Local Coverage Determination (LCD): MolDX: CYP2C19, CYP2D6, CYP2C9, and VKORC1 Genetic Testing (L36310)

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Noridian Healthcare Solutions, LLC	A and B MAC	01111 - MAC A	J - E	California - Entire State
Noridian Healthcare Solutions, LLC	A and B MAC	01112 - MAC B	J - E	California - Northern
Noridian Healthcare Solutions, LLC	A and B MAC	01182 - MAC B	J - E	California - Southern
Noridian Healthcare Solutions, LLC	A and B MAC	01211 - MAC A	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01212 - MAC B	J - E	American Samoa Guam Hawaii Northern Mariana Islands
Noridian Healthcare Solutions, LLC	A and B MAC	01311 - MAC A	J - E	Nevada
Noridian Healthcare Solutions, LLC	A and B MAC	01312 - MAC B	J - E	Nevada
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LCD Information

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N/A

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, §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 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% - 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 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 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

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 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. It has been suggested that confirmation 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 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 standards as set forth in National Coverage Determination 90.1.

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

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 standards as set forth in National Coverage Determination 90.1.

Non-covered Indications

Genetic testing for the *VKORC1* gene is considered investigational at this time for all other medications.

Summary of Evidence

NA

Analysis of Evidence
(Rationale for Determination)

NA

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.

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.

N/A

CPT/HCPCS Codes

Group 1 Paragraph:

N/A

Group 1 Codes:

CODE	DESCRIPTION
81225	CYP2C19 (CYTOCHROME P450, FAMILY 2, SUBFAMILY C, POLYPEPTIDE 19) (EG, DRUG METABOLISM), GENE ANALYSIS, COMMON VARIANTS (EG, *2, *3, *4, *8, *17)
81479	UNLISTED MOLECULAR PATHOLOGY PROCEDURE

Group 2 Paragraph:

N/A

Group 2 Codes:

CODE	DESCRIPTION
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)
0070U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, COMMON AND SELECT RARE VARIANTS (IE, *2, *3, *4, *4N, *5, *6, *7, *8, *9, *10, *11, *12, *13, *14A, *14B, *15, *17, *29, *35, *36, *41, *57, *61, *63, *68, *83, *XN)

Group 3 Paragraph:

N/A

Group 3 Codes:

CODE	DESCRIPTION
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 VARIANT(S) (EG, -1639G>A, C.173+1000C>T)

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

N/A

Group 1 Codes:

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
I21.9	Acute myocardial infarction, unspecified

ICD-10 CODE	DESCRIPTION
I21.A1	Myocardial infarction type 2
I21.A9	Other myocardial infarction type
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.1	Dressler's syndrome
I24.8	Other forms of acute ischemic heart disease
I24.9	Acute ischemic heart disease, unspecified
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	Atherosclerosis of autologous vein coronary artery bypass graft(s) with unspecified angina pectoris
I25.720	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unstable angina pectoris
I25.721	Atherosclerosis of autologous artery coronary artery bypass graft(s) with angina pectoris with documented spasm
I25.728	Atherosclerosis of autologous artery coronary artery bypass graft(s) with other forms of angina pectoris
I25.729	Atherosclerosis of autologous artery coronary artery bypass graft(s) with unspecified

ICD-10 CODE	DESCRIPTION
	angina pectoris
I25.730	Atherosclerosis of nonautologous biological coronary artery bypass graft(s) with unstable angina pectoris
I25.731	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	Atherosclerosis of native coronary artery of transplanted heart with other forms of angina pectoris
I25.759	Atherosclerosis of native coronary artery of transplanted heart with unspecified angina pectoris
I25.760	Atherosclerosis of bypass graft of coronary artery of transplanted heart with unstable angina
I25.761	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

Group 2 Paragraph:

N/A

Group 2 Codes:

