I. Description

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.

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. 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 (EM;
normal). Poor metabolizers (PM) lack active enzyme gene alleles, and intermediate metabolizers (IM), 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 (UM) 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, UM may suffer adverse effects and PMs may not respond.

However, it is very important to realize that 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.

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.
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 U.S. Food and Drug Administration (FDA) approval but which must meet CLIA quality standards for high complexity testing. The AmpliChip (Roche Molecular Systems, Inc.) is the only FDA-cleared test for CYP450 genotyping. 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. 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. 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.”

II. Criteria/Guidelines

CYP450 phenotyping for CYP2C19 *2 and *3 alleles is covered (subject to Limitations/Exclusions and Administrative Guidelines) once per lifetime for patients with cardiovascular disease undergoing treatment with clopidogrel (Plavix) in order to identify those who are poor metabolizers of the drug (patients with CYP2C19 *2/2,*3/3, and *2/3 genotypes) and who are, therefore, likely to exhibit poor response to the drug.

III. Limitations/Exclusions

A. CYP450 genetic polymorphisms for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity is not medically necessary for all other indications, including not limited to the following applications:

1. Selection or dose of selective serotonin reuptake inhibitor (SSRI)
2. Selection or dose of antipsychotic drugs
3. Deciding whether to prescribe codeine for nursing mothers
4. Dose of atomoxetine HCl (approved for treatment of attention-deficit/hyperactivity disorder)
5. Dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection)
6. Dose of immunosuppressant for organ transplantation
7. Selection or dose of beta blockers (e.g., metoprolol)

B. CYP450 phenotyping for CYP2C19 is limited to once per lifetime for patients undergoing treatment with clopidogrel.
IV. Administrative Guidelines

A. Precertification is not required.

B. Applicable CPT codes:

<table>
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<th>CPT</th>
<th>Description</th>
</tr>
</thead>
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<tr>
<td>83890-83914</td>
<td>Molecular diagnostic code range (less than 11 probes)</td>
</tr>
<tr>
<td>88384</td>
<td>Array-based evaluation of multiple molecular probes: 11 through 50 probes</td>
</tr>
<tr>
<td>88385</td>
<td>51 through 250 probes</td>
</tr>
<tr>
<td>88386</td>
<td>251 through 500 probes</td>
</tr>
</tbody>
</table>

Modifier Description

9B CYP2 genes, commonly called cytochrome p 450 (drug metabolism)

V. Rationale

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 study(ies) 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. (1) 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. (2)

• 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 interindividual 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. (3-8) 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. (9, 10)

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. (11, 12) 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. (13, 14)

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

**Selection or dose of SSRI.** CYP2D6 and CYP2C19 are primary CYP450 enzymes involved in the metabolism of SSRIs. 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. 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 non-psychotic depression. (15) 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." (16)

Two recent reports have focused on use of genotyping in patients treated with paroxetine. Gex-Fabry et al. (17) 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. (18) 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.

Serretti et al. (19) in a retrospective study of 287 patients on antidepressants demonstrated no association between response and allelic variations for P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6.

Tsai et al. (20) 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.

Finally Sim et al. (21) 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.

In spite of growing circumstantial evidence that genotype has an impact on drug levels and/or on clinical outcomes, to date no study has actually demonstrated either the clinical validity or utility for such testing.

Selection or dose 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. (22-24) Moreover, plasma concentration of antipsychotic drugs may not be correlated with treatment outcome or adverse effects. (25) 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. (26-30)

Fleeman et al. (29) 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. (32)

Two additional reports on use of risperidone have been published since the last policy update. Jovanovic et al. (33) 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. (34) 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.

Deciding whether to prescribe codeine for nursing mothers. Codeine is metabolized by CYP2D6 to morphine. Enhanced CYP2D6 activity (i.e., in CYP2D6 UM) predisposes to opioid intoxication. On August 17, 2007, the U.S. Food and Drug Administration (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. (35) 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.” (36,37) 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. (38) 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.

A prospective clinical trial (NCT010504000) “CYP2D6 Screening for Adverse Drug Reactions to Codeine in Breast Milk” is currently actively recruiting patients. This trial will include a pharmacogenetically directed study of pain therapy in women undergoing cesarean sections. The target study completion date is December 2012.

Determining risk of atherothrombotic events in patients treated with clopidogrel after an acute coronary syndrome or a percutaneous coronary intervention. Dual antiplatelet therapy with aspirin and clopidogrel is currently recommended 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 (39); higher loading and/or maintenance doses decrease reactivity even in initial nonresponders, presumed to be CYP2C19 PMs. (40-42) Higher platelet reactivity has also been associated with a higher rate of subsequent thrombotic events. (43) 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. (44)

Recently, several publications have evaluated patients treated with clopidogrel by CYP2C19 genetic status for clinical outcomes, summarized in the table below. Simon et al. (45) and Mega et al. (46) found significant, although modest, increases in risk of subsequent thrombotic events for CYP2C19 variant carriers in unselected patient populations; Collet et al. (47) found a stronger risk in a highly selected population of younger patients with family history.

