APPENDIX to Pharmacogenomics Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Several cytochrome P450 (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) deoxyribonucleic acid (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 PMs. 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 may not reach therapeutic concentrations, while PMs may suffer more adverse events at usual dosage levels 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.

It is 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, genes and environment, and 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 interindividual 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 achieve an effective dose.

Cytochrome P450 enzyme phenotyping (identifying the 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, (i.e., 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 has been proposed to speed the process of achieving a therapeutic dose and avoid 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 United States Food and Drug Administration (FDA) approval but which must meet clinical laboratory improvement amendments quality standards for high complexity testing. The AmpliChip™ (Roche Diagnostics, Corp, Indianapolis, IN) 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. 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.” Another test is the Invader® UGT1A1 Molecular Assay (Third Wave Technologies, Inc., Madison, WI).

According to the FDA, this test is approved "as an in vitro diagnostic test for the detection and genotyping of the *1 (TA6) and *28 (TA7) alleles of the uridine diphosphate (UDP) glucuronosyltransferase 1A1 (UGT1A1) gene in genomic DNA from whole peripheral blood as an aid in the identification of patients with greater risk for decreased UDP-glucuronosyltransferase activity."

Validation of genotyping to improve pharmacologic treatment outcomes is a multistep process. In general, major suggested steps in the validation process are as follows:

- Establish the specific genotyping test performance characteristics, (i.e., does the test accurately and reproducibly detect the gene markers of interest (analytic validity))
- For each drug of interest, conduct preliminary performance studies in relevant populations or population subsets to evaluate the strength of the associations between the selected genetic markers and dose, therapeutic efficacy, and/or adverse events. This may be retrospective (clinical validity)
- Conduct prospective trials 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 Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Special Report, Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status, on which this policy is based. 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 publication suggests that the Roche AmpliChip™ may have a low sensitivity for the CYP2D6 UM genotype (Rebsamen et al., 2009)
- 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 non-genetic significant confounders statistically explains up to 60% of the variation in final dose (Zhu et al., 2007; Wadelius et al., 2007; Schelleman et al., 2008; Gage et al., 2008; Wu et al., 2008; Hatch et al., 2008). 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 (Anderson et al., 2007; BCBSA TEC, 2008)

- 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., (2001, 2004) reviewed CYP2D6 and CYP2C19 polymorphisms and pharmacokinetic data for several antidepressant 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 (Bishop & Ellingrod, 2004; Seeringer & Kirchheiner, 2008).

Clopidogrel

Dual antiplatelet therapy with aspirin and clopidogrel is currently recommended for the prevention of atherothrombotic events after acute myocardial infarction. 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 (Frere et al., 2008). Higher loading and/or maintenance doses decrease reactivity even in initial non-responders, presumed to be CYP2C19 PMs (Aleil et al., 2008; Gladding et al., 2008; Gladding et al., 2008). Higher platelet reactivity has also been associated with a higher rate of subsequent thrombotic events (Gurbel et al., 2008). 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 (Gladding et al., 2008).

Several publications have evaluated patients treated with clopidogrel by CYP2C19 genetic status for clinical outcomes. Simon et al., (2009) and Mega et al., (2009) found significant, although modest, increases in risk of subsequent thrombotic events for CYP2C19 variant carriers in unselected patient populations. Collet et al., (2009) found a stronger risk in a highly selected population of younger patients with family history.

Shuldiner et al., (2009) demonstrated platelet response to clopidogrel was highly heritable in a population of 429 healthy Amish patients matching genotype results for CYP450 (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 ischemic event or death rate during one year of follow-up (hazard ration 2.42).

Sibbing et al., (2009) reported that in a study of 2485 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).

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., (2010) in a recent study (n = 1524) noted that 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.

Reports of adverse events in patients varied 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 one or two mutations.

In patients treated more generally for acute myocardial infarction, adverse events (death from cardiovascular cause, non-fatal myocardial infarction or stroke/revascularization) in wild type patients ranged from 6% to 14% compared to 12% to 21% in patients with one or two mutations and 19% in patients specifically identified as having two 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 PMs 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 PMs
- Advise healthcare professionals to consider alternative dosing or use of other medications in patients identified as potential PMs

Campo et al., (2010) summarized options available for use in patients with 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 thienopoyridine, 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 (Porto et al., 2009). However, in patients resistant to clopidogrel, it has been shown to be active and may be considered a potential treatment option (Campo et al., 2010).

Prasugrel, another thienopyridine approved in 2009 by the 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 (Wiviott et al., 2007). 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 years 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.

Another 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 (Angiolillo et al., 2007). However, not all patients responded optimally.

Finally, several reports have suggested improved outcomes in clopidogrel-resistant patients by use of supplementary antiplatelet drugs, notably the glycoprotein IIb/IIIa inhibitors (Cuisset et al., 2008; Valgimigli et al., 2009). This work is promising but preliminary.

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 PMs.

Warfarin

Warfarin is an anticoagulant drug, generic for Coumadin®, administered for the prevention and treatment of thromboembolic events in high-risk individuals. Patients are typically given a starting dose of 2 to 5 milligrams (mg) and monitored frequently with dose adjustments until a stable International Normalized Ratio (INR) value between 2 and 3 is achieved. During this adjustment period, a patient is at high risk for bleeding.

Maintenance warfarin dosing is a challenging process as it varies among individuals. Factors influencing stable dosing include body mass index, age, interacting drugs, and the indication for therapy. Algorithms have also been developed that incorporate not only genetic variation but also other significant patient characteristics and clinical factors to predict the best starting dose.

Warfarin is metabolized by the cytochrome P450 2C9 enzyme (CYP2C9). Genetic variants of CYP2C9 result in enzymes with decreased activity, increased serum warfarin concentration at standard doses, and a higher risk of serious bleeding. Application to warfarin dosing and important non-genetic influences are discussed in several publications (Wadelius et al., 2004; Gage et al., 2004; Hillman et al., 2004; Jonas & McLeod, 2009). Vitamin K epoxide reductase subunit C1 (VKORC1) genetic variants alter the degree of warfarin effect on its molecular target and are associated with differences in maintenance doses (Rieder et al., 2005; Yuan et al., 2005; Geisen et al., 2005; D'Andrea et al., 2005; Wadelius et al., 2005). Cytochrome P450 2C9 (CYP2C9) and VKORC1 genetic variation account for approximately 55% of the variability in the warfarin maintenance dose (Wadelius et al., 2005; Sconce et al., 2005). A genome-wide association study identified a single nucleotide polymorphism (SNP), found in the gene CYP4F2 that is also associated with warfarin dose (Takeuchi et al., 2009). This association was confirmed in a separate, candidate gene study (Caldwell et al., 2008). Other studies predict the CYP4F2 polymorphism explains 2% to 7% of the variability in warfarin dose in models including other genetic and non-genetic factors (Caldwell et al., 2008; Borgiani et al., 2009).

