Local Coverage Determination (LCD): CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (DL 35478)

Coverage Guidance
Coverage Indications, Limitations, and/or Medical Necessity
This policy limits CYP2C19 (CPT 81225) and CYP2D6 (CPT 81226) genetic testing to defined indications. All other testing for CYP2C19 and CYP2D6 is non-covered until definitive clinical utility is established to justify coverage.

This policy non-covers CYP2C9 (CPT 81227) and VKORC1 (CPT 81355) genetic testing for all medications.

CYP2C19 Genotyping

Background on CYP2C19 Testing
The CYP450 gene superfamily is composed of many isoenzymes that are involved in the metabolism of about 75% of commonly prescribed drugs. CYP2C19 metabolizes 15% of all currently used drugs, whereas CYP2D6 enzymes metabolize approximately 20-25%, and CYP2C9 metabolizes approximately 10%.

Genetic alterations or “polymorphisms” are common in these isoenzymes, with more than 30 polymorphisms identified in CYP2C19. These
polymorphisms can lead to differences in individual drug response secondary to variation in metabolism.

CYP2C19 phenotypes include poor, intermediate, extensive and ultra-rapid metabolizers. The frequency of the various metabolizers phenotypes has been estimated as follows:

- 2-15% - poor metabolizers
- 18-45% - intermediate metabolizers
- 35-50% - extensive metabolizers
- 5-30% - ultrarapid metabolizers

The genotypic rates vary by ethnicity. Approximately 2% of whites, 4% of blacks and 14% of Chinese are poor CYP2C19 metabolizers.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2C19-metabolized drugs including clopidogrel, proton pump inhibitors, and tricyclic antidepressants, among others. In certain scenarios, an individual patient may benefit from genetic testing in determining dosage and likely response to specific medications.

Clopidogrel bisulfate (Plavix) is a widely prescribed medication to/for:

- Prevent blood clots in patients with acute coronary syndrome (ACS),
- Other cardiovascular (CV) disease-related events,
- Undergoing percutaneous coronary intervention
- Amitriptyline
- Clopidogrel for indications other than above
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors
- Warfarin

Clopidogrel response varies significantly due to genetic and acquired factors including obesity, smoking and noncompliance. Patients with poor response to clopidogrel may experience recurrent CV event or thrombotic events while taking clopidogrel. They are at greater risk for major adverse CV events such as heart attack, stroke and death. These individuals are typically poor to
intermediate metabolizers of clopidogrel due to the presence of the associated CYP2C19 polymorphisms. These individuals should be given an alternate treatment strategy (Plavix PI). As such, the clinical utility of CYP2C19 genotyping has been supported with net benefits on improving health outcomes for individuals with ACS who are undergoing percutaneous coronary interventions (PCI). There is insufficient evidence of clinical utility of CYP2C19 genotyping for individuals considering clopidogrel therapy for other indications, such as medical management of ACS without PCI, stroke, or peripheral artery disease.

With regards to CYP2C19 testing for antidepressant treatment, recent evidence has suggested genetic testing prior to initiating certain tricyclic antidepressants, namely amitriptyline, due to the effects of the genotype on drug efficacy and safety. Use of this information to determine dosing has been proposed to improve clinical outcomes and reduce the failure rate of initial treatment. However, the Clinical Pharmaco-genetics Implementation Consortium did not have enough evidence to make a strong recommendation for dose modification based on genotype, and a moderate recommendation was given based on data outside of randomized trials. Additionally, even with genotype information, a suggestion is given to start patients on low dose, gradually increasing to avoid adverse side effects. Consequently, genotyping is not needed with this approach.

Proton pump inhibitors are used to treat several gastric acid-related conditions including duodenal ulcer, gastric ulcer and gastroesophageal reflux disease. Proton pump inhibitors can also be used to treat Helicobacter pylori. Several proton pump inhibitors are metabolized by CYP2C19. However, there is insufficient data to warrant CYP2C19 genotyping to determine health outcomes or adverse drug reactions in treatment with proton pump inhibitors.

With regards to Serotonin reuptake inhibitors, there is insufficient evidence to support CYP2C19 genotyping to determine medical management for the treatment of obsessive compulsive disorder at this time.
Covered Indications
In summary, genetic testing of the CYP2C19 gene is considered medically necessary for patients with ACS undergoing PCI who are initiating or reinitiating Clopidogrel (Plavix) therapy.

Non-covered Indications
Genetic testing for the CYP2C19 gene is considered investigational at this time for the following medications including but not limited to:

- Amitriptyline
- Clopidogrel for indications other than above
- Proton pump inhibitors
- Selective serotonin reuptake inhibitors
- Warfarin

CYP2D6 Genotyping

Background on CYP2D6 Testing
Genetic alterations or “polymorphisms” are common in these isoenzymes, with more than 100 polymorphisms identified in CYP2D6. These polymorphisms can lead to differences in individual drug response secondary to variation in metabolism.

