Medical Policy

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Title: Cytochrome p450 Genotyping

See Also:
- *Genetic Testing for Helicobacter pylori Treatment*
- *Genetic Testing for Tamoxifen Treatment*
- *Genetic Testing for Warfarin Dose*

Professional
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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.

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.

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 2 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 2 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.

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 Clinical Laboratory Improvement Act (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 2 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 2 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."

POLICY

A. CYP450 genotyping for the purpose of aiding in the choice of clopidogrel versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered **medically necessary**.

B. CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered **experimental / investigational**. This includes, but is not limited to, CYP450 genotyping for 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. selection and dosing of selective norepinephrine reuptake inhibitors
   5. selection and dosing of tricyclic antidepressants
   6. dose of efavirenz (common component of highly active antiretroviral therapy for HIV [human immunodeficiency virus] infection)
   7. dosing of immunosuppressant for organ transplantation
   8. selection or dose of beta blockers (e.g., metoprolol)
   9. dosing and management of antituberculosis medications

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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 (UM) 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 selective serotonin reuptake inhibitors (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 nonpsychotic 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 metabolizers (EMs) and UMs showed steady decreases in concentrations during the course of pregnancy, with increase in depressive symptoms. Intermediate metabolizers (IMs) and poor metabolizers (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 10 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.

Conclusions: 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 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., (31) 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, [OR]: 2.08 and 1.83) and patients with homozygous mutations at increased risk for Parkinsonism (OR: 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. 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.

In 2011 Fleeman et al. (32) 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.

Conclusions: 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.

***Deciding whether to prescribe codeine for nursing mothers*.** Codeine is metabolized by CYP2D6 to morphine. Enhanced CYP2D6 activity (i.e., in CYP2D6 ultrarapid metabolizers [UMs]) 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 central nervous system (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.

Conclusions: The relationship between genetic variants of cytochrome p450, codeine metabolism, and nursing mothers is not certain. A clinical trial is underway to test dosing based on genotype.

Selection and dosing of clopidogrel. 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)

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. (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. 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 [HR]: 2.42). Sibbing et al. (49) 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 (HR: 3.81).

Mega et al. (46) 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 intervention (PCI), 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.

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, based on the available data at that time, 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.

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. (50) 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).

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., (51) in a recent study (n=1,524) 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. Tiroch et al., (52) 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). 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.

Two systematic reviews and a meta-analysis were reported in 2011 that review both the observational evidence and the clinical trial evidence. Both of these reviews suggest that *CYP2C19* gene polymorphisms do not have a substantial or consistent influence on the clinical efficacy of clopidogrel.

Bauer et al. (53) 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 odds ratio 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. (54) searched online sites PubMed and EMBASE for studies linking CYP2C19 testing to treatment with clopidogrel. They 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. In a recent editorial, Beitelshees (55) notes that the results of this analysis may have been compromised by the fact that patients who did not undergo PCI were included. They concluded that the association between CYP2C19 genotype and adverse outcomes with clopidogrel treatment may not be present in all settings and may be strongest for clopidogrel indications with the greatest effects, such as patients undergoing PCI. This observation is supported by observations in the CHARISMA genetics study reported by Bhatt.(56) A total of 4,819 patients were genotyped in this study, and no relationship between CYP2C19 status and ischemic outcomes in stable patients was observed. Bhatt also observed significantly less bleeding in this subgroup.

Roberts et al. (57) 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.

Conclusions: 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.

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. 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 warning suggests changes in doses or changes in drug. Recent studies (58, 59) have suggested that changes in platelet reactivity in carriers may be dose-dependent and that in PCI patients, heterozygous carriers might require up to triple dosing of clopidogrel to reach a desired target platelet reactivity level. In homozygous carriers, it has been reported that even with higher clopidogrel doses, platelet reactivity cannot be raised to the level of clopidogrel treatment in non-carriers. In these patients, other drugs such as prasugrel or ticagrelor may be used as treatment alternatives.

Selection and dosing of selective norepinephrine reuptake inhibitors (SNRIs). SNRIs are used most commonly as antidepressants. Available agents in the U.S. include venlafaxine, duloxetine, and nefazodone. All of these drugs are metabolized by the cytochrome p450 system, and medication levels vary according to cytochrome p450 status. (60) 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.

Lobello et al. (61) 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.

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. (62)

Atomoxetine HCl is a serotonin norepinephrine reuptake inhibitor (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 EMs, 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 2 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; 4 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.

Conclusions: 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 reanalysis 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. It has a narrow therapeutic window, and there is potential for PMs 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- to 10-fold higher than patients who are EMs.

(70) 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. (71) However, these authors reported that the differences observed were not likely to have clinically important effects.

It has been reported that patients with TCA overdose may have different risk depending on cytochrome p450 genetic status. (71, 72) 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.