Genetic testing for CYP2C9 and VKORC1 is available at a number of laboratories that have developed in-house tests; these do not require FDA clearance, and information on analytic validity may not be generally available. Some laboratory-developed assays use commercially available reagents that are individually cleared by the FDA as analytic-specific reagents. Test kits cleared for marketing by the FDA include:

- eSensor® XT-8 Warfarin Sensitivity Test (Osmetech plc, Pasadena, CA)
- Rapid Genotyping Assay (ParagonDx, Research Triangle Park, NC,)
- Verigene® Warfarin Metabolism Nucleic Acid Test (Nanosphere Inc., Northbrook, IL)
- INFINITI 2C9-VKORC1 Multiplex Assay for Warfarin (AutoGenomics Inc., Carlsbad, CA)
- eQ-PCR™ LightCycler Warfarin Genotyping Kit (TrimGen Corporation, Sparks, MD)

Kit inserts for FDA-cleared test kits summarize the extensive analytic validity data required for FDA clearance. Two studies compared kits with FDA clearance and laboratory-developed assays using commercially available reagents and assay platforms; in each the authors concluded that the assays provided accurate and rapid genotype information for the most common polymorphisms evaluated (King et al., 2008; Langley et al., 2009). However, a recent review noted that due to lack of standardization, tests may detect as few as two CYP2C9 variants or as many as six (Langley et al., 2009). For VKORC1, several known polymorphisms are in strong linkage disequilibrium with one another, thus haplotypes formed from various combinations can be used to assess status. Whether specific haplotypes can improve predictive value is not known (Rosove & Grody, 2009). Turnaround times for these assays range from about one to eight hours. Patients who are not near a testing lab may be subject to longer turnaround times to accommodate sample transport to distant laboratories; it is not known how soon test results might be needed during the warfarin initiation phase should outcome studies indicate net benefit of testing.

A systematic review (McClain et al., 2008), commissioned by the American College of Medical Genetics, evaluated CYP2C9 and VKORC1 genetic testing prior to warfarin dosing and concluded the following:

- Clinical validity: CYP2C9 and VKORC1 genotypes contribute significant and independent information to the stable warfarin dose and, compared to the most common combination, some individuals with other genotype combinations will need more than the usual dose, while others would require less
- Clinical utility: The purpose of genetic testing in this clinical scenario is to predict an individual's likely stable warfarin dose by incorporating demographic, clinical, and genotype data (CYP2C9 and VKORC1), and initiate warfarin at that predicted dose as a way to limit high INR values (over-anticoagulation) that are associated with an increased risk of serious bleeding events. No large study has yet shown this to be acceptable or effective. Based on limited clinical data, the number needed to treat to avoid one serious bleeding event is estimated to range from 48 to 385

Authors of several additional studies of clinical validity have developed algorithms that incorporate VKORC1 and CYP2C9 genetic variant information as well as patient characteristics and other clinical information. They have evaluated the extent to which these algorithms predict

various outcomes such as maintenance dose, time to stable INR, time spent in target INR range, and serious bleeding events (Zhu et al., 2007; Wadelius et al., 2007; Schelleman et al., 2008; Gage et al., 2008; Wu et al., 2008; Hatch et al., 2008). These algorithms vary in the non-genetic variables included, and in general account for up to about 60% of warfarin maintenance dose variance. More recently, similarly designed cohort studies have evaluated the initiation phase of warfarin treatment, reporting the significance of genetic factors on time to therapeutic INR, time to first supratherapeutic (overcoagulation) INR, time above therapeutic range, etc (Schwarz et al., 2008; Meckley et al., 2008; Wadelius et al., 2009). Limdi et al., (2009) estimated CYP2C9 and VKORC1 explained 6.3% of the variance in dose change over the first 30 days of therapy. Pautas et al., (2009) reported on elderly patients with multiple comorbidities and polypharmacy who were starting warfarin. Individuals with multiple variant alleles were at highest risk for over anticoagulation, at an odds ratio of 12.8.

Cohort studies have evaluated algorithm-guided dosing, which include genetic and non-genetic factors, in patients beginning warfarin treatment, with algorithm variables explaining 69% to 79% of the variance in maintenance dose (Millican et al., 2007; Wen et al., 2008). Four algorithms have been compared for accuracy in predicting warfarin dose in a retrospective analysis of a local patient population on long-term, stable warfarin therapy. The predicted doses from two algorithms in particular showed the best correlation with actual warfarin doses (Langley et al., 2009). The International Warfarin Pharmacogenetics Consortium (2009) compared an algorithm based only on clinical variables with one that also included genetic factors in a validation cohort of 1,009 subjects treated with warfarin. The pharmacogenetic algorithm was significantly more accurate at predicting an initial dose that was close to the maintenance dose in 46% of patients who required low (< 21 mg/week) or high (> 49 mg/week) warfarin doses. The authors of the study note their analysis did not address the issue of whether a precise initial dose of warfarin results in improved clinical end points. They do comment that this study lays the groundwork for a prospective clinical trial to detect potential benefits.

In 2008, the California Technology Assessment Forum reviewed the scientific literature for the use of genetic testing to guide the initial dosing of warfarin when initiating therapy for anticoagulation. The review advised significant uncertainty remains and the use of genetic testing to guide initial warfarin dosing does not meet their technology assessment criteria for safety, effectiveness and improvement in health outcomes.

Kangelaris et al., (2009), conducted a systematic review of randomized trials comparing pharmacogenetic dosing of warfarin versus a "standard" dose control algorithm in adult patients taking warfarin for the first time. The review included three studies (423 patients). The authors concluded that the study did not find sufficient evidence to support the use of pharmacogenetics to guide warfarin therapy.

The 8th edition of the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines on Antithrombotic and Thrombolytic Therapy, published in 2008 and reviewed in 2009, states, “At the present time, for patients beginning (vitamin K antagonist) therapy, without evidence from randomized trials, we suggest against the use of pharmacogenetic-based initial dosing to individualize warfarin dosing (Grade 2C).”

In a study of 229 patients, a gene-based dosing algorithm was compared with standard of care dosing in patients receiving warfarin to prevent venous thromboembolism after elective joint replacement surgery (McMillin et al., 2010). The study concluded gene-based dosing did not improve warfarin management as defined by INR dose response. Findings suggest alternative strategies for dosing based on the presence of absence of genetic variants is needed.

The impact of genetic testing for warfarin dosing on clinical outcomes (clinical utility) is not currently known, therefore, it is considered investigational.

Helicobacter Pylori

Helicobacter pylori (H. pylori) is a bacterium associated with a range of gastrointestinal disorders such as peptic ulcer disease, chronic gastritis, and gastric malignancy. Eradication of H. pylori has been proven beneficial for a number of indications.

Currently, multiple regimens are available for treating H. pylori infection. These include proton pump inhibitors or polyphosphoinositide (PPI) (as well as similar medication(s)) to suppress acid production, in combination with antibiotic treatment, consisting of one or more agents such as amoxicillin, clarithromycin, or metronidazole. These first-line regimens generally achieve eradication rates in the 70% to 90% range. Differences in eradication rates are dependent on the regimen used and the population being treated. Treatment failures are most often attributed to antibiotic resistance or poor patient compliance. Resistance to clarithromycin is an important factor associated with treatment failure, with high rates of treatment failure for standard first-line regimens in patients infected with clarithromycin-resistant strains of H. pylori. A 2002 survey from the United States estimated that 13% of H. pylori strains are resistant to clarithromycin and that the rate of resistance was rising in comparison to earlier studies.

Genetic factors may influence the success of H. pylori treatment through effects on PPI metabolism. Individuals with polymorphisms in the CYP2C19 gene metabolize PPIs slower than normal. Differences in PPI metabolism lead to variability in gastric acid suppression, with associated variability in gastric pH, and potential impact on the efficacy of H. pylori treatment. Observational research suggests that patients who are EMs of PPIs have lower eradication rates following standard treatment for H. pylori, compared with PMs.

Polymorphisms of the CYP2C19 gene are relatively common and vary by ethnicity. Extensive metabolizers have no reduction in their ability to metabolize PPIs. Heterozygous polymorphisms or IMs are found in 27% to 37% of the Caucasian population and 46% to 50% of the Asian population. These patients have a minor reduction in their ability to eliminate PPIs. Homozygous polymorphisms or PMs of the CYP2C19 gene are found in 3% to 6% of Caucasians and in 12% to 20% of Asians. These patients eliminate PPIs from the circulation substantially much slower than unaffected patients.