Shuldiner et al. (48) 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. (49) 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).

In contrast, however, Pare et al. (50) retrospectively genotyped 5,059 patients from two 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).

Mega et al. (46) recently 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 noncarriers.

Variation in clopidogrel response is an extremely complicated process impacted by a wide range of both genetic and environmental factors (including patient compliance, metabolic state, and drug and food intake). For example, Sibbing et al. (44) in another recent study (n=1524) have noted the presence of the CYP2C19*17 allele appears to result in decreased platelet aggregation when compared to wild-type homozygotes with an increased 30-day risk of bleeding but no change in the occurrence of stent thrombosis. Over time, more information about gene drug associations may refine both testing needs and our ability to use results to optimize choice or dosing of drugs.

### CYP2C19 Clopidogrel Data Summary

<table>
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<tr>
<th>Study</th>
<th>CYP2C19 alleles tested</th>
<th>Follow-up (months)</th>
<th>Hazard ratio for adverse events (adjusted for wt 1:00)</th>
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<td></td>
<td></td>
<td></td>
<td>Adverse Events</td>
</tr>
<tr>
<td>Simon et al. (45)</td>
<td>*2, *3, *4, *5, *17</td>
<td>12</td>
<td>Death from CV cause, nonfatal MI or stroke</td>
</tr>
</tbody>
</table>
n=2,208 |  |  | (0.51-0.93) | (1.10-3.58) |
Simon et al. (45) | *2,*3,*4,*5,*17 | 12 | Death from CV cause, nonfatal MI or stroke | 0.78 | 3.58 |

Mega et al. (46) | *1A,*2A,*3,*4,*5A, *6,*7,*8,*9,*10, *12,*13,*14,*17 | 15 | Death from CV cause, nonfatal MI or stroke | 1.53 | 1.07-2.19 |
Collet et al. (47) | *2,*3,*4,*5,*6 | Median | Death from CV, nonfatal MI or urgent revascularization | 5.38 | 2.32-12.47 |
Shuldiner et al. (48)n=227 | *2 | 12 | Stent thrombosis | 2.42 | 1.18-4.49 |
Sibbing et al. (49) | *2 | 30 days | Stent thrombosis | 3.81 | 1.45-10.02 |
Pare et al. (50) | *2,*3, *17 | | Primary outcome was the composite of death from CV disease, nonfatal MI, or stroke or stroke, systemic embolism outside the CNS, MI, or death from vascular causes | No significant difference observed based on genotype | Yes |

Reports of adverse events in patients varied by study and by study design. For patients specifically undergoing stent placement (percutaneous coronary intervention), adverse events (stent thrombosis) in wild type patients ranged from 0.4% to 10% compared to 1.5% to 21% in patients with 1 or 2 mutations.

In patients treated more generally for acute MI, adverse events (death from CV cause, nonfatal MI or stroke/revascularization) in wild type patients ranged from 6% to 14% compared to 12% to 21% in patients with 1 or 2 mutations and 19% in patients specifically identified as having 2 mutations.

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.

 Campo et al. (53) summarized options available for use in patients with poor response to clopidogrel but avoided specific recommendations on which alternatives might be most effective in part because of the paucity and preliminary nature of the current evidence.

 One option is the substitution of alternative drugs in patients identified to be PMs. Ticlopidine, the first FDA-approved thienopyridine, has effects very similar to clopidogrel and is available in generic formulations. It has generally been avoided for first-line therapy because of the presence of bone marrow toxicity. (54) However, in patients resistant to clopidogrel, it has been shown to be active (55) and may be considered a potential treatment option. Tantry et al. (56) recently evaluated CYP219 variants in 174 patients randomized to receive either ticagrelor or clopidogrel. Ticagrelor exhibited lower platelet reactivity than clopidogrel irrespective of CYP2C19 type. Loss of function carriers had greater platelet reactivity during clopidogrel therapy. Clinical outcomes were not reported.

 Prasugrel, another thienopyridine approved in 2009 by FDA, has been shown to have a favorable treatment profile when compared to clopidogrel with up to a 19% reduction in relative risk for ischemic events. (57) Unfortunately, this improvement in performance is complicated by a significant increase in the rate of bleeding, including a significant increase in fatal major hemorrhage. Three subgroups at particular risk for bleeding include patients with a history of stroke or transient ischemic attacks before enrollment, the elderly (patients 75 yrs. or older), and those with a body weight of under 60 kilograms. Again the presence of clopidogrel resistance may create a reason to select this alternative.

