metabolism of (SSIs). Thus, understanding a patient's metabolizer status might be helpful in choosing an initial SSRI and/or dose that is most likely to be effective.

Systemic Reviews
In January 2007, an Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center systematically reviewed the evidence on CYP450 testing for adults treated with SSRIs for nonpsychotic depression. Following this commissioned report, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group published the following recommendation: “The EGAPP Working Group found insufficient evidence to support a recommendation for or against use of CYP450 testing in adults beginning SSRI treatment for non- psychotic depression. In the absence of supporting evidence, and with consideration of other contextual issues, EGAPP discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed.”

Observational Studies
Several studies focused on specific drugs including paroxetine and escitalopram. Gex-Fabry et al. studied paroxetine levels and clinical response in 71 patients with depression who had been genotyped for CYP2D6 and ABCBA polymorphisms. In this prospective observational study, CYP2D6 heterozygous extensive metabolizer phenotype showed a marginal impact on paroxetine levels and no impact on treatment response.

Ververs et al. in a cohort study of 74 pregnant women, demonstrated that differences in CYP2D6 genotype caused differential effects on paroxetine plasma concentrations. Extensive and UMs showed steady decreases in concentrations during the course of pregnancy with increase in depressive symptoms. IMs and PMs showed an increase in concentrations with no change in symptoms. It was suggested that knowledge about CYP2D6 genotype would be indispensable in this setting. However, no information on the use or outcome of use of such information was provided.
Tsai et al., recently evaluated 100 patients diagnosed with major depressive disorder in an Asian population treated with escitalopram. These investigators evaluated ten alleles involving CYP2D6, CYP2C19, and CYP3A4 and concluded genetic polymorphisms of cytochrome P450 enzymes appeared to influence drug metabolism and treatment response. However, results were variable, and they were unable to provide a confident estimate of the ability of various allelic combinations to predict drug levels or treatment outcomes.

Hodgson et al evaluated the association between CYP450 genotype, antidepressant serum concentration, and treatment response in patients taking escitalopram (N=223) or the tricyclic antidepressant nortriptyline (N=161). Genetic variation in CYP2C19 was significantly associated with serum escitalopram levels, while genetic variation in CYP2D6 was significantly associated with serum nortriptyline and 10-hydroxynortriptyline. However, there was no significant relationship between genotype and treatment response for either medication.

Chang et al evaluated the relationship between CYP2C19 polymorphisms and exposure to escitalopram and citalopram measured by serum/plasma levels in a meta-analysis of 14 studies. Compared with EM homozygotes, citalopram or escitalopram concentrations significantly differed for other metabolizer states, as shown in Table 1:

**Table 1: (Es)citalopram Serum Concentration by CYP2C19 Genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>% Change in Serum (Es)citalopram Level</th>
<th>95% Confidence Interval, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM/PM (CYP2C19*2 or *3/*3 or *3)</td>
<td>95</td>
<td>40 to 149</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EM/PM (CYP2C19*1/*2 or *3)</td>
<td>30</td>
<td>4 to 55</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UM/PM (CYP2C19*17/*2 or *3)</td>
<td>25</td>
<td>1 to 49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UM/UM (CYP2C19*17/*17)</td>
<td>-36</td>
<td>-46 to 27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>UM/EM (CYP2C19*17/*1)</td>
<td>-14</td>
<td>-27 to -1</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

EM: extensive metabolizer; PM: poor metabolizer

Other studies have evaluated the association of p450 genotype variants with response to multiple antidepressants. Serretti et al., in a retrospective study of 287 patients on antidepressants demonstrated no association between response and allelic variations for P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6.