In patients treated with PPIs, intragastric pH has been shown to correlate with CYP2C19 status. Patients homozygous for a CYP2C19 mutation (PM) exhibit a less acidic pH when compared to patients without a CYP2C19 mutation, with heterozygous patients exhibiting intermediate values. Intragastric pH has important implications for treating H. pylori. H. pylori is more sensitive to antibiotics at less acidic pH levels. Less acidic pH levels also lead to greater stability and bioavailability of antibiotics. Therefore, it is expected that treatment of H. pylori will be

more successful if there is maximal suppression of gastric acid production and higher intragastric pH levels.

If CYP2C19 status is known prior to treatment, adjustments can be made in the selection of PPI and/or the dosing schedule to achieve optimal acid suppression in all patients. Improved eradication rates for H. pylori could lead to improved health outcomes by reducing the need for re-treatment following treatment failure, reducing recurrences of H. pylori-associated disorders, and reducing the morbidity and mortality associated with disease recurrence.

Observational research has suggested that there is a correlation between CYP2C19 status and success rates for eradication of H. pylori. For the most part, these studies are trials of different regimens for H. pylori eradication in which CYP2C19 status was evaluated as a secondary objective (Sapone et al., 2003; Schwab et al., 2004; Sheu et al., 2005).

Padol et al., (2006) conducted a meta-analysis which included clinical trials of H. pylori eradication that used dual or triple therapy antibiotic regimens and reported eradication rates by CYP2C19 status. The authors identified 19 trials that met their inclusion criteria, and reported pooled eradication rates by genetic status and specific PPI agent. For all PPIs, the pooled eradication rate was highest in the PM group (89%), intermediate in the IM group (83%), and lowest in the EM group (71%), with the difference between these groups significant at the $p < 0.0001$ level. The greatest difference in eradication rates between EM groups and PM groups was seen for omeprazole (93% versus 63%). The difference in eradication rates was less pronounced for lansoprazole (88% versus 74%), and least evident for rabeprazole (81% versus 77%).

Kang et al., (2008) performed a study in which eradication rates were compared among patients who were EM, IM, and/or PM in 327 Korean patients with H. pylori infection. The treatment regimen consisted of amoxicillin, clarithromycin, and a PPI (either pantoprazole or esomeprazole) for seven days. The eradication rate was higher in the PM group compared to the EM group (97.4% versus 83.3%, $p = 0.016$). Mielhke et al., (2008) studied 103 consecutive patients who had failed at least one prior treatment regimen and had H. pylori infection that was resistant to metronidazole and clarithromycin. All patients were treated with moxifloxacin, rifabutin, and esomeprazole for seven days. Eradication rates were higher in PM/IM patients (93.1%) compared with EM patients (78.8%), but this difference did not reach statistical significance ($p = 0.14$).

Alternative treatment strategies exist for eradicating H. pylori that address some of the issues raised by CYP2C19 variability but do not rely on testing for CYP2C19 status. For example, empiric treatment with higher-dose PPI for all patients might be reasonable, particularly for non-Asian populations in which CYP2C19 mutation rates are lower. This approach may be as effective as regimens tailored by pharmacogenomics, with little additional risk. The use of a PPI that is less susceptible to CYP2C19 status, such as rabeprazole, might also be justified, given that there is no reason to suspect other advantages to use of omeprazole or lansoprazole. Ideally, a clinical trial will evaluate whether a tailored pharmacogenomics approach is superior to other empiric approaches such as these.

Finally, expert opinion does not appear to favor the use of genetic testing as part of a treatment protocol for H. pylori infection (Sheu & Fock, 2008; Klotz, 2009). Rather, alternative strategies to mitigate the differences in eradication rates by genetic status are suggested. Klotz (2009)

recommends using higher doses of PPIs in all patients as an alternative to genetic testing and tailoring of PPI dose. Sheu and Fock (2008) suggested that the use of PPIs that are less influenced by genetic status, such as rabeprazole, might be the preferred agents for H. pylori eradication.

In summary, the scientific evidence does not permit conclusions on whether the use of a pharmacogenomics-based treatment regimen for H. pylori improves eradication rates. In addition, routine testing of CYP2C19 genetic testing is not recommended in current clinic practice.

Tamoxifen

Tamoxifen (TAM) is prescribed as a component of adjuvant endocrine therapy to prevent endocrine receptor-positive breast cancer recurrence, as treatment of metastatic breast cancer, and to prevent disease in high-risk populations and in women with ductal carcinoma in situ (DCIS). Variant DNA gene sequences resulting in proteins with reduced or absent enzyme function may be associated with lower plasma levels of active tamoxifen metabolites, which could have an impact on TAM treatment efficacy.

Because a small, but significant, proportion of most ethnic populations have markedly reduced CYP2D6 metabolic capacity, there is concern that similar proportions of patients treated with TAM may have poorer outcomes than patients with relatively normal CYP2D6 activity. Some have recommended that patients who are to be prescribed TAM be genotyped for CYP2D6, and patients who are PMs be treated with alternative therapy, if possible.

Tamoxifen metabolites, rather than TAM itself, are likely the primary effectors of TAM benefit. Tamoxifen undergoes extensive primary and secondary metabolism, and the plasma concentrations of TAM and its metabolites vary widely. 4-Hydroxytamoxifen (4-OH TAM) has demonstrated 100-fold greater affinity for the estrogen receptor and 30- to 100-fold greater potency in suppressing estrogen-dependent in vitro cell proliferation when compared with the parent drug (Goetz et al., 2008). Another metabolite, 4-hydroxy-N-desmethyl tamoxifen (endoxifen), has identical properties and potency compared with 4-OH TAM (Stearns et al., 2003; Johnson et al., 2004; Lim et al., 2005; Lim et al., 2006). Because 4-OH TAM represents less than 20% of the product of TAM primary metabolism and steady-state plasma endoxifen concentrations are on average 5- to 10-fold higher than 4-OH TAM, it has been assumed that endoxifen is the major active metabolite of TAM.

The metabolism of TAM to 4-OH TAM is catalyzed by multiple enzymes. However, endoxifen is formed predominantly by CYP2D6. The plasma concentration of endoxifen exhibits high interindividual variability, as described in breast cancer patients (Stearns et al., 2003). The CYP2D6 enzyme has known interindividual variability in activity and therefore has been of great interest in investigating TAM metabolism and variation in circulating active metabolite levels.

Potential indications for CYP2D6 pharmacogenomic testing include patients who are to be treated with tamoxifen (TAM; alone or prior to treatment with an aromatase inhibitor) for prevention of breast cancer in high risk women or women with DCIS), for adjuvant treatment to prevent breast cancer recurrence, or for treatment of metastatic disease, and who have no contraindications to treatment with aromatase inhibitors (for treatment of existing disease) or

raloxifene (for prevention of disease). Post-menopausal patients determined to be CYP2D6 PMs could avoid TAM therapy and be treated with aromatase inhibitors alone. Pre-menopausal patients might consider ovarian ablation. For any indication, co-administration of drugs that inhibit CYP2D6 activity should be taken into account.

Three studies evaluated CYP2D6 genotype as a prognostic marker in patients not treated with TAM to ensure that a prognostic association would not confound the effect of genotype on TAM outcomes (Nowell et al., 2005; Schroth et al., 2007; Wegman et al., 2005). None of the studies found evidence that CYP2D6 genotype is prognostic, but limitations to the analyses of each warrant further study.

One way to evaluate the effect of genotype on TAM response is to compare TAM-treated women with those not receiving TAM, with stratification by CYP2D6 genotype. Wegman et al., (2005) conducted such a study retrospectively, on archived samples from a TAM randomized controlled trial. Paradoxically, the authors found that EMs treated with TAM received no statistically significant clinical benefit compared to EMs not treated with TAM, and that carriers of a CYP2D6*4 variant allelle obtained significant benefit from TAM treatment. There were several limitations to this study: tissue samples were available for only 33% of originally enrolled patients; only 47 patients carried a *4 allele (only four were homozygous PMs); TAM dose was 40 mg/day instead of the standard 20 mg/day; and was administered for only two years instead of the standard five years. Because of these limitations, the study results are questionable.