 Finally, several recent reports (58, 59) have suggested improved outcomes in clopidogrel-resistant patients by use of supplementary anti-platelet drugs, notably the glycoprotein IIb/IIIa inhibitors. This work is promising but preliminary.

 Two recent studies (60, 61) have suggested that use of triple antiplatelet therapy adding cilostazol to clopidogrel and aspirin may lead to enhanced inhibition of platelet activity. The clinical consequences of such a regimen, however, have not been reported.

 A final option in addressing clopidogrel resistance is use of increased drug dosing. A small study comparing high versus conventional doses of clopidogrel showed changes in platelet function. However, the sample size was small and not all patients responded optimally. Clinical outcomes were not evaluated (51). Barker et al. (62) recently confirmed in 41 subjects with on-treatment platelet reactivity that use of increased maintenance dosing significantly decreased reactivity. Again, however, no clinical outcomes were reported.
It does appear that a number of treatment options exist for addressing the issue of what to do with patients likely to exhibit poor metabolic response to clopidogrel. These options must be carefully evaluated in the context of the risks and benefits each offers. Further study is needed to better define optimal choices for alternative therapy in poor metabolizers.

_Dose of atomoxetine HCl._ Atomoxetine HCl is a selective norepinephrine reuptake inhibitor 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. (63, 64) After titration, mean doses for EMs and PMs also do not differ significantly. (64, 65) However, more EM patients discontinued in one trial due to lack of efficacy (65) and PMs improved inattention scores more than EMs in another (64), 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. (66, 67)

Indeed, Ramoz et al. (68) 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. (69) 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.

_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. (70) 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. (71, 72) Simulations of such dose adjustments support this position. (73)
Cabrera et al. (74) 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. It is clear that larger studies are needed to support changes in current drug dosing practices and guidelines.

**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. (75) 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. (76) Zhao et al. (77) recently developed a population pharmacokinetic model of tacrolimus in pediatric kidney transplant patients using 50 de novo pediatric kidney transplant patients. They found oral clearance of tacrolimus was higher in patients with low hematocrit and lower in patients with CYP3A5*3/*3 polymorphisms. 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.” Randomized trials are currently underway to test genotype-directed initial tacrolimus dose versus standard dose. While pharmacogenetic applications for sirolimus and cyclosporine have been investigated, results are far less clear that genotyping is likely to have a significant clinical influence.

**Selection and management of patients on beta blockers.** Several recent reports (78,79) 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. (78) 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. (80) 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.

**Summary**

In general, most published CYP450 pharmacogenomic studies 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 under-powered 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 poor metabolizers are consequently difficult to interpret and decision making about how to use genotyping information is poorly defined with uncertain outcomes. As a result for most of the indications described above, CYP450 genotyping is investigational. This includes, but is not limited to, CYP450 genotyping for the following applications:

- selection or dose of selective serotonin reuptake inhibitor (SSRI)
- selection or dose of antipsychotic medications
- deciding whether to prescribe codeine for nursing mothers
- dose of atomoxetine HCl (approved for treatment of attention-deficit/hyperactivity disorder)
- dose of efavirenz (common component of highly active antiretroviral therapy for HIV infection)
- dose of immunosuppressant for organ transplantation
- selection or dose of beta blockers (e.g., metoprolol)

Data on the impact of clopidogrel appears to be particularly strong with multiple studies demonstrating that patients defined as poor metabolizers (CYP2C19 *2/2, *3/3, or *2/3) are at significantly increased risk of a variety of life-threatening adverse cardiovascular events. Because of this strong and significant link between metabolic state and clinical outcomes, FDA has recently issued a public safety communication and re-labeled the drug with a boxed warning about the availability of genetic testing and alternative drug therapies in patients who are found to be poor metabolizers. Alternative treatments, including several that are FDA approved, do exist although each has its own unique safety and efficacy profile, and none of the alternatives are without their own well-described risks.

Therefore, genotyping for CYP2C19 *2 and *3 alleles may be considered medically necessary to identify poor metabolizers in patients receiving clopidogrel. Treatment alternatives should be carefully selected according to the unique characteristics of each patient found to be a poor metabolizer and careful follow-up performed. More evidence is needed to assist in the decision making in this clinical situation.

VI. 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),
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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.

VII. References


63. de Leon J. The crucial role of the therapeutic window in understanding the clinical relevance of the poor versus the ultrarapid metabolizer phenotypes in subjects taking drugs metabolized by CYP2D6 or CYP2C19. *J Clin Psychopharmacol* 2007; 27(3):241-5.