ICD-10 CODE	DESCRIPTION
F31.30	Bipolar disorder, current episode depressed, mild or moderate severity, unspecified
F31.31	Bipolar disorder, current episode depressed, mild
F31.32	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	Bipolar disorder, current episode mixed, unspecified
F31.61	Bipolar disorder, current episode mixed, mild
F31.62	Bipolar disorder, current episode mixed, moderate
F31.63	Bipolar disorder, current episode mixed, severe, without psychotic features
F31.64	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
F31.9	Bipolar disorder, unspecified
F32.9	Major depressive disorder, single episode, unspecified
F33.0	Major depressive disorder, recurrent, mild
F33.1	Major depressive disorder, recurrent, moderate
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.40	Major depressive disorder, recurrent, in remission, unspecified
F33.41	Major depressive disorder, recurrent, in partial remission
F33.42	Major depressive disorder, recurrent, in full remission
F33.9	Major depressive disorder, recurrent, unspecified
F53.0	Postpartum depression
G10	Huntington's disease

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

General Information

Associated Information

N/A

Sources of Information

References:

1. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and Management of the Vitamin K Antagonists*: American College of Chest Physicians EvidenceBased Clinical Practice Guidelines (8th Edition) Antithrombotic and Thrombolytic Therapy, 8th Ed : ACCP Guidelines. *Chest.* 2008;133(6_suppl):160S198S. doi:10.1378/chest.080670

2. ARHQ Evidence Report/Technology Assessment Number 146. Testing for Cytochrome P450 Polymorphisms in Adults With NonPsychotic Depression Treated With Selective Serotonin Reuptake Inhibitors (SSRIs). *AHRQ Publication No. 07E002* January 2007.

3. Berger JS, Bhatt DL, Steinhubl SR, et al. Smoking, Clopidogrel, and Mortality in Patients with Established Cardiovascular Disease. *Circulation*. Dec 8, 2009 ; 120(23): 2337. 1161/CIRCULATIONAHA.109.866533

4. Brandl EJ, Tiwari AK, Zhou X, et al. Influence of CYP2D6 and CYP2C19 gene variants on antidepressant response in obsessivecompulsive disorder. *Pharmacogenomics J.* Apr 2, 2013. doi: 10.1038/tpj.2013.12.

5. Capon DA, Bochner F, Kerry N, Mikus G, Danz C, Somogyi AA. The influence of CYP2D6 polymorphism and quinidine on the disposition and antitussive effect of dextromethorphan in humans. *Clinical Pharmacology & Therapeutics.* 1996; 60: 295–307. doi:10.1016/S00099236(96)900569.

6. Chianella C, Gragnaniello D, Maisano Delser P, et al. BCHE and CYP2D6 genetic variation in Alzheimer's disease patients treated with cholinesterase inhibitors. *Eur J Clin Pharmacol.* 2011 Nov;67(11):114757. doi: 10.1007/s002280111064x.

7. Clarke JA, Cutler M, Gong I, Schwarz UI, Freeman D, Dasgupta M. Cytochrome P450 2D6 phenotyping in an elderly population with dementia and response to galantamine in dementia: a pilot study. *Am J Geriatr Pharmacother.* 2011 Aug;9(4):22433. doi: 10.1016/j.amjopharm.2011.07.003.

8. CMS 100-3, §90.1 Pharmacogeneomic Testing for Warfarin Response. http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Downloads/ncd103c1_Part2.pdf. Accessed October 1, 2013.

9. Crews KR, Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines for Codeine Therapy in the Context of Cytochrome P450 2D6 (CYP2D6) Genotype *Clin Pharmacol Ther.* 2012; 91(2): 321–326. doi: 10.1038/clpt.2011.287.

10. CYP2C9 Allele Nomenclature. http://www.cypalleles.ki.se/cyp2c9.htm. Accessed September 3, 2013.

11. Dezentjé VO, Guchelaar HJ, Nortier JW, van de Velde CJ, Gelderblom H. Clinical implications of CYP2D6 genotyping in tamoxifen treatment