CYP2D6 phenotypes include poor, intermediate, extensive and ultra-rapid metabolizers. The frequency of the poor metabolizer phenotype varies by ethnicity with 7-10% in Caucasians, 1.9-7.3% in African-Americans, and ≤ 1% in most Asian populations studied. The extensive metabolizer phenotype, observed in 50% of Caucasians, is the most common in this population. Genetic variation, as well as drug-drug interactions, can influence the classification of CYP2D6 metabolism into one of the above phenotypes. In addition, chronic dosing of a CYP2D6 drug can inhibit its own metabolism over time as the concentration of the drug approaches a steady state.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2D6-metabolized drugs including tamoxifen, antidepressants, opioid analgesics, and tetrabenazine for chorea, among others. In certain scenarios, an individual patient may benefit from this
genetic testing in determining dosage and likely response to specific medications.

**Tamoxifen**
Available evidence fails to support direct evidence of clinical utility for testing of CYP2D6 in treatment with tamoxifen. Tamoxifen metabolism and the causes for resistance are complex rather than the result of a single polymorphism.

**Antidepressants**
In regards to CYP2D6 testing for antidepressant treatment, there was insufficient evidence in the past to support testing to determine treatment. More recently, evidence has supported the use of genetic testing prior to initiating certain tricyclic antidepressants due to the effects of genotype on drug efficacy and safety. Use of this information to determine dosing can improve clinical outcomes and reduce the failure rate of initial treatment. However, there is insufficient evidence for CYP2D6 genotyping for individuals considering antipsychotic medications or other antidepressants with CYP2D6 as a metabolizing enzyme.

**Codeine**
In addition, the role of CYP2D6 genotyping has been evaluated for use in opioid analgesic drug therapy, specifically codeine analgesia. The efficacy and toxicity, including severe or life-threatening toxicity after normal doses of codeine has been linked to an individual’s CYP2D6 genotype. However, genotyping would indicate avoidance of codeine due to risk of adverse events in only 1-2% of the populations, and there is considerable variation in the degree of severity of adverse events, with most not classified as serious. Furthermore, codeine is widely used without genotyping. At this time, there is insufficient evidence to support clinical utility of genotyping for management of codeine therapy.

**Tetrabenazine**
The dosing of tetrabenazine is based, in part, on CYP2D6 genotyping. However, a recent study suggests that the necessity to genotype may need to be reconsidered. The Xenazine® manufacturer package insert indicates
that poor metabolizers of CYP2D6 should not exceed a maximum does of 50 mg/day.

**Drugs for Alzheimer’s Disease**
Galantamine is an antidementia drug used in the treatment of Alzheimer’s disease. Studies have been performed that reveal the CYP2D6 genotype significantly influences galantamine concentrations in blood. Still other studies have revealed that urinary assays for CYP2D6 phenotype are technically feasible. At this time, the association between phenotype and drug responsiveness remains unknown. It has been suggested that confirmation studies in larger populations are necessary to establish evidence regarding individuals most likely to benefit from galantamine, including information on treatment efficacy and tolerability.

Donepezil (Aricept) is a drug used to treat Alzheimer’s disease. Some studies have reported an influence of the CYP2D6 on the response to treatment with this drug. Other studies suggest that therapy based on CYP2D6 genotype is unlikely to be beneficial for treating Alzheimer’s disease patients in routine clinical practice. Additional studies are needed to determine the efficacy and utility of CYP2D6 genotyping in those patients who are treated with donepezil.

**Covered Indications**
In summary, genetic testing of the CYP2D6 gene is considered medically necessary to guide medical treatment and/or dosing for individuals for whom initial therapy is planned with:

- Amitriptyline or nortriptyline for treatment of depressive disorders
- Tetrabenazine doses greater than 50 mg/day, or re-initiation of therapy with doses greater than 50 mg/day

**Non-covered indications**
There is insufficient evidence to demonstrate that genetic testing for the CYP2D6 gene improves clinical outcomes. Consequently, genetic testing for the CYP2D6 gene is considered investigational including but not limited to the following medications:
• Antidepressants other than those listed above
• Antipsychotics
• Codeine
• Donepezil
• Galantamine
• Tamoxifen

CYP2C9 Genotyping

Background on CYP2C9 Testing
CYP2C9 metabolizes approximately 10-15% of all currently used drugs. Genetic alternations or “polymorphisms” are common in these isoenzymes, with 57 polymorphisms identified in CYP2C9, which can lead to differences in individual drug response secondary to variation in metabolism.

Pharmacogenetic testing has been proposed to predict individual response to a variety of CYP2C9-metabolized drugs including celecoxib, fluorbipofen, fluvoxamine and warfarin, among others. In certain scenarios, an individual patient may benefit from this genetic testing in determining dosage and likely response to specific medications. However, there is insufficient evidence to support CYP2C9 genotyping to determine medical management and alter outcomes at this time.