The best evidence for whether CYP2D6 genotype predicts outcomes of TAM treatment comes from Goetz et al., (2007) and Schroth et al., (2007). Both studies retrospectively enrolled relatively homogeneous populations of patients who were estrogen-receptor-positive, node-positive in 63% to 64%, and grade 1 to 2 in 78% to 91% of women, and for the primary analyses had been treated with TAM alone (no chemotherapy) following resection of the tumor. Target treatment duration was five years in Goetz et al., (2007) but was not reported in Schroth et al., (2007). The studies differed in that Goetz et al., (2007) only genotyped for the CYP2D6*4 non-functional variant (most common), whereas Schroth et al., (2007) also tested for the *5 non-functional variant, and for the *10 and *41 reduced function variants. In both studies, negative results for the tested variants were assumed to represent wild type genotypes.

Newman et al., (2008) studied 115 patients with familial, early-onset breast cancer (47 BRCA1 and 68 BRCA2 mutations) treated with adjuvant TAM. Of these, 7% were CYP2D6 PMs, and 3.5% were considered PMs due to administration of CYP2D6 inhibitor drugs. CYP2D6 PMs had reduced time to recurrence, disease-free, and overall survival, but this effect was significant only for those with BRCA2 mutations. The results of this study cannot be generalized to women with sporadic breast cancer.

Okishiro et al., (2009) studied the impact of the CYP2D6*10 reduced activity variant in Japanese breast cancer patients treated with adjuvant TAM. Patients who were homozygous for the CYP2D6*10 variant (n = 40), compared to heterozygous or wild type patients (n = 133) did not differ in recurrence-free survival even after adjustment for established prognostic factors. Patients administered CYP2D6 inhibitor medication were excluded from this study. The authors also conducted a meta-analysis of their results plus previously reported results of similar studies

conducted in Japanese and Chinese patients and similarly found no significant effect of homozygous CYP2D6*10 on recurrence-free survival (Kiyotani et al., 2008; Xu et al., 2008).

In summary, evidence suggests that women who are functional PMs or IMs, whether by genotype or by co-medication with CYP2D6 inhibitors, treated with TAM have significantly reduced time to recurrence and recurrence-free survival (but not overall survival) compared to EMs. The significance levels are marginal but might have been stronger and more convincing if PMs alone could have been compared to EMs, but numbers of PMs were insufficient. Few variant alleles have been typed in these studies; more extensive genotyping and better categorization might also strengthen results.

Further, there is no direct evidence of clinical utility. Evidence is insufficient to permit conclusions regarding the use of CYP2D6 genotyping for directing endocrine therapy regimen selection for women at high risk for or with breast cancer; this testing is considered investigational.

Selective Serotonin Reuptake Inhibitors

Cytochrome 2D6 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 Evidence-based Practice Center systematically reviewed the evidence on CYP450 testing for adults treated with SSRIs for non-psychotic depression (Matchar et al., 2007). Following this commissioned report, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (2007) 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.

Two reports have focused on use of genotyping in patients treated with paroxetine. Gex-Fabry et al., (2008) studied paroxetine levels and clinical response in 71 patients with depression who had been genotyped for CYP2D6 and ABCB1 polymorphisms. In this prospective observational study, CYP2D6 heterozygous EM phenotype showed a marginal impact on paroxetine levels and no impact on treatment response.

Ververs et al., (2009) in a cohort study of 74 pregnant women demonstrated that differences in CYP2D6 genotype caused differential effects on paroxetine plasma concentrations. Extensive metabolizers and UMs showed steady decreases in concentrations during the course of pregnancy with increase in depressive symptoms. Intermediate metabolizers and PMs showed an increase in concentrations with no change in symptoms. However, no information on the use or outcome of use of such information was provided.

Serretti et al., (2009) 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. (2010) 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. (2010) 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 and Dosing of Selective Norepinephrine Reuptake Inhibitors (SNRIs)

SNRIs are used most commonly as antidepressants. Available agents in the United States 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 (Bertilsson, 2007) 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. (2010) 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 (Skinner et al., 2003).

Atomoxetine Hydrochloride

Atomoxetine hydrochloride (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 kilogram 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 (de Leon, 2007; Trzepacz et al., 2008). After titration, mean doses for EMs and PMs also do not differ significantly (Michelson et al., 2007; Trzepacz et al., 2008). However, more EM patients discontinued in one trial due to lack of efficacy (Michelson et al., 2007) and PMs improved inattention scores more than EMs in another (Trzepacz et al., 2008), 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 (Wernicke & Kratochvil, 2002; Eli Lilly and Company, 2002).

Ramoz et al. (2009) recently reported on two independent cohorts of 160 and 105 ADHD children treated for six 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 norepinerpherine 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. (2010) 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.

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 results are inconsistent (Smoller, 2006; Maier & Zobel,

2008; Crescenti et al., 2008). Moreover, plasma concentration of antipsychotic drugs may not be correlated with treatment outcome or adverse effects (Panagiotidis et al., 2007). 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. 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 (Murray, 2006; Murray & Petrovic, 2006; Dorado et al., 2006; Bondy & Spellmann, 2007; Vandel et al., 2007).

Fleeman et al., (2010) in a 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 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.

Two additional reports on use of risperidone have been published since the last policy update. Jovanovic et al. (2010) evaluated the role of CYP2D6 in 83 drug-napatients 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. (2010) 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. 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.

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 (Macaluso & Preskorn, 2011). In 2011, de Vos et al. studied 678 patients treated with TCAs and reported that EMs had increased metabolism and lower serum levels of amitriptyline and citalopram, but not clomipramine. However, these authors reported that the differences observed were not likely to have clinically important effects.

It has been reported that patients with TCA overdose may have different risk depending on cytochrome p450 genetic status (de Vos et al., 2011; Jornil et al., 2011). 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.

Codeine for Nursing Mothers

Codeine is metabolized by CYP2D6 to morphine. Enhanced CYP2D6 activity (i.e., in CYP2D6 UMs) predisposes to opioid intoxication. On August 17, 2007, the FDA issued a warning regarding codeine use by nursing mothers. Nursing infants “may be at increased risk of morphine overdose if their mothers are taking codeine and are UMs of codeine.” 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 (Madadi et al., 2009). 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” (Koren et al., 2006; FDA, 2007).

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. 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.

Efavirenz

Current guidelines recommend efavirenz as the preferred non-nucleoside reverse transcriptase inhibitor component of highly active antiretroviral therapy for human immunodeficiency virus-infected patients. Forty percent to 70% of patients report adverse central nervous system effects. While most resolve in the first few weeks of treatment, about 6% of patients discontinue efavirenz due to adverse effects (King & Aberg, 2008). 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 (Gatanaga et al., 2007; Torno et al., 2008). Simulations of such dose adjustments support this position (Nyakutira et al., 2008).

Cabrera et al., (2009) 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 (intermediate metabolizers) genotype and 75% with the T/T (poor metabolizers) 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 TDM and assessment of clinical efficacy. It is clear that larger studies are needed to support changes in current drug dosing practices and guidelines.

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 TDM 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 (Mourad et al., 2008). CYP3A5*1 carriers have been reported to have a significant delay in reaching target tacrolimus concentrations compared to non-carriers. Although the overall rate of acute rejection episodes was not higher in CYP3A5*1 carriers, their rejection episodes did occur earlier (MacPhee & Holt, 2008). Zhao et al. (2009) recently developed a population pharmacokinetic model of tacrolimus in pediatric kidney transplant patients using 50 de novo pediatric kidney transplant patients. They 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.