Finally Sim et al. retrospectively studied 1,472 Swedish subjects looking for associations between CYP2C19 polymorphisms and depressive symptoms. They concluded that PMs exhibited a significantly lower level of depressive symptoms than extensive metabolizers (EMs). In the absence of drug-specific treatment outcomes or data related to drug levels, they suggested the need for further investigation of the functional link between CYP2C19 and depressive symptoms to further evaluate this observation.
**Section Summary: Selection or Dosing of SSRIs**

Individuals with variants in multiple p450 genes have altered metabolism of SSRI drugs. However, the impact of genetic variants on clinical response and clinical outcomes is less clear, and the evidence is not sufficient to conclude that patients with genetic variants have reduced efficacy of SSRIs. Therefore, the clinical utility of testing for SSRI dose is uncertain.

**Selection and Dosing of Serotonin-Norepinephrine and Selective Norepinephrine Reuptake Inhibitors**

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are used most commonly as antidepressants. Available agents in the U.S. include venlafaxine, duloxetine, milnacipran, levomilnacipran, and sibutramine. All of these drugs are metabolized by the cytochrome p450 system, and medication levels vary according to cytochrome p450 status. Some of these agents, for example venlafaxine, are metabolized to an active metabolite by the CYP2D6 enzyme, and other agents such as duloxetine are inhibitors of cytochrome p450 activity. There also exist a number of selective norepinephrine reuptake inhibitors, 2 of which (atomoxetine and maprotiline) are approved for use in the United States.

Lobello et al. tested patients from 4 randomized controlled trials (RCTs) of venlafaxine versus placebo for CYP2D6 status and correlated genetic status, defined as either extensive metabolizers (EM) or poor metabolizers (PM), with response to treatment. There were no significant differences in dose of the drug according to genetic status. In 4 of 5 comparisons, patients who were EMs had a better response to treatment as determined by depression rating scales. There was also a significantly greater percent of responders in the EM group compared to the PM. There were no differences in discontinuation of therapy or adverse event rates between the EM and PM group.

Waade et al retrospectively evaluated the association between age, serum levels of venlafaxine and the SSRI escitalopram for different CYP2D6 and CYP2C19 genotype subgroups. The study included 462 serum concentration measurements from 255 patients treated with venlafaxine and 953 serum concentration measurements from 541 patients treated with escitalopram. Patients were divided into 3 CYP2D6 (venlafaxine) or CYP2C19 (escitalopram) phenotype subgroups according to inherited genotype. (PMs, heterozygous extensive metabolizers [HEMs], and EMs). An age-related difference (comparing patients <40 years, 40-65 years, and >65 years) was seen for venlafaxine, with a higher mean dose-adjusted serum concentration of venlafaxine for patients older than 65 years compared with those younger than 40 years in the PM group: 18.8 versus 2.4 (p<0.001). There were no significant age-related differences in serum venlafaxine concentration for HEM and EM patients and no association between age and escitalopram concentration regardless of genotype.

For duloxetine, the inhibitory effects on cytochrome p450 activity are manifested by higher drug concentrations for other medications metabolized by cytochrome p450, such as tricyclic antidepressants and/or SSRIs. Similarly, other inhibitors of cytochrome p450 such as paroxetine, will increase levels of duloxetine.

Atomoxetine HCl is a SNRI that is approved to treat attention-deficit/hyperactivity disorder
(ADHD). Atomoxetine, the active moiety, is primarily metabolized by CYP2D6. The therapeutic window for atomoxetine is wide, and dosing is weight based, initiated at a standard dose per kg and adjusted thereafter according to clinical response and adverse effects. At steady state dosing, CYP2D6 PMs have substantially higher atomoxetine plasma concentrations than extensive metabolizers, although because it is generally well tolerated across a wide range, adverse effects do not appear to be significantly associated with PMs. After titration, mean doses for EMs and PMs also do not differ significantly. However, more EM patients discontinued in one trial due to lack of efficacy and PMs improved inattention scores more than EMs in another, perhaps suggesting a need to re-examine recommended dosing limits. The FDA decided not to include a recommendation to perform genotyping prior to prescribing atomoxetine. Dosing directions recommend a low starting dose to be increased to the target dose if well tolerated. Thus, genotyping for CYP2D6 PMs of atomoxetine is not recommended because the margin of safety is not exceeded and evidence to support guidelines for dosing such that patient outcomes are improved has not been collected.

