CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing

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CMS National Coverage Policy

- Title XVIII of the Social Security Act, §1862(a)(1)(A)allows coverage and payment for only those services that are considered to be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member
- Title XVIII of the Social Security Act, §1862(a)(1)(D) items and services related to research and experimentation
- Title XVIII of the Social Security Act, §1833(e), prohibits Medicare payment for any claim which lack the necessary information to process the claim.
- 42 CFR 410.32(a) Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions
- 42CFR411.15(k)(1) Particular services excluded from coverage
- CMS On-Line Manual, Publication 100-08, Medicare Program Integrity Manual, Chapter 3, §3.4.1.3, diagnosis code requirements

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 medications to defined indications. All other testing for *CYP2C9*and *VKORC1* is non-covered until definitive clinical utility is established to justify coverage.

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% - ultra-rapid 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

Clopidogrel response varies significantly due to genetic and acquired factors including obesity, smoking and non-compliance. 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, 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 Helicobactor 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

There is insufficient evidence to demonstrate that genetic testing for the CYP2C19 gene improves clinical outcomes. Consequently, genetic testing for the CYP2C19 gene outside of the specified covered indications is considered investigational.

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 tetrabenzine 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. Conformational studies in larger populations are necessary to establish evidence regarding individuals most likely to benefit from galatamine, including information on treatment efficacy and tolerability.

Donepezil (Aricept) is a drugs used to treat an 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 outside of the specified covered indications is considered investigational.

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.*

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.

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 in randomized controlled study testing.

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.*

Non-covered Indications

There is insufficient evidence to demonstrate that genetic testing for the VKORC1 gene improves clinical outcomes. Consequently, genetic testing for the*VKORC1* gene outside of the specified covered indications is considered investigational.

Bill Type Codes:
Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.
N/A

Revenue Codes:
Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory; unless specified in the policy services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

CPT/HCPCS Codes

Group 1 Paragraph: N/A

Group 1 Codes:

81225 CYP2C19 (CYTOCHROME P450, FAMILY 2 SUBFAMILY C, POLYPEPTIDE 19) (EG, DRUG METABOLISM), GENE ANALYSIS, COMMON VARIANTS (EG, *2, *3, *4, *8, *17)

Group 2 Paragraph: N/A

Group 2 Codes:

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)

Group 3 Paragraph: N/A

Group 3 Codes:

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)

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph: The correct use of an ICD-10-CM code listed in the “ICD-10 Codes that Support Medical Necessity” section does not guarantee coverage of a service. The service must be reasonable and necessary in the specific case and must meet the criteria specified in this LCD.

ICD-10 codes must be coded to the highest level of specificity. Consult the ‘Official ICD-10-CM Guidelines for Coding and Reporting’ in the current ICD-10-CM book for correct coding guidelines. This LCD does not take precedence over the Correct Coding Initiative (CCI).

Group 1 Codes:

Group 1Codes	
ICD-10 CODE	**DESCRIPTION**
I20.0	Unstable angina
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified

I21.09	ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall
I21.11	ST elevation (STEMI) myocardial infarction involving right coronary artery
I21.19	ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I21.4	Non-ST elevation (NSTEMI) myocardial infarction
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischemic heart disease
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris
I25.700	Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris
I25.701	Atherosclerosis of coronary artery bypass graft(s), unspecified, with angina pectoris with documented spasm
I25.708	Atherosclerosis of coronary artery bypass graft(s), unspecified, with other forms of angina pectoris
I25.709	Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris
I25.710	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris
I25.711	Atherosclerosis of autologous vein coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.718	Atherosclerosis of autologous vein coronary artery bypass graft(s) with other forms of

	angina pectoris
I25.719 - I25.721- Opens in a new window	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris - Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.728 - I25.731- Opens in a new window	Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris - Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.738	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with other forms of angina pectoris
I25.739	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unspecified angina pectoris
I25.750	Atherosclerosis of native coronary artery of transplanted heart with unstable angina
I25.751	Atherosclerosis of native coronary artery of transplanted heart with angina pectoris with documented spasm
I25.758 - I25.761- Opens in a new window	Atherosclerosis of native coronary artery of transplanted heart with other forms of angina pectoris - Atherosclerosis of bypass graft of coronary artery of transplanted heart with angina pectoris with documented spasm
I25.768	Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris
I25.769	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris
I25.790	Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris
I25.791	Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.798	Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris
I25.799	Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris
L24.9	Irritant contact dermatitis, unspecified cause

Group 2 Codes:

Group 2Codes	
ICD-10 CODE	**DESCRIPTION**
F31.30 - F31.32- Opens in a new window	Bipolar disorder, current episode depressed, mild or moderate severity, unspecified - Bipolar disorder, current episode depressed, moderate
F31.4	Bipolar disorder, current episode depressed, severe, without psychotic features
F31.5	Bipolar disorder, current episode depressed, severe, with psychotic features
F31.60 - F31.64- Opens in a new window	Bipolar disorder, current episode mixed, unspecified - Bipolar disorder, current episode mixed, severe, with psychotic features
F31.75	Bipolar disorder, in partial remission, most recent episode depressed
F31.76	Bipolar disorder, in full remission, most recent episode depressed
F31.77	Bipolar disorder, in partial remission, most recent episode mixed
F31.78	Bipolar disorder, in full remission, most recent episode mixed
F33.0 - F33.3- Opens in a new window	Major depressive disorder, recurrent, mild - Major depressive disorder, recurrent, severe with psychotic symptoms
F33.40 - F33.42- Opens in a new window	Major depressive disorder, recurrent, in remission, unspecified - Major depressive disorder, recurrent, in full remission
F33.9	Major depressive disorder, recurrent, unspecified

Associated Information
N/A

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