Beta blockers

Several recent reports have indicated 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., 2008; Yuan et al., 2008). Bijl et al., (2008) in a population based cohort study of 1,553 patients noted increased risk of bradycardia in patients

found to be PMs (CYP2D6 *4/*4). The clinical significance of this observation remains to be defined.

In summary, 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). In addition, they tend to be small and under-powered or not designed to examine the clinical effects of homozygous variant PMs and of UMs, where the strongest effects, if any, would be seen. The hazards associated with PMs 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.

Data on the impact of clopidogrel appears to be particularly strong with multiple studies demonstrating that patients defined as PMs (CYP2C19 *2/2, *3/3, or *2/3) are at significantly increased risk of a variety of life-threatening adverse cardiovascular events. 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.

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 (Holmes et al., 2010). The recommendations for practice included the following statements:

- Adherence to existing ACCF/AHA guidelines for the use of antiplatelet therapy should remain the foundation for therapy. Careful clinical judgment is required to assess the importance of the variability in response to clopidogrel for an individual patient and its associated risk to the patient.
- Clinicians must be aware that genetic variability in CYP enzymes alter clopidogrel metabolism, which in turn can affect its inhibition of platelet function. Diminished responsiveness to clopidogrel has been associated with adverse patient outcomes in registry experiences and clinical trials.
- The specific impact of the individual genetic polymorphisms on clinical outcome remains to be determined
- Information regarding the predictive value of pharmacogenomic testing is very limited at this time; resolution of this issue is the focus of multiple ongoing studies. The selection of the specific test, as well as the issue of reimbursement, is both important additional considerations.
- The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time.
- There are several possible therapeutic options for patients who experience an adverse event while taking clopidogrel in the absence of any concern about medication compliance.

Medicare National Coverage Decisions

None.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	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)
	81355	VKORC1 (vitamin K epoxide reductase complex, subunit 1) (eg, warfarin metabolism), gene analysis, common variants (eg, -1639/3673)
	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) ***[when specified as]:*** • *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)

Type	Number	Description
	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]) ***[when specified as]:*** • *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) ***[when specified as]:*** • *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 ***[when specified as]:*** • *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
HCPC	G9143	Warfarin responsiveness testing by genetic technique using any method, any number of specimen(s)

Type	Number	Description
ICD9 Procedure	None	
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

N/A

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

N/A

Key / Related Searchable Words

- ADHD
- AmpliChip
- Antipsychotic drugs
- Antituberculosis medications
- Atomoxetine hydrochloride
- Beta Blockers (Metoprolol)
- Clopidogrel
- Codeine
- Coumadin
- Cytochrome P450 2C9
- Cytochrome P450 genotyping
- CYP1A2
- CYP2B6
- CYP2C19

- CYP2C9
- CYP2D6
- CYP2D6 PM
- CYP3A4
- CYP3A5
- CYP450
- Drug-Metabolizer Status
- Duloxetine
- Efavirenz eSensor XT-8 Warfarin Sensitivity Test
- eQ-PCR LightCycler Warfarin Genotyping Kit
- Genotyping for Cytochrome P450 Polymorphisms
- Helicobacter pylori
- H. pylori
- Immunosuppressive drugs
- Immunosuppressant for organ transplantation
- INFINITI 2C9-VKORC1 Multiplex Assay for Warfarin
- Invader UGT1A1 Molecular Assay
- Morphine
- Pharmacodynamic testing
- Pharmacogenetic testing
- Pharmacogenomic testing
- Plavix
- Prasugrel
- Rapid Genotyping Assay
- Selective norepinephrine reuptake inhibitors
- SNRI
- Selective serotonin reuptake inhibitors
- SSRI
- TAM
- Tamoxifen
- TCA
- Ticlopidine
- Tricyclic antidepressants
- Venlafaxine
- Verigene Warfarin Metabolism Nucleic Acid Test
- Vitamin K epoxide reductase subunit C1
- VKORC1
- Warfarin

References

- Aleil B, Jacquemin L, De Poli F et al. Clopidogrel 150 mg/day to overcome low responsiveness in patients undergoing elective percutaneous coronary intervention: Results from the VASP-02 (Vasodilator-Stimulated Phosphoprotein-02) randomized study. JACC Cardiovasc Interv 2008; 1(6):631-8.
- Anderson JL, Horne BD, Stevens SM et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. Circulation 2007; 116(22):2563-70.
- Angiolillo DJ, Shoemaker SB, Desai B et al. Randomized comparison of a high clopidogrel maintenance dose in patients with diabetes mellitus and coronary artery disease: results of the Optimizing Antiplatelet Therapy in Diabetes Mellitus (OPTIMUS) study. Circulation 2007; 115(6):708-16.
- Bertilsson L. Metabolism of antidepressant and neuroleptic drugs by cytochrome p450s: clinical and interethnic aspects. Clin Pharmacol Ther. 2007; 82(5):606-9.
- Bijl MJ, Visser LE, van Schaik RH et al. Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in beta blocker users. Clin Pharmacol Ther 2008; 85(1):45-50.
- Bishop JR, Ellingrod VL. Neuropsychiatric pharmacogenetics: moving toward a comprehensive understanding of predicting risks and response. Pharmacogenomics 2004; 5(5):463-77.
- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.38 (October 2013).
- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.48.
- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.50.
- Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.51.
- Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment Program. CYP2D6 Pharmacogenomics of Tamoxifen Treatment. 2008; 23(1).
- Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Assessment Program. Pharmacogenomics-Based Treatment of Helicobacter pylori Infection. 2008; 23(2).
- Blue Cross Blue Shield Association. Technology Evaluation Center (TEC) Special Report: Genotyping for Cytochrome P450 Polymorphisms to Determine Drug-Metabolizer Status. TEC Assessment. 2004; 19(9).
- Bondy B, Spellmann I. Pharmacogenetics of antipsychotics: useful for the clinician? Curr Opin Psychiatry 2007; 20(2):126-30.
- Borgiani P, Ciccacci C, Forte V et al. CYP4F2 genetic variant (rs2108622) significantly contributes to warfarin dosing variability in the Italian population. Pharmacogenomics 2009; 10(2):261-266.
- Cabrera SE, Santos D, Valverde MP et al. Influence of the cytochrome P450 2B6 genotype on population pharmacokinetics of efavirenz in human immunodeficiency virus patients. Antimicrob Agents Chemother 2009; 53(7):2791-8.
- Caldwell MD, Awad T, Johnson JA et al. CYP4F2 genetic variant alters required warfarin dose. Blood 2008; 111(8):4106-4112.