Indeed, Ramoz et al. recently reported on two independent cohorts of 160 and 105 ADHD children treated for 6 weeks with atomoxetine. Interindividual response to the drug appeared independent of the genetic variants of CYP2D6. The authors did observe drug treatment and genomic associations, but these were found between drug response and a haplotype of the norepinephrine transporter (NET) gene - Slc6a2. It was suggested further study be applied to assessment of this region to better manage patients being treated with this drug.

Most recently ter Laak et al. evaluated 100 patients treated for ADHD with standard doses of atomoxetine. A neurologist identified 10 of these who, based on late response or adverse effects, were subject to CYP P450 testing. Eight of the 10 were found to have a nonfunctional or less functional 2D6 allele. Four of these children showed improved responses on decreased atomoxetine; four were taken off treatment because of initial adverse events. While it is plausible that pretreatment testing could yield improved results, the study was not designed to evaluate the actual effect of testing on treatment outcomes.

**Section Summary: Selection and Dosing of SNRIs**

SNRI metabolism is affected by genetic status of cytochrome p450, with the greatest potential clinical effect seen for venlafaxine. For this agent, EMs of CYP2D6 have higher levels of the active metabolite, and genetic status may have an impact on treatment response. A post-hoc re-analysis of data from multiple RCTs has correlated treatment response to venlafaxine with genetic status. No studies have yet established that outcomes are improved as a result of genetic testing prior to initiating venlafaxine or other SNRIs.

Atomoxetine is a SNRI that is used for ADD. Although it has a wide therapeutic window, there is potential for PMs who require relatively high doses to reach serum levels that may be toxic. However, current recommendations for starting atomoxetine at a low dose and watching closely for adverse effects while titrating higher should minimize the risk of toxicity for PMs.
Selection and dosing of tricyclic antidepressants
Nortriptyline and other tricyclic antidepressants (TCA) are metabolized by the CYP2D6 enzyme. Patients who are PMs will develop serum concentrations of nortriptyline that are 3-10-fold higher than patients who are EMs. de Vos et al. studied 678 patients treated with TCAs and reported that EMs had increased metabolism and lower serum levels of amitriptyline and citalopram, but not clomipramine. However, these authors reported that the differences observed were not likely to have clinically important effects. In the study by Hodgson et al previously discussed, CYP2D6 genotype was associated with nortriptyline levels, but not with clinical improvement in 161 patients treated with nortriptyline.

It has been reported that patients with TCA overdose may have different risk depending on cytochrome p450 genetic status. Simulations and case reports have reported that PMs may be at higher risk for toxic levels of nortriptyline and that toxic levels are maintained for longer periods of time. There are no clinical studies that demonstrate that measuring genetic status improves outcomes for patients who have had a TCA overdose.

Section Summary: Selection and Dosing of Tricyclic Antidepressants
Cytochrome p450 genetic status affects the metabolism and serum levels of multiple TCAs, including nortriptyline, but the clinical impact of these differences in metabolism are not clear. There is some evidence to suggest that patients who are PMs are more prone to toxic levels in the setting of a TCA overdose. There is no evidence available to support that prospective testing of patients treated with TCAs improves outcomes.