Individuals with low enzyme activity for CYP2C9 substrates are at risk of adverse drug reactions. However, pharmacogenetic testing for individuals being treated with drugs, such as warfarin, may experience little or no benefit from testing. This is, in part, because the CYP2C9 genotype accounts for only part of the variability in drug sensitivity.

Warfarin
While there is extensive literature regarding warfarin and the CYP2C9 genotype, the clinical utility of such testing remains unproven at this time. In fact, pharmacogenetic testing for warfarin treatment has been recommended against by the American College of Medical Genetics and the American College of Chest Physicians. These guidelines suggest that genetic testing for warfarin metabolism is not medically necessary, and evidence of
clinical utility remains to be proven. Obstacles for determining clinical utility have been reviewed with suggestions for researchers in this area.

**Celecoxib**
In addition, limited information is available regarding celecoxib metabolism in individuals with CYP2C9 polymorphisms. More trials are needed to determine clinical utility and appropriateness of pharmacogenetic testing in this population.

**Covered Indications**
Effective August 3, 2009, the Centers for Medicare & Medicaid Services (CMS) believes that the available evidence supports that coverage with evidence development (CED) under §1862(a)(1)(E) of the Social Security Act (the Act) is appropriate for pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness by any method, and is therefore covered only when provided to Medicare beneficiaries who are candidates for anticoagulation therapy with warfarin who:

- Have not been previously tested for CYP2C9 or VKORC1 alleles; and
- Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
- Are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards set forth in the Coverage with Evidence Development (CED) information found on the CMS website.

**Non-covered Indications**
All other coverage for genetic testing for the CYP2C9 gene is considered investigational at this time. There is currently no proven clinical utility related to any medication, including but not limited to:

- Celecoxib
- Fluorbiprofen
- Flovoxamine
VKORC1 Genotyping

Background on VKORC1 Testing
The vitamin K epoxide reductase complex subunit 1, encoded by the gene VKORC1, is critical in the vitamin K pathway for coagulation. Warfarin therapy targets VKORC1 to reduce clotting risk.

Variation in response to warfarin therapy has been linked to genetic variations. Retrospective study of European-American patients undergoing long term warfarin therapy identified 5 major haplotypes that were most predictive of approximately 25% of variance in warfarin dose. These are classified into A: low dose haplotype and B: high dose haplotype. This was validated in two European-American populations. Average maintenance dose for A/A haplotypes was approximately 2.7 mg per day; 4.9 mg per day for A/B, and 6.2 mg per day for B/B (p<0.001).

Review by the American College of Medical Genetics (2008) confirmed the analytic validity of testing VKORC1 and confirmed that there is sufficient evidence to support association with final therapeutic dose of warfarin. However, safe warfarin dosing requires careful monitoring and there is insufficient evidence is available to support routine VKORC1 genotyping for determination of final dosing. Further study in prospective clinical trials are needed to determine clinical utility.

Clinical Pharmacogenetics Implementation Consortium guidelines recommend that pharmacogenetic algorithms be used to determine ideal dosing, and recommend including VKORC1 genotyping when available. However the evidence from randomized prospective trials is limited, and impact on clinical outcomes is not yet known, limiting the ability to recommend that genotyping be performed for initial warfarin prescribing.

Prospective study of 30 healthy subjects assessed for warfarin dosing with daily INR measurements determined that VKORC1 (p=0.02) variant carriers require lower cumulative doses of warfarin to achieve INR ≥ 2.0. Participants who carried variants in both CYP2C9 and VKORC1 required fewer days to achieve INR ≥ 2.0 that wild type subjects (p=0.01) resulting in an estimated genetic contribution to dose variability of 62%.
Meta-analysis of CYP2C9 and VKORC1 genotypes influence the risk of hemorrhagic complications in warfarin treated patients and increase the risk for over-coagulation and hemorrhagic complications with CYP2C9*3 carriers. No significant association was noted between VKORC1 genotypes and hemorrhagic complications.

Randomized controlled study assessing 109 adult patients and the influence of VKORC1 genotyping data on clinical outcomes of initial warfarin dosing was performed. Primary endpoints included time in therapeutic range over 90 days and number of anticoagulation visits. Hospitalizations, emergency visits, time to reach therapeutic dose, INR >4, hemorrhagic events, thrombotic events and mortality were secondary endpoints. No difference in the primary endpoints was noted between patients who received initial dosing by clinical and genotype information as compared to those whose initial dosing was determined by clinical information alone. No statistical difference was noted between either group in secondary events, however fewer of these events were noted among patients whose dosing included genotypic data.

**Covered Indications**

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- Have not been previously tested for CYP2C9 or VKORC1 alleles; and
- Have received fewer than five days of warfarin in the anticoagulation regimen for which the testing is ordered; and
- Are enrolled in a prospective, randomized, controlled clinical study when that study meets the following standards set forth in the Coverage with Evidence Development (CED) information found on the CMS website.
Non-covered Indications
Genetic testing for the VKORC1 gene is considered investigational at this time for all other medications.