- California Technology Assessment Forum. Use of Genetic Testing to Guide the Initiation of Warfarin Therapy. A Technology Assessment. San Francisco, CA. 2008. Retrieved August 10, 2010 from http://www.ctaf.org/content/assessment/detail/814 .
- Campo G, Fileti L, Valgimigli M et al. Poor response to clopidogrel: current and future options for its management. J Thromb Thrombolysis 2010 [E-pub ahead of print].
- Collet JP, Hulot JS, Pena A et al. Cytochrome P450 2C19 polymorphism in young patients treated with clopidogrel after myocardial infarction: a cohort study. Lancet 2009; 373(9660):309-17.
- Crescenti A, Mas S, Gasso P et al. Cyp2d6*3, *4, *5 and *6 polymorphisms and antipsychotic-induced extrapyramidal side-effects in patients receiving antipsychotic therapy. Clin Exp Pharmacol Physiol 2008; 35(7):807-11.
- Cuisset T, Frere C, Quilici J et al. Glycoprotein IIb/IIIa inhibitors improve outcome after coronary stenting in clopidogrel non-responders: a prospective, randomized study. JACC Cardiovas Interv 2008; 1(6):649-53.
- D'Andrea G, D'Ambrosio RL, Di Perna P et al. A polymorphism in the VKORC1 gene is associated with an interindividual variability in the dose-anticoagulant effect of warfarin. Blood 2005; 105(2):645-9.
- 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.
- 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.
- de Vos A, van der Weide J, Loovers HM. Association between CYP2C19*17 and metabolism of amitriptyline, citalopram and clomipramine in Dutch hospitalized patients. Pharmacogenomics J. 2011; 11(5):359-67.
- Dorado P, Berecz R, Penas-Lledo EM et al. Clinical implications of CYP2D6 genetic polymorphism during treatment with antipsychotic drugs. Curr Drug Targets 2006; 7(12):1671-80.
- Eli Lilly and Company. Strattera™ (atomoxetine HCl) product information. Retrieved August 27, 2010 from http://pi.lilly.com/us/strattera-pi.pdf .
- Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: testing for cytochrome P450 polymorphisms in adults with nonpsychotic depression treated with selective serotonin reuptake inhibitors. Genet Med 2007; 9(12):819-25.
- Fleeman N, Dundar Y, Dickson R et al. Cytochrome P450 testing for prescribing antipsychotics in adults with schizophrenia: systematic review and meta-analyses. Pharmacogenomics J. 2011; 11(1):1-14.
- Fleeman N, McLeod C, Bagust A et al. The clinical effectiveness and cost-effectiveness of testing for cytochrome P450 polymorphisms in patients with schizophrenia treated with antipsychotics: a systematic review and economic evaluation. Health Technol Assess 2010; 14(3):1-157.

- Frere C, Cuisset T, Morange PE et al. Effect of cytochrome p450 polymorphisms on platelet reactivity after treatment with clopidogrel in acute coronary syndrome. Am J Cardiol 2008; 101(8):1088-93.
- Gage BF, Eby C, Johnson JA et al. Use of pharmacogenetic and clinical factors to predict the therapeutic dose of warfarin. Clin Pharmacol Ther 2008; 84(3):326-31.
- Gage BF, Eby C, Milligan PE et al. Use of pharmacogenetics and clinical factors to predict the maintenance dose of warfarin. Thromb Haemost 2004; 91(1):87-94.
- Gatanaga H, Hayashida T, Tsuchiya K et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007; 45(9):1230-7.
- Geisen C, Watzka M, Sittinger K et al. VKORC1 haplotypes and their impact on the inter-individual and inter-ethnical variability of oral anticoagulation. Thromb Haemost 2005; 94(4):773-9.
- Gex-Fabry M, Eap CB, Oneda B et al. CYP2D6 and ABCB1 genetic variability: influence on paroxetine plasma level and therapeutic response. Ther Drug Monit 2008; 30(4):474-82.
- Gladding P, Webster M, Ormiston J et al. Antiplatelet drug nonresponsiveness. Am Heart J 2008; 155(4):591-9.
- Gladding P, Webster M, Zeng I et al. The antiplatelet effect of higher loading and maintenance dose regimens of clopidogrel: the PRINC (Plavix Response in Coronary Intervention) trial. JACC Cardiovasc Interv 2008; 1(6):612-9.
- Gladding P, Webster M, Zeng I et al. The pharmacogenetics and pharmacodynamics of clopidogrel response: an analysis from the PRINC (Plavix Response in Coronary Intervention) trial. JACC Cardiovasc Interv 2008; 1(6):620-7.
- Goetz MP, Kamal A, Ames MM. Tamoxifen pharmacogenomics: the role of CYP2D6 as a predictor of drug response. Clin Pharmacol Ther 2008; 83(1):160-6.
- Goetz MP, Knox SK, Suman VJ et al. The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast Cancer Res Treat 2007; 101(1):113-21.
- Gurbel PA, Antonino MJ, Bliden KP et al. Platelet reactivity to adenosine diphosphate and long-term ischemic event occurrence following percutaneous coronary intervention: a potential antiplatelet therapeutic target. Platelets 2008; 19(8):595-604.
- Hatch E, Wynne H, Avery P et al. Application of a pharmacogenetic-based warfarin dosing algorithm derived from British patients to predict dose in Swedish patients. J Thromb Haemost 2008; 6(6):1038-40.
- Hillman MA, Wilke RA, Caldwell MD et al. Relative impact of covariates in prescribing warfarin according to CYP2C9 genotype. Pharmacogenetics 2004; 14(8):539-47.
- Hirsh J, Guyatt G, Albers GW et al. American College of Chest Physicians. Antithrombotic and thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 suppl):110S-112S.
- Holmes DR, Jr., Dehmer GJ, Kaul S et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on clinical expert consensus documents and the American Heart

Association endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2010; 56(4):321-41.
- http://www.ehs.lilly.com/msds/msds_atomoxetine_hydrochloride_tablets_and_capsules.pdf. Retrieved March 20, 2011.
- Johnson MD, Zuo H, Lee KH et al. Pharmacological characterization of 4-hydroxy-N-desmethyl tamoxifen, a novel active metabolite of tamoxifen. Breast Cancer Res Treat 2004; 85(2):151-9.
- Jonas DE, McLeod HL. Genetic and clinical factors relating to warfarin dosing. Trends Pharmacol Sci 2009; 30(7):375-86.
- Jornil J, Jensen KG, Larsen F et al. Risk assessment of accidental nortriptyline poisoning: the importance of cytochrome P450 for nortriptyline elimination investigated using a population-based pharmacokinetic simulator. Eur J Pharm Sci. 2011; 44(3):265-72.
- Jovanovic N, Bozina N, Lovric M et al. The role of CYP2D6 and ABCB1 pharmacogenetics in drug-naive patients with first-episode schizophrenia treated with risperidone. Eur J Clin Pharmacol. 2010; 66(11):1109-17.
- Kang JM, Kim N, Lee DH et al. Effect of the CYP2C19 polymorphism on the eradication rate of Helicobacter pylori infection by 7-day triple therapy with regular proton pump inhibitor dosage. J Gastroenterol Hepatol 2008; 23(8 Pt 1):1287-91.
- Kangelaris KN, Bent S, Nussbaum RL et al. Genetic testing before anticoagulation? A systematic review of pharmacogenetic dosing of warfarin. J Gen Intern Med 2009 May;24(5):656-64. Epub 2009 Mar 21.
- King CR, Porche-Sorbet RM, Gage BF et al. Performance of commercial platforms for rapid genotyping of polymorphisms affecting warfarin dose. Am J Clin Pathol 2008; 129(6):876-83.
- King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS 2008; 22(14):1709-17.
- Kirchheiner J, Brosen K, Dahl ML et al. CYP2D6 and CYP2C19 genotype-based dose recommendations for antidepressants: a first step towards subpopulation-specific dosages. Acta Psychiatr Scand 2001; 104(3):173-92.
- Kirchheiner J, Nickchen K, Bauer M et al. Pharmacogenetics of antidepressants and antipsychotics: the contribution of allelic variations to the phenotype of drug response. Mol Psychiatry 2004; 9(5):442-73.
- Kiyotani K, Mushiroda T, Sasa M et al. Impact of CYP2D6*10 on recurrence-free survival in breast cancer patients receiving adjuvant tamoxifen therapy. Cancer Sci 2008; 99(5):995-9.
- Klotz U. Impact of CYP2C19 polymorphisms on the clinical action of proton pump inhibitors (PPIs). Eur J Clin Pharmacol 2009; 65(1):1-2.
- Koren G, Cairns J, Chitayat D et al. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. Lancet 2006; 368(9536):704.
- Langley MR, Booker JK, Evans JP et al. Validation of clinical testing for warfarin sensitivity: Comparison of CYP2C9-VKORC1 genotyping assays and warfarin-dosing algorithms. J Mol Diagn 2009; 11(3):216-225.

