Local Coverage Determination (LCD):
CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L35698)

Contractor Information

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<tr>
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LCD Information

Document Information

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<td>For services performed on or after 10/01/2015</td>
<td>For services performed on or after 04/02/2018</td>
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Original ICD-9 LCD ID
L35366

LCD Title
CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing

Proposed LCD in Comment Period
N/A

Source Proposed LCD
N/A

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CMS National Coverage Policy
Language quoted from CMS National Coverage Determination (NCDs) and coverage provisions in interpretive manuals are italicized throughout the Local Coverage Determination (LCD). NCDs and coverage provisions in interpretive manuals are not subject to the LCD Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See §1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, italicized text represents quotation from one or more of the following CMS sources:

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, §1862(a)(1)(E) research conducted pursuant to section 1142, which is not reasonable and necessary to carry out the purposes of that section

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

42 CFR 411.15(k)(1) Particular services excluded from coverage

CMS On-Line Manual, Publication 100-03, Medicare National Coverage Determinations Manual, Chapter 1, §90.1 Pharmacogenomic Testing to Predict Warfarin Responsiveness

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 81226/0028U) 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 as not reasonable and necessary under §1862(a)(1)(A). The available literature does not support that CYP2C9 and VKORC1 testing for drug responsiveness improves health outcomes in beneficiaries.

This policy is not addressing coverage with evidence development (CED) under section 1862(a)(1)(E). CYP2C9 and VKORC1 when performed for CED for warfarin responsiveness [Healthcare Common Procedure Coding System (HCPCS) code G9143] will be covered when provided in accordance to the coverage limitations of the National Coverage Determination (NCD) for Pharmacogenomic Testing for Warfarin Response. For CED 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, the Clinical Pharmacogenetics 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 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 \( \text{CYP2C19} \) 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 \( \text{CYP2C19} \) 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 \( \text{CYP2D6} \). These polymorphisms can lead to differences in individual drug response secondary to variation in metabolism.

\( \text{CYP2D6} \) 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 \( \text{CYP2D6} \) metabolism into one of the above phenotypes. In addition, chronic dosing of a \( \text{CYP2D6} \) 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 \( \text{CYP2D6} \)-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 \( \text{CYP2D6} \) 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 \( \text{CYP2D6} \) 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 \( \text{CYP2D6} \) genotyping for individuals considering antipsychotic medications or other antidepressants with \( \text{CYP2D6} \) as a metabolizing enzyme.

**Codeine**

In addition, the role of \( \text{CYP2D6} \) 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 \( \text{CYP2D6} \) 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 \( \text{CYP2D6} \) 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 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 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. 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 CYP2C9-metabolized drugs 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

The CMS believes that the available evidence does not demonstrate that pharmacogenomic testing of CYP2C9 or VKORC1 alleles to predict warfarin responsiveness improves health outcomes in beneficiaries outside the context of CED, and is therefore not reasonable and necessary under §1862(a)(1)(A) of the Act. (NCD 90.1)

Celecoxib
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.

**Non-covered Indications**

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
- Fluoribiprofen
- Flovoxamine

**VKORC1 Genotyping**

**Non-covered Indications**

VKORC1 (CPT 81355) genetic testing for all medications is considered investigational at this time. The available literature does not support that VKORC1 testing for drug responsiveness improves health outcomes in beneficiaries.

**Summary of Evidence**

N/A

**Analysis of Evidence (Rationale for Determination)**

N/A

**Coding Information**

**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.

- 012x Hospital Inpatient (Medicare Part B only)
- 013x Hospital Outpatient
- 014x Hospital - Laboratory Services Provided to Non-patients
- 022x Skilled Nursing - Inpatient (Medicare Part B only)
- 023x Skilled Nursing - Outpatient
- 071x Clinic - Rural Health
- 072x Clinic - Hospital Based or Independent Renal Dialysis Center
- 075x Clinic - Comprehensive Outpatient Rehabilitation Facility (CORF)
- 077x Clinic - Federally Qualified Health Center (FQHC)
- 085x Critical Access Hospital

**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.

030X  Laboratory - General Classification
031X  Laboratory Pathology - General Classification

CPT/HCPCS Codes

**Group 1 Paragraph:** N/A

**Group 1 Codes:**


**Group 2 Paragraph:** N/A

**Group 2 Codes:**


CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE 0028U ANALYSIS, COPY NUMBER VARIANTS, COMMON VARIANTS WITH REFLEX TO TARGETED SEQUENCE ANALYSIS

**Group 3 Paragraph:** N/A

**Group 3 Codes:**


81355  VKORC1 (VITAMIN K EPOXIDE REDUCTASE COMPLEX, SUBUNIT 1) (EG, WARFARIN METABOLISM), GENE ANALYSIS, COMMON VARIANT(S) (EG, -1639G>A, C.173+1000C>T)

ICD-10 Codes that Support Medical Necessity

**Group 1 Paragraph:**

N/A

**Group 1 Codes:**

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<td>Angina pectoris with documented spasm</td>
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<td>Other forms of angina pectoris - Angina pectoris, unspecified</td>
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<td>ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall</td>
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<td>I21.11</td>
<td>ST elevation (STEMI) myocardial infarction involving right coronary artery</td>
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<td>I21.29</td>
<td>ST elevation (STEMI) myocardial infarction involving other sites</td>
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<td>I21.3</td>
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<td>Non-ST elevation (NSTEMI) myocardial infarction</td>
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<td>I21.9</td>
<td>Acute myocardial infarction, unspecified</td>
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<td>I24.0</td>
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<td>Bipolar disorder, in partial remission, most recent episode depressed - Bipolar disorder, in full remission, most recent episode mixed</td>
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<td>G10</td>
<td>Huntington's disease</td>
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**ICD-10 Codes that DO NOT Support Medical Necessity**
Sources of Information


**Bibliography**

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**Revision History Information**

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<td>Revision Number: 3</td>
<td>• Revisions Due To CPT/HCPCS Code Changes</td>
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<td>Publication: May 2018 Connection LCR A/B2018-033</td>
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<td>Explanation of Revision: Based on CR 10515 (April 2018 Update of the Hospital Outpatient Prospective Payment System [OPPS]) and CR 10445 (Quarterly Update for Clinical Laboratory Fee Schedule and Laboratory Services Subject to Reasonable Charge Payment), the LCD was revised to add procedure code 0028U. The effective date of this revision is for claims processed on or after 04/02/2018, for dates of service on or after 01/01/2018. 04/02/2018: At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination and therefore not all the fields included on the LCD are applicable as noted in this policy.</td>
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<td>Explanation of Revision: Based on CR 10153 (Annual 2016 HCPCS Update) the LCD was revised. Added ICD-10-CM diagnosis code I21.9, I21.A1 – I21.A9 for procedure code 81225. The effective date of this revision is based on date of service. 10/01/2017: At this time 21st Century Cures Act will apply to new and revised LCDs that restrict coverage which requires comment and notice. This revision is not a restriction to the coverage determination and therefore not all the fields included on the LCD are applicable as noted in this policy.</td>
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Associated Documents
Attachments
N/A

Related Local Coverage Documents
Article(s) A53848 - NCD - Pharmacogenomic Testing for Warfarin Response

Related National Coverage Documents
NCD(s) 90.1 - Pharmacogenomic Testing for Warfarin Response

Keywords
N/A