Conclusions. 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.

***Dose of efavirenz*.** Current guidelines recommend efavirenz as the preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for human immunodeficiency virus (HIV)-infected patients. Forty to 70% of patients report adverse central nervous system (CNS) effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects. (73) 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. (74, 75) Simulations of such dose adjustments support this position. (76)

Cabrera et al. (77) 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 have been published, one evaluating 373 patients for polymorphisms in CYP2B6 and constitutive androstane receptor (CAR) (78), and one evaluating genotyping for 23 markers in 15 genes (79). Both demonstrated an association between markers and early efavirenz discontinuation. Both articles recommended further study to determine the clinical utility of these associations.

Conclusions. 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.

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. (80) 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. (81) Population-based pharmacokinetic models for clearance of tacrolimus in kidney transplant recipients have been developed for both adult and children. (82, 83) These models predict clearance based on CYP3A5*3/*3, as well as clinical factors. Results show that oral clearance of tacrolimus is impacted by body weight, hematocrit and time since transplant, in addition to 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 posttransplantation 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.

Conclusions: There is currently limited evidence on the impact of genotype on dosing on immunosuppressant medications. Clinical utility for this test is lacking at the current time.

Selection and management of patients on beta blockers. Several recent reports (84, 85) 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., (84) 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. (86) 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.

Dosing and management of antituberculosis medications. A number of studies have reported an association between CYP2E1 status and the risk of liver toxicity from antituberculosis medications. A meta-analysis of available trials was reported by Deng et al. in 2013. (87) 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 antituberculosis medications, compared to the usual strategy of monitoring liver enzymes and adjusting medications based on enzyme levels.

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.

Summary

CYP450 genotyping has been demonstrated in a number of studies to identify 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 (PCI). Genotyping may be used to consider treatment alternatives, e.g., higher doses of clopidogrel or alternative drug choices. FDA has 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. As a result, genetic testing for selection and dosing of clopidogrel may be considered medically necessary.

For other medications, 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 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 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 and dosing of serotonin norepinephrine reuptake inhibitors (SNRIs)
- selection and dosing of tricyclic antidepressant medications
- selection or dose of antipsychotic medications
- deciding whether to prescribe codeine for nursing mothers
- 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).
- dosing and management of antituberculosis medications

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. (88) 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.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81225	CYP2C19 (cytochrome P450, family 2, subfamily C, polypeptide 19 (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *8, *17)
81226	CYP2D6 (cytochrome P450, family 2, subfamily D, polypeptide 6) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *4, *5, *6, *9, *10, *17, *19, *29, *35, *41, *1XN, *2XN, *4XN)
81227	CYP2C9 (cytochrome P450, family 2, subfamily C, polypeptide 9) (eg, drug metabolism), gene analysis, common variants (eg, *2, *3, *5, *6)

- Effective in 2012, there is specific CPT coding for this testing: 81225, 81226, 81227.
- There are also Tier 2 CPT codes that include cytochrome P450 testing:
  - 81401: Molecular pathology procedure, Level 2 (eg, 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) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6)
    - CYP3A5 (cytochrome P450, family 3, subfamily A, polypeptide 5) (eg, drug metabolism), common variants (eg, *2, *3, *4, *5, *6)
  - 81402: Molecular pathology procedure, Level 3 (eg, >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) (eg, congenital adrenal hyperplasia, 21-hydroxylase deficiency), common variants (eg, 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 (eg, 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) (eg, primary congenital glaucoma), full gene sequence
- 81405: Molecular pathology procedure, Level 6 (eg, 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) (eg, congenital adrenal hyperplasia), full gene sequence
  - CYP17A1 (cytochrome P450, family 17, subfamily A, polypeptide 1) (eg, congenital adrenal hyperplasia), full gene sequence
  - CYP21A2 (cytochrome P450, family 21, subfamily A, polypeptide 2) (eg, steroid 21-hydroxylase isoform, congenital adrenal hyperplasia), full gene sequence

ICD-9 Diagnoses

410.00-410.92	Acute Myocardial infarction, code range
411.0	Post-myocardial infarction syndrome
411.1	Intermediate coronary syndrome
434.10-434.91	Occlusion of cerebral arteries, code range
443.9	Peripheral vascular disease, unspecified

ICD-10 Diagnoses

I20.0	Unstable angina
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
I24.1	Dressler's syndrome
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.710	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris
I25.720	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.730	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris
I25.750	Atherosclerosis of native coronary artery of transplanted heart with unstable angina