- Lim YC, Desta Z, Flockhart DA et al. Endoxifen (4-hydroxy-N-desmethyl-tamoxifen) has anti-estrogenic effects in breast cancer cells with potency similar to 4-hydroxy-tamoxifen. Cancer Chemother Pharmacol 2005; 55(5):471-8.
- Lim YC, Li L, Desta Z et al. Endoxifen, a secondary metabolite of tamoxifen, and 4-OH-tamoxifen induce similar changes in global gene expression patterns in MCF-7 breast cancer cells. J Pharmacol Exp Ther 2006; 318(2):503-12.
- Limdi NA, Wiener H, Goldstein JA et al. Influence of CYP2C9 and VKORC1 on warfarin response during initiation of therapy. Blood Cells Mol Dis 2009; 43(1):119-28.
- Lobello KW, Preskorn SH, Guico-Pabia CJ et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry. 2010; 71(11):1482-7.
- Locatelli I, Kastelic M, Koprivsek J et al. A population pharmacokinetic evaluation of the influence of CYP2D6 genotype on risperidone metabolism in patients with acute episode of schizophrenia. Eur J Pharm Sci. 2010; 41(2):289-98.
- Macaluso M, Preskorn SH. CYP 2D6 PM status and antidepressant response to nortriptyline and venlafaxine: is it more than just drug metabolism? J Clin Psychopharmacol. 2011; 31(2):143-5.
- MacPhee IA, Holt DW. A pharmacogenetic strategy for immunosuppression based on the CYP3A5 genotype. Transplantation 2008; 85(2):163-5.
- Madadi P, Ross CJ, Hayden MR et al. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. Clin Pharmacol Ther 2009; 85(1):31-5.
- Maier W, Zobel A. Contribution of allelic variations to the phenotype of response to antidepressants and antipsychotics. Eur Arch Psychiatry Clin Neurosci 2008; 258(Suppl 1):12-20.
- Matchar DB, Thakur ME, Grossman I et al. Testing for cytochrome P450 polymorphisms in adults with non-psychotic depression treated with selective serotonin reuptake inhibitors (SSRIs). Evid Rep Technol Assess (Full Rep). 2007 Jan;(146):1-77. Retrieved August 27, 2010 from http://www.ahrq.gov/clinic/tp/cyp450tp.htm .
- McClain MR, Palomaki GE, Piper M et al. A rapid ACCE1 review of CYP2C9 and VKORC1 allele testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. Genet Med 2008; 10(2):89-98.
- McMillin GA, Milis R, Wilson A, et al. Gene-based warfarin dosing compared with standard of care practices in an orthopedic surgery population: a prospective, parallel cohort study. Ther Drug Monit. 2010 Jun;32(3):338-45.
- Meckley LM, Wittkowsky AK, Rieder MJ et al. An analysis of the relative effects of VKORC1 and CYP2C9 variants on anticoagulation related outcomes in warfarin-treated patients. Thromb Haemost 2008; 100(2):229-39.
- Mega JL, Close SL, Wiviott SD et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med 2009; 360(4):354-62.
- Michelson D, Read HA, Ruff DD et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry 2007; 46(2):242-51.

- Michelson D, Read HA, Ruff DD et al. CYP2D6 and clinical response to atomoxetine in children and adolescents with ADHD. J Am Acad Child Adolesc Psychiatry. 2007; 46(2):242-51.
- Miehlke S, Schneider-Brachert W, Kirsch C et al. One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent Helicobacter pylori resistant to both metronidazole and clarithromycin. Helicobacter 2008; 13(1):69-74.
- Millican E, Lenzini PA, Milligan PE et al. Genetic-based dosing in orthopaedic patients beginning warfarin therapy. Blood 2007; 110(5):1511-5.
- Mourad M, Wallemacq P, De Meyer M et al. Biotransformation enzymes and drug transporters pharmacogenetics in relation to immunosuppressive drugs: impact on pharmacokinetics and clinical outcome. Transplantation 2008; 85(7 Suppl):S19-24.
- Murray M, Petrovic N. Cytochromes P450: decision-making tools for personalized therapeutics. Curr Opin Mol Ther 2006; 8(6):480-6.
- Murray M. Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. J Pharm Pharmacol 2006; 58(7):871-85.
- Newman WG, Hadfield KD, Latif A et al. Impaired tamoxifen metabolism reduces survival in familial breast cancer patients. Clin Cancer Res 2008; 14(18):5913-8.
- Nowell SA, Ahn J, Rae JM et al. Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast Cancer Res Treat 2005; 91(3):249-58.
- Okishiro M, Taguchi T, Jin Kim S et al. Genetic polymorphisms of CYP2D6 10 and CYP2C19 2, 3 are not associated with prognosis, endometrial thickness, or bone mineral density in Japanese breast cancer patients treated with adjuvant tamoxifen. Cancer 2009; 115(5):952-61.
- Padol S, Yuan Y, Thabane M et al. The effect of CYP2C19 polymorphisms on H. pylori eradication rate in dual and triple first-line PPI therapies: a meta-analysis. Am J Gastroenterol 2006; 101(7):1467-75.
- Panagiotidis G, Arthur HW, Lindh JD et al. Depot haloperidol treatment in outpatients with schizophrenia on monotherapy: impact of CYP2D6 polymorphism on pharmacokinetics and treatment outcome. Ther Drug Monit 2007; 29(4):417-22.
- Pautas E, Moreau C, Gouin-Thibault I et al. Genetic factors (VKORC1, CYP2C9, EPHX1, and CYP4F2) are predictor variables for warfarin response in very elderly, frail inpatients. Clin Pharmacol Ther 2010 Jan;87(1):57-64. Epub 2009 Sept 30.
- Porto I, Giubilato S, De Maria GL et al. Platelet P2Y212 receptor inhibition by thienopyridines: status and future. Expert Opin Investig Drugs 2009; 18(9):1317-32.
- Ramoz N, Boni C, Downing AM et al. A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology. 2009; 34(9):2135-42.
- Ramoz N, Boni C, Downing AM. A haplotype of the norepinephrine transporter (Net) gene Slc6a2 is associated with clinical response to atomoxetine in attention-deficit hyperactivity disorder (ADHD). Neuropsychopharmacology 2009; 34(9):2135-42.

- Rebsamen MC, Desmeules J, Daali Y et al. The AmpliChip CYP450 test: cytochrome P450 2D6 genotype assessment and phenotype prediction. Pharmacogenomics J 2009; 9(1):34-41.
- Rieder MJ, Reiner AP, Gage BF et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. N Engl J Med 2005; 352(22):2285-93.
- Roche Diagnostics. AmpliChip CYP450 test package insert. Roche Molecular Systems, Inc. Indianapolis, IN. 2007. Retrieved August 27, 2010 from http://www.amplichip.us/documents/CYP450_P.I._US-IVD.pdf .
- Rosove MH, Grody WW. Should we be applying warfarin pharmacogenetics to clinical practice? No, not now. Ann Intern Med 2009; 151(4):270-3.
- Sapone A, Vaira D, Trespidi S et al. The clinical role of cytochrome P450 genotypes in Helicobacter pylori management. Am J Gastroenterol 2003; 98(5):1010-5.
- Schelleman H, Chen J, Chen Z et al. Dosing algorithms to predict warfarin maintenance dose in Caucasians and African Americans. Clin Pharmacol Ther 2008; 84(3):332-9.
- Schroth W, Antoniadou L, Fritz P et al. Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 2007; 25(33):5187-93.
- Schwab M, Schaeffeler E, Klotz U et al. CYP2C19 polymorphism is a major predictor of treatment failure in white patients by use of lansoprazole-based quadruple therapy for eradication of Helicobacter pylori. Clin Pharmacol Ther 2004; 76(3):201-9.
- Schwarz UI, Ritchie MD, Bradford Y et al. Genetic determinants of response to warfarin during initial anticoagulation. N Engl J Med 2008; 358(10):999-1008.
- Sconce EA, Khan TI, Wynne HA et al. The impact of CYP2C9 and VKORC1 genetic polymorphism and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005; 106(7):2329-33.
- Seeringer A, Kirchheiner J. Pharmacogenetics-guided dose modifications of antidepressants. Clin Lab Med 2008; 28(4):619-26.
- Serretti A, Calati R, Massat I et al. Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes are not associated with response and remission in a sample of depressive patients. Int Clin Psychopharmacol 2009; 24(5):250-6.
- Sheu BS, Fock KM. CYP2C19 genotypes and Helicobacter pylori eradication. J Gastroenterol Hepatol 2008; 23(8 Pt 1):1163.
- Sheu BS, Kao AW, Cheng HC et al. Esomeprazole 40mg twice daily in triple therapy and the efficacy of Helicobacter pylori eradication related to CYP2C19 metabolism. Aliment Pharmacol Ther 2005; 21(3):283-8.
- Shuldiner AR, O'Connell JR, Bliden KP et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy of clopidogrel therapy. JAMA 2009; 302(8):849-57.
- Sibbing D, Koch W, Gebhard D et al. Cytochrome 2C19*17 allelic variant, platelet aggregation, bleeding events, and stent thrombosis in clopidogrel-treated patients with coronary stent placement. Circulation 2010; 121(4):512-8.

