CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing

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LCD Title
Pathology and Laboratory: 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 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**

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 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 antideementia 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
- Fluoribiprofen
- Floxoxamine

**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:


Group 2 Paragraph: N/A

Group 2 Codes:


Group 3 Paragraph: N/A

Group 3 Codes:


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:

<table>
<thead>
<tr>
<th>ICD-10 CODE</th>
<th>DESCRIPTION</th>
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</thead>
<tbody>
<tr>
<td>I20.0</td>
<td>Unstable angina</td>
</tr>
<tr>
<td>I20.1</td>
<td>Angina pectoris with documented spasm</td>
</tr>
<tr>
<td>I20.8</td>
<td>Other forms of angina pectoris</td>
</tr>
<tr>
<td>I20.9</td>
<td>Angina pectoris, unspecified</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>I21.09</td>
<td>ST elevation (STEMI) myocardial infarction involving other coronary artery of anterior wall</td>
</tr>
<tr>
<td>I21.11</td>
<td>ST elevation (STEMI) myocardial infarction involving right coronary artery</td>
</tr>
<tr>
<td>I21.19</td>
<td>ST elevation (STEMI) myocardial infarction involving other coronary artery of inferior wall</td>
</tr>
<tr>
<td>I21.29</td>
<td>ST elevation (STEMI) myocardial infarction involving other sites</td>
</tr>
<tr>
<td>I21.3</td>
<td>ST elevation (STEMI) myocardial infarction of unspecified site</td>
</tr>
<tr>
<td>I21.4</td>
<td>Non-ST elevation (NSTEMI) myocardial infarction</td>
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<tr>
<td>I24.0</td>
<td>Acute coronary thrombosis not resulting in myocardial infarction</td>
</tr>
<tr>
<td>I24.1</td>
<td>Dressler's syndrome</td>
</tr>
<tr>
<td>I24.8</td>
<td>Other forms of acute ischemic heart disease</td>
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<td>I25.110</td>
<td>Atherosclerotic heart disease of native coronary artery with unstable angina pectoris</td>
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<td>I25.111</td>
<td>Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm</td>
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<td>I25.118</td>
<td>Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris</td>
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<td>I25.119</td>
<td>Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris</td>
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<td>I25.700</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with unstable angina pectoris</td>
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<td>I25.701</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with angina pectoris with documented spasm</td>
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<tr>
<td>I25.708</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with other forms of angina pectoris</td>
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<tr>
<td>I25.709</td>
<td>Atherosclerosis of coronary artery bypass graft(s), unspecified, with unspecified angina pectoris</td>
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<tr>
<td>I25.710</td>
<td>Atherosclerosis of autologous vein coronary artery bypass graft(s) with unstable angina pectoris</td>
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<tr>
<td>I25.711</td>
<td>Atherosclerosis of autologous vein coronary artery bypass graft(s) with angina pectoris with documented spasm</td>
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<tr>
<td>I25.718</td>
<td>Atherosclerosis of autologous vein coronary artery bypass graft(s) with other forms of</td>
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<td>Code</td>
<td>Description</td>
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<td>I25.719 - I25.721</td>
<td>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</td>
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<td>I25.728 - I25.731</td>
<td>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</td>
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<td>I25.738</td>
<td>Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with other forms of angina pectoris</td>
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<td>I25.750</td>
<td>Atherosclerosis of native coronary artery of transplanted heart with unstable angina</td>
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<td>I25.751</td>
<td>Atherosclerosis of native coronary artery of transplanted heart with angina pectoris with documented spasm</td>
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<td>I25.758 - I25.761</td>
<td>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</td>
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<td>I25.768</td>
<td>Atherosclerosis of bypass graft of coronary artery of transplanted heart with other forms of angina pectoris</td>
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<td>I25.769</td>
<td>Atherosclerosis of bypass graft of coronary artery of transplanted heart with unspecified angina pectoris</td>
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<td>I25.790</td>
<td>Atherosclerosis of other coronary artery bypass graft(s) with unstable angina pectoris</td>
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<td>I25.791</td>
<td>Atherosclerosis of other coronary artery bypass graft(s) with angina pectoris with documented spasm</td>
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<td>Atherosclerosis of other coronary artery bypass graft(s) with other forms of angina pectoris</td>
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<td>I25.799</td>
<td>Atherosclerosis of other coronary artery bypass graft(s) with unspecified angina pectoris</td>
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<td>L24.9</td>
<td>Irritant contact dermatitis, unspecified cause</td>
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**Group 2 Codes:**
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<th>DESCRIPTION</th>
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<td>F31.30 - F31.32 - Opens in a new window</td>
<td>Bipolar disorder, current episode depressed, mild or moderate severity, unspecified - Bipolar disorder, current episode depressed, moderate</td>
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<tr>
<td>F31.4</td>
<td>Bipolar disorder, current episode depressed, severe, without psychotic features</td>
</tr>
<tr>
<td>F31.5</td>
<td>Bipolar disorder, current episode depressed, severe, with psychotic features</td>
</tr>
<tr>
<td>F31.60 - F31.64 - Opens in a new window</td>
<td>Bipolar disorder, current episode mixed, unspecified - Bipolar disorder, current episode mixed, severe, with psychotic features</td>
</tr>
<tr>
<td>F31.75</td>
<td>Bipolar disorder, in partial remission, most recent episode depressed</td>
</tr>
<tr>
<td>F31.76</td>
<td>Bipolar disorder, in full remission, most recent episode depressed</td>
</tr>
<tr>
<td>F31.77</td>
<td>Bipolar disorder, in partial remission, most recent episode mixed</td>
</tr>
<tr>
<td>F31.78</td>
<td>Bipolar disorder, in full remission, most recent episode mixed</td>
</tr>
<tr>
<td>F33.0 - F33.3 - Opens in a new window</td>
<td>Major depressive disorder, recurrent, mild - Major depressive disorder, recurrent, severe with psychotic symptoms</td>
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<tr>
<td>F33.40 - F33.42 - Opens in a new window</td>
<td>Major depressive disorder, recurrent, in remission, unspecified - Major depressive disorder, recurrent, in full remission</td>
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<tr>
<td>F33.9</td>
<td>Major depressive disorder, recurrent, unspecified</td>
</tr>
</tbody>
</table>

**Associated Information**

**Sources of Information and Basis for Decision**


Local Coverage Determination (LCD) Disclaimer

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