Selection or Dosing of antipsychotic drugs
Classical antipsychotic agents (e.g., haloperidol, perphenazine, and risperidone) have therapeutic ranges that are often narrow, adverse effects that can be severe, and highly variable clinical responses. Case reports and small studies have reported associations between clinically significant adverse reactions or clinical responsiveness and specific CYP450 genotypes (e.g. CYP2D6, CYP3A4 variants), but most studies are small and results are inconsistent. Moreover, plasma concentration of antipsychotic drugs may not be correlated with treatment outcome or adverse effects. Because most patients with schizophrenia take combinations of psychoactive agents for extended periods of time, drug-drug and drug-environmental interactions may influence the CYP450 metabolic phenotype in addition to genotype. For example, carbamazepine, phenytoin, smoking, and alcohol consumption can induce CYP450 activity, whereas caffeine and fluvoxamine are inhibitors of CYP1A2. Some antipsychotic medications are metabolized by multiple CYP450 enzymes and dominant pathways may vary. Several classical antipsychotic drugs inhibit the CYP450 enzyme required for their metabolism, and may render the patient a phenotypic PM despite an EM genotype. Thus, initial dosing algorithms need to accommodate both genetic influences and other interactions; therapeutic drug monitoring will probably continue to be needed to reflect the metabolic phenotype during ongoing treatment.

Systemic Reviews
Fleeman et al. in a 2010 health technology assessment reviewed 51 articles on clinical validity of testing for cytochrome P450 in patients with schizophrenia treated with antipsychotic medications. The authors concluded that patients with heterozygous or
homozygous mutations for CYP2D6 were at increased risk for tardive dyskinesia (odds ratio respectively of 2.08 and 1.83) and patients with homozygous mutations at increased risk for Parkinsonism (odds ratio of 1.64). However, no published reports on clinical utility were identified. The authors concluded “further evidence is required to link phenotype to genotype.” This assessment has recently been published in the medical literature.

In 2011 Fleeman et al. published a systematic review and meta-analyses of cytochrome p450 testing for use in prescribing antipsychotics in adults with schizophrenia. After search of 2,841 papers, they identified 47 papers that described clinical validity but no published papers on clinical utility of testing. They found no convincing evidence of an association between test results and either drug efficacy or toxicity. Differences when seen (an association, for example, with tardive dyskinesia) were considered too small to be clinically meaningful.

**Observational Studies**

Other studies have reported on CYP2D6 polymorphisms and response to risperidone. Jovanovic et al. evaluated the role of CYP2D6 in 83 drug-naïve patients undergoing a first episode of psychosis and treated with risperidone. While significant improvements were observed in positive and general symptoms using this drug, the investigators were unable to identify an association between treatment response and variations in either genetic or drug concentration findings. Locatelli et al. evaluated CYP2D6 genotypes in 50 patients hospitalized for acute schizophrenia and also treated with risperidone. They found elevations in risperidone plasma levels in patients classified as PMs or IMs based on genotyping. Drug efficacy is not reported, but these authors observed an association between genotype, levels of risperidone, and the occurrence of extrapyramidal syndromes. They were uncertain whether these observations were strong enough to support routine testing as an aid to assessment of drug toxicity and suggested further study was needed. In a study of 76 white adult males with schizophrenia who were being treated with risperidone, Almoguera et al reported that CYP2D6 phenotype was associated with improved scores on the total and negative symptoms scales of the Positive and Negative Syndrome Scale.

Van der Weide and van der Weide retrospectively evaluated CYP2D6 and CYP3A4 polymorphisms and serum drug concentrations among 834 adults treated with aripiprazole, haloperidol, pimozide, or risperidone (n=130, 312, 86, and 396, respectively).77 CYP3A4 genotype was not associated with dose-corrected serum antipsychotic concentration. However, CYP2D6 genotype was associated with dose-corrected concentrations of all 4 antipsychotics. Clinical outcomes are not reported.