I25.760	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery
I63.413	Cerebral infarction due to embolism of bilateral middle cerebral arteries
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.423	Cerebral infarction due to embolism of bilateral anterior cerebral arteries
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.433	Cerebral infarction due to embolism of bilateral posterior cerebral arteries
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.443	Cerebral infarction due to embolism of bilateral cerebellar arteries
I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63513	Cerebral infarction due to unspecified occlusion or stenosis of bilateral middle arteries
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.523	Cerebral infarction due to unspecified occlusion or stenosis of bilateral anterior arteries
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.533	Cerebral infarction due to unspecified occlusion or stenosis of bilateral posterior arteries
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.543	Cerebral infarction due to unspecified occlusion or stenosis of bilateral cerebellar arteries
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.8	Other cerebral infarction
I66.01	Occlusion and stenosis of right middle cerebral artery
I66.02	Occlusion and stenosis of left middle cerebral artery
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries
I66.11	Occlusion and stenosis of right anterior cerebral artery
I66.12	Occlusion and stenosis of left anterior cerebral artery
I66.13	Occlusion and stenosis of bilateral anterior cerebral arteries
I66.21	Occlusion and stenosis of right posterior cerebral artery
I66.22	Occlusion and stenosis of left posterior cerebral artery

I66.23	Occlusion and stenosis of bilateral posterior cerebral arteries
I66.3	Occlusion and stenosis of cerebellar arteries
I66.8	Occlusion and stenosis of other cerebral arteries
I73.9	Peripheral vascular disease, unspecified
I20.0	Unstable angina
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending coronary artery
I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
I22.2	Subsequent non-ST elevation (NSTEMI) myocardial infarction
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
I24.1	Dressler's syndrome
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.710	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris
I25.720	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.730	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris
I25.750	Atherosclerosis of native coronary artery of transplanted heart with unstable angina
I25.760	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery

I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.8	Other cerebral infarction
I66.01	Occlusion and stenosis of right middle cerebral artery
I66.02	Occlusion and stenosis of left middle cerebral artery
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries
I66.11	Occlusion and stenosis of right anterior cerebral artery
I66.12	Occlusion and stenosis of left anterior cerebral artery
I66.13	Occlusion and stenosis of bilateral anterior cerebral arteries
I66.21	Occlusion and stenosis of right posterior cerebral artery
I66.22	Occlusion and stenosis of left posterior cerebral artery
I66.23	Occlusion and stenosis of bilateral posterior cerebral arteries
I66.3	Occlusion and stenosis of cerebellar arteries
I66.8	Occlusion and stenosis of other cerebral arteries
I73.9	Peripheral vascular disease, unspecified

REVISIONS

10-26-2010	Policy added to the bcbsks.com web site.
08-12-2011	Rationale section updated.
	In Coding section: Updated nomenclature for CPT codes: 88385, 88386
	Reference section updated.
02-14-2012	In Coding section: ▪ Added CPT codes: 81225, 81226, 81227 (effective 01-01-2012) ▪ Added the following notations: ▪ "Use 81225, 81226, 81227 when indicated, otherwise use 88384, 88385, 88386. ▪ See the policies below for genetic testing related to these items: o Genetic Testing for Helicobacter pylori Treatment medical policy o Genetic Testing for Tamoxifen Treatment medical policy o Genetic Testing for Warfarin Dose medical policy"
01-01-2013	In Coding section: ▪ Removed CPT codes: 88384, 88385, 88386 (effective 12-31-2012)
03-31-2014	Description section updated
	In Policy section: ▪ In Item A revised wording from: "CYP450 phenotyping for CYP2C19 *2 and *3 alleles may be considered medically necessary in 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." To: "CYP450 genotyping for the purpose of aiding in the choice of clopidogrel

	versus alternative antiplatelet agents, or in decisions on the optimal dosing for clopidogrel, may be considered medically necessary." ▪ In Item B revised the wording from: "Aside from the use with clopidogrel treatment noted above, genotyping to determine specific cytochrome p450 (CYP450) genetic polymorphisms for the purpose of aiding in the choice of drug or dose increase efficacy and/or avoid toxicity is considered experimental / investigational. This includes, but is not limited to, CYP450 genotyping for the following applications:" To: "CYP450 genotyping for the purpose of aiding in the choice of drug or dose to increase efficacy and/or avoid toxicity for all other drugs is considered experimental / investigational. This includes, but is not limited to, CYP450 genotyping for the following applications:" ▪ In Item B removed E/I indication, "dose of atomoxetine HCl (approved for treatment of attention-deficit/hyperactivity disorder)" ▪ In Item B added E/I indications: "4. selection and dosing of selective norepinephrine reuptake inhibitors", "5. selection and dosing of tricyclic antidepressants", and "9. dosing and management of antituberculosis medications"
	Rationale section updated
	In Coding section: ▪ CPT Coding Instructions added ▪ ICD-10 Diagnoses Codes added
	References updated
10-01-2016	In Coding section: ▪ ICD-10 Codes Added Effective 10-01-2016: I63.413, I63.423, I63.433, I63.443, I63513, I63.523, I63.533, I63.543

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