- Sibbing D, Stegherr J, Latz W et al. Cytochrome P450 2C19 loss-of-function polymorphism and stent thrombosis following percutaneous coronary intervention. Eur Heart J 2009; 30(9):916-22.
- Sim SC, Nordin L, Andersson TM et al. Association between CYP2C19 polymorphism and depressive symptoms. Am J Med Genet B Neuropsychiatr Genet. 2010; 153B(6):1160-6.
- Simon T, Verstuyft C, Mary-Krause M et al. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009; 360(4):363-75.
- Skinner MH, Kuan HY, Pan A et al. Duloxetine is both an inhibitor and a substrate of cytochrome P4502D6 in healthy volunteers. Clin Pharmacol Ther. 2003; 73(3):170-7.
- Smoller JW. Incorporating pharmacogenetics into clinical practice: reality of a new tool in psychiatry. Practical issues related to medication selection. CNS Spectr 2006; 11(3 Suppl 3):5-7.
- Stearns V, Johnson MD, Rae JM et al. Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. J Natl Cancer Inst 2003; 95(23):1758-64.
- Takeuchi F, McGinnis R, Bourgeois S et al. genome-wide association study confirms VKORC1, CYP2C9, and CYP4F2 as principal genetic determinants of warfarin dose. PLoS Genet 2009; 5(3): e1000433.
- ter Laak MA, Temmink AH, Koeken A et al. Recognition of impaired atomoxetine metabolism because of low CYP2D6 activity. Pediatr Neurol. 2010; 43(3):159-62.
- The International Warfarin Pharmacogenetics Consortium. Estimation of the warfarin dose with clinical and pharmacogenetic data. N Engl J Med 2009; 360(8):753-64.
- Torno MS, Witt MD, Saitoh A et al. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. Pharmacotherapy 2008; 28(6):782-7.
- Trzepacz PT, Williams DW, Feldman PD et al. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. Eur Neuropsychopharmacol 2008; 18(2):79-86.
- Trzepacz PT, Williams DW, Feldman PD et al. CYP2D6 metabolizer status and atomoxetine dosing in children and adolescents with ADHD. Eur Neuropsychopharmacol. 2008; 18(2):79-86.
- Tsai MH, Lin KM, Hsiao MC et al. Genetic polymorphisms of cytochrome P450 enzymes influence metabolism of the antidepressant escitalopram and treatment response. Pharmacogenomics. 2010; 11(4):537-46.
- United States Food and Drug Administration. Information for Healthcare Professionals: Use of Codeine Products in Nursing Mothers. Retrieved August 27, 2010 from http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889.htm .
- Valgimigli M, Campo G, de Cesare N et al. Intensifying platelet inhibition with tirofiban in poor responders to aspiring, clopidogrel, or both agents undergoing elective coronary intervention: results from the double-blind prospective, randomized Tailoring Treatment

with Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel study. Circulation 2009; 119(25):3215-22.
- Vandel P, Talon JM, Haffen E et al. Pharmacogenetics and drug therapy in psychiatry--the role of the CYP2D6 polymorphism. Curr Pharm Des 2007; 13(2):241-50.
- Ververs FF, Voorbij HA, Zwarts P et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. Clin Pharmacokinet 2009; 48(1):677-83.
- Wadelius M, Chen LY, Downes K et al. Common VKORC1 and GGCX polymorphisms associated with warfarin dose. Pharmacogenomics J 2005; 5(4):262-70.
- Wadelius M, Chen LY, Eriksson N et al. Association of warfarin dose with genes involved in its action and metabolism. Hum Genet 2007; 121(1):23-34.
- Wadelius M, Chen LY, Lindh JD et al. The largest prospective warfarin-treated cohort supports genetic forecasting. Blood 2009; 113(4):784-92.
- Wadelius M, Sorlin K, Wallerman O et al. Warfarin sensitivity related to CYP2C9, CYP3A5, ABCB1 (MDR1) and other factors. Pharmacogenomics J 2004; 4(1):40-8.
- Wegman P, Vainikka L, Stal O et al. Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res 2005; 7(3):R284-90.
- Wen MS, Lee M, Chen JJ et al. Prospective study of warfarin dosage requirements based on CYP2C9 and VKORC1 genotypes. Clin Pharmacol Ther 2008; 84(1):83-9.
- Wernicke JF, Kratochvil CJ. Safety profile of atomoxetine in the treatment of children and adolescents with ADHD. J Clin Psychiatry 2002; 63(suppl 12):50-5.
- Wernicke JF, Kratochvil CJ. Safety profile of atomoxetine in the treatment of children and adolescents with ADHD. J Clin Psychiatry. 2002; 63 Suppl 12:50-5.
- Wiviott SD, Braunwald E, McCabe CH et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med 2007; 357(20):2001-15.
- Wu AH, Wang P, Smith A et al. Dosing algorithm for warfarin using CYP2C9 and VKORC1 genotyping from a multi-ethnic population: comparison with other equations. Pharmacogenomics 2008; 9(2):169-78.
- Xu Y, Sun Y, Yao L et al. Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol 2008; 19(8):1423-9.
- Yuan H, Huang Z, Yang G et al. Effects of polymorphism of the beta(1) adrenoreceptor and CYP2D6 on the therapeutic effects of metoprolol. J Int Med Res 2008; 36(6):1354-62.
- Yuan HY, Chen JJ, Lee MT et al. A novel functional VKORC1 promoter polymorphism is associated with inter-individual and inter-ethnic differences in warfarin sensitivity. Hum Mol Genet 2005; 14(13):1745-51.
- Zhao W, Elie V, Roussey G et al. Population pharmacokinetics and pharmacogenetics of tacrolimus in de novo pediatric kidney transplant recipients. Clin Pharmacol Ther 2009; 86(6):609-18.
- Zhu Y, Shennan M, Reynolds KK et al. Estimation of warfarin maintenance dose based on VKORC1 (-1639 G>A) and CYP2C9 genotypes. Clin Chem 2007; 53(7):1199-205.

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/1/2010	New policy Combined the following BSC policies: • Cytochrome p450 Genotyping • Genetic Testing for Initial Warfarin Dose with BCBSA Medical Policy adoption	Medical Policy Committee
3/12/2012	Coding Update	Administrative Review
2/22/2013	Coding Update	Administrative Review
4/4/2014	Policy revision with position change. Coding Update.	Medical Policy Committee

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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