**Section Summary: Selection or Dosing of Antipsychotic Drugs**

Individuals with genetic variants in the CYPD6 gene may be at increased risk for adverse effects of antipsychotic drugs, particularly extrapyramidal effects such as tardive dyskinesia. However, the clinical utility of testing is uncertain, since management changes as a result of genetic testing have not been evaluated.
Selection of Dosing of Codeine

Codeine is metabolized by CYP2D6 to morphine. Enhanced CYP2D6 activity (i.e., in CYP2D6 UMs) predisposes to opioid intoxication. On August 17, 2007, the FDA issued a warning regarding codeine use by nursing mothers. Nursing infants “may be at increased risk of morphine overdose if their mothers are taking codeine and are ultra-rapid metabolizers of codeine.” Information about genetic variation and risk of accelerated codeine metabolism is now included in package insert information. The warning was prompted by a 2006 case report concerning an infant who died of morphine overdose. The mother, prescribed codeine for episiotomy pain, was a CYP2D6 UM, with high levels of circulating morphine. Not mentioned in the original case report, but noted in a later publication, is the fact that the mother was also homozygous for the UGT2B7*2 metabolizing enzyme variant, which is believed to also contribute to higher than normal production of active opioids from codeine. Currently, the FDA is not recommending genotyping for any population prior to prescribing codeine because “there is only limited information about using this test for codeine metabolism.” Information is limited to associations of genotype with morphine exposure and adverse effects such as sedation in adults, and association of mothers’ genotype with morphine exposure in mothers and with infant CNS depression. Studies have been small, with correspondingly few PMs and UMs for drawing conclusions. Madadi et al. have recently described the use of a pedigree approach to aid in diagnosis, identification of other at risk family members and simplification of pharmacogenomic analysis. However, they note that for most medical centers, the framework for performing this work may not exist, and its applicability and relevance to general use remain unestablished.

In 2013, in response to reports of deaths that have occurred in children with obstructive sleep apnea who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being UMs of codeine due to a cytochrome CYP2D6 polymorphism, FDA added a black box warning to the labeling for codeine listing its use for postoperative pain management in children following tonsillectomy and/or adenoidectomy as a contraindication. The FDA’s guidelines state, “Routine CYP2D6 genotype testing is not being recommended for use in this setting because patients with normal metabolism may, in some cases, convert codeine to morphine at levels similar to ultra-rapid metabolizers.”

Section Summary: Selection or Dosing of Codeine
Enhanced CYP2D6 activity is associated with risk of accelerated codeine metabolism with 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. There is little evidence about the clinical utility of testing for CYP2D6 genotype.

Selection and Dosing of Highly Active Antiretroviral Agents

Dose of Efavirenz
Current guidelines recommend efavirenz as the preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for HIV-infected patients. Forty to 70% of patients report adverse CNS effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse
effects. Efavirenz is primarily metabolized by CYP2B6, and inactivating polymorphisms are associated with higher efavirenz exposure, although plasma levels appear not to correlate with adverse effects. Limited reports suggest that CYP2B6 PMs have markedly reduced side effects while maintaining viral immunosuppression at substantially lower doses. Simulations of such dose adjustments support this position.

Cabrera et al. have recently reported on an evaluation in 32 patients of the relationship between CYP2B6 polymorphisms and efavirenz clearance. Although they reported that CYP2B6 polymorphisms could be used to account for only 27% of interindividual variability, they noted decreased clearance of 50% in the patient group with the G/T genotype and 75% with the T/T genotype. Based on this observation, they suggested a gradual reduction in dose of efavirenz be considered in patients with these phenotypes. They proposed use of a model to incorporate factors that affect drug levels. However, based on the complexity of factors involved in dosing they concluded drug treatment should be carefully evaluated using therapeutic drug monitoring and assessment of clinical efficacy.

Two recent studies, one evaluating 373 patients for polymorphisms in CYP2B6 and constitutive androstane receptor (CAR) (78) and one genotyping for 23 markers in 15 genes. Both demonstrated an association between markers and early efavirenz discontinuation. Both articles recommended further study to determine the clinical utility of these associations.

Lee et al evaluated the effect of CYP2B6 G516T polymorphisms on the plasma efavirenz concentrations in HIV-infected patients, with or without concomitant rifampicin use. The study included 171 HIV-infected patients including 18 with tuberculosis, 113 (66.1%) with CYP2B6 G516G, 55 (32.2%) with GT, and 3 (1.8%) with TT genotype. Patients with GT or TT genotype had a significantly higher plasma efavirenz concentration than those with GG genotype (2.50 vs 3.47 mg/L for GT genotype and 8.78 mg/L for TT genotype; p<0.001).

Bienvenu et al evaluated the effect of single nucleotide polymorphisms (SNPs) in 5 drug metabolizing enzymes on plasma efavirenz levels and treatment response in patients treated with efavirenz alone (N=28) and when treated with cotreated with efavirenz and rifampicin-based TB treatment (N=62). Serum efavirenz levels differed based on CYP1A2 genotype (T/G vs T/T) when patients were cotreated with efavirenz and rifampicin, but not when patients received efavirenz alone. High serum efavirenz levels were associated with CYP2B6 516T/T genotype, both with and without rifampicin treatment. CYP2B6 516T/T and 983T/T genotypes predicted supratherapeutic efavirenz levels (positive predictive value, 100%), particularly in the absence of rifampicin.

**Other Antiretroviral Therapies**

While the preponderance of the evidence related to CYP450 genetic testing for antiretroviral therapies has focused on efavirenz, there has been some investigation of pharmacogenomics testing for other antiretroviral therapies. In a case-control analysis of 27 patients with nevirapine- induced Stevens-Johnson syndrome (SJS) induced by the non-nucleoside reverse transcriptase inhibitor nevirapine and 78 controls, Ciccacci et al found
that polymorphisms in CYP2B6, but not in CYP3A4 and CYP3A5, were associated with SJS risk. Lu et al reported that CYP3A5 polymorphisms are associated with serum concentrations of maraviroc, a CCR5 receptor antagonist used for HIV treatment, in healthy control subjects.

**Section Summary: Selection and Dosing of Highly Active Antiretroviral Agents**

Genetic variants in CYP2B6 are associated with increased side effects for patients treated with efavirenz, leading to some recommendations to reduce dosing based on genotype results. The impact of this strategy on health outcomes has yet to be evaluated; therefore the clinical utility of genotyping for efavirenz dose is uncertain. Preliminary evidence suggests that CYP450 polymorphisms may be associated with serum levels and adverse effects of other antiretroviral therapies, but the clinical utility of these findings is also uncertain.

**Dose of immunosuppressant for Organ Transplantation**

Immunosuppressive drugs administered to organ transplant patients have a narrow therapeutic index with the consequences of rejection or toxicity on either side. In addition, there is variability in patient response, requiring close clinical follow-up and routine therapeutic drug monitoring to maintain safety and efficacy. Tacrolimus blood levels are related to CYP3A5 genetic variants, with an approximately 2.3-fold difference in daily dose required to maintain target concentration between CYP3A5*3 and CYP3A5*1 homozygous variants. CYP3A5*1 carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to noncarriers; although the overall rate of acute rejection episodes was not higher in CYP3A5*1 carriers, their rejection episodes did occur earlier. Studies have reported associations between CYP3A5 genotype and tacrolimus exposure in pediatric renal transplant recipients and the required tacrolimus dose in heart transplant recipients.97 In a 2015 systematic review and meta-analysis which included 37 studies evaluating the effect of CYP3A5 polymorphisms on outcomes in kidney transplant recipients treated with tacrolimus, Rojas et al found that CYP3A5*1 carriers had significantly lower plasma tacrolimus concentration per daily dose per body weight than carriers of the CYP3A5*3/*3 genotype.

Population pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children. These models predict clearance based on CYP3A5*3/*3, as well as clinical factors, including body weight, hematocrit, and time since transplant. Although they applied a number of bootstrap techniques to validate their model, they did not perform an independent clinical validation of their model and concluded “a prospective study in a larger number of patients is warranted to evaluate the clinical benefits of individualizing tacrolimus dosage in the immediate post-transplantation period on the basis of a pretransplant determination of CYP3A5 polymorphism.”

Passey et al used tacrolimus blood trough and dose information from 681 kidney transplant recipients to develop a predictive tool for tacrolimus apparent clearance, from which individual tacrolimus dosing could be extrapolated. The study’s final model included CYP3A5 genotype, along with other clinical factors, but was not validated in an independent population. In a subsequent study, Boughton et al evaluated the previously-developed
model in a single-center cohort of renal transplant recipients. The study found a weak correlation ($R=0.431$) between clearance based on dose-normalized tacrolimus trough concentrations and the algorithm-predicted clearance.

Based on observations that patients with genetic variants of CYP3A5 require higher tacrolimus doses to achieve a therapeutic trough concentration (C0), Thervet et al conducted an RCT to compare the proportion of tacrolimus-treated renal transplant patients within a targeted C0 range for 2 tacrolimus dosing strategies, CYP3A5 genotype-informed dosing or standard dosing. The study included 280 patients, 140 who received standard dosing and 140 who received CYP3A5 genotype-specific dosing. The genotype-directed therapy group was more likely to achieve the study’s primary outcome, proportion of patients with tacrolimus C0 in the target range after 6 oral doses, than the control group (43.2% [95% CI, 36% to 51.2%] vs 29.1% [95% CI, 22.8% to 35.5%]; $p=0.030$). The genotype-directed therapy group had fewer dose adaptations (281 vs 420; $p=0.004$). Graft function and survival were similar between groups.

Less evidence is available for other immunosuppressants, such as sirolimus and cyclosporine. Xue et al developed a pharmacokinetic predictive model based on data on cyclosporine blood trough and dose information, combined with demographics, hematological indices, biochemical levels, concurrent drugs, and genetic polymorphisms of CYP3A4, CYP3A5, and ABCB1, from 117 allogeneic hematopoietic stem cell transplant recipients. However, the model has not been validated in clinical populations.

**Section Summary: Dosing of Immunosuppressant for Organ Transplantation**

CYP3A5 genetic variants may be used to predict tacrolimus clearance. One randomized trial demonstrated that the use of a CYP3A5 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, which the authors attribute to a patient population at low risk of acute rejection or other clinical events. Additional studies of the clinical utility of CYP3A5 genetic testing-based algorithms in tacrolimus management are needed. There is limited evidence on the impact of genotype on dosing on immunosuppressant medications.

**Selection and management of patients on beta blockers**

Several recent reports have indicated that lipophilic beta selective adrenergic receptor antagonists such as metoprolol used in treating hypertension may exhibit impaired elimination in patients with CYP2D6 polymorphisms. Bijl et al. in a population based cohort study of 1,553 patients noted increased risk of bradycardia in patients found to be PMs (CYP2D6 *4/*4). Recently, Baudhuin et al. studied the relationship between CYP2D6, ADRB1, and UGT1A1 and response in 93 patients with congestive heart failure treated with metoprolol or carvedilol and observed no differences according to genotype. In contrast, Wojtczak et al analyzed the association between CYP2D6 polymorphisms and metoprolol concentration in a cohort of 50 patients. Patients with PM genotypes had significantly higher plasma metoprolol concentrations than patients with EM genotypes (mean 92.25 ng/mL vs 168.22 ng/mL, respectively; $p<0.000$). However, the clinical consequences are uncertain.
Other studies have not demonstrated similar associations. Baudhuin et al. studied the relationship between CYP2D6, ADRB1, and UGT1A1 and response in 93 patients with heart failure treated with metoprolol or carvedilol and observed no differences according to genotype. Similarly, Wu et al. reported no significant associations between CYP2D6 polymorphisms and treatment outcomes (systolic blood pressure decrease of 10 mmHg or more) in 93 patients with hypertension treated with metoprolol.

In a subanalysis of the MERIT-HF trial, Batty et al. evaluated the role of polymorphisms in the CYP2D6 locus in metoprolol pharmacokinetics and clinical response. In the study population of 605 subjects, serum metoprolol concentrations were inversely associated with the number of functional CYP2D6 alleles; median serum metoprolol concentration was 2.1- and 4.6-fold greater in the IM and PM groups, compared with the EM group, respectively (p<0.000). During dose titration, EMs had a smaller mean reduction in heart rate from baseline compared with IMs (7.9 vs 10.5 at 4 weeks, p=0.02; 9.7 vs 13.2 after 6 weeks, p=0.01).

**Section Summary: Selection and Management of Patients on β-Blockers**

CYP2D6 genetic variants may be associated with response to beta-blocker treatment, but little evidence currently exists on the clinical utility of testing for CYP2D6 variants in improving outcomes from beta-blocker treatment.

**Dosing and management of anti-tuberculosis medications**

A number of studies have reported an association between CYP2E1 status and the risk of liver toxicity from anti-tuberculosis medications. A meta-analysis of available trials was reported by Deng et al. in 2013. Compared with wild type genotype, patients with any variant genotype had an increased risk of liver toxicity (OR 1.36, 95% CI 1.09-1.69). Patients who were slow metabolizers had the highest risk of toxicity (OR 1.88, 95% CI 1.14-3.09), and this overall risk was also increased in Asian patients. This study does not address the question of whether genetic testing can reduce liver damage from anti-tuberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels.

**Clinical Utility of Genetic Panel Testing for CYP450 Polymorphisms**

Panel testing for CYP450-related polymorphisms may be considered in the category of panels for genetic conditions for the purposes of risk assessment of asymptomatic individuals, for which the following criteria apply:

1. All individual components of the panel have demonstrated clinical utility OR the tests that have not demonstrated clinical utility do not have the potential to cause harm.
2. Testing is performed in a CLIA-approved lab.
3. Analytic validity of panel approaches that of direct sequencing.
4. Panel testing offers substantial advantages in efficiency compared with sequential analysis of individual genes.
5. The yield of testing is acceptable for the target population.
For panel testing for CYP450 polymorphisms, the individual components of the tests generally have not demonstrated clinical utility.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollme</th>
<th>Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous</td>
<td>5270</td>
<td>Aug 2016</td>
</tr>
<tr>
<td></td>
<td>Study of Clopidogrel and Ticagrelor Anti-Platelet Treatment Using an Individualized Strategy Based on Genotyping in</td>
<td>20</td>
<td>Aug 2016</td>
</tr>
<tr>
<td></td>
<td>Effects and Cost-Effectiveness of Pharmacogenetic Screening Among Elderly Starters With Antidepressants: A Pragmatic</td>
<td>75</td>
<td>Sep 2016</td>
</tr>
<tr>
<td></td>
<td>Prospective Cytochrome P450 Genotyping and Clinical Outcomes in Patients With</td>
<td>26</td>
<td>Mar 2019</td>
</tr>
</tbody>
</table>

**Summary of Evidence**

The evidence for testing for CYP2C19 metabolizer status by CYP2C19 genotyping in patients with need for antiplatelet therapy who are undergoing or being considered for clopidogrel therapy includes 1 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 genotypedirected 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.

SUPPLEMENTAL INFORMATION

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 4 physician specialty societies and 4 academic medical centers while this policy was under review in 2012. Opinions on use of genotyping for testing in patients being considered for clopidogrel treatment were mixed, with 5 suggesting the test be considered investigational and 3 suggesting it be considered medically necessary.

Practice Guidelines and Position Statements
A consensus statement by the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) on genetic testing for selection and dosing of clopidogrel was published in 2010. The recommendations for practice included the following statements:

- 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.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined
- 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.
• The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
• There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for cytochrome p450 have been identified.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician. Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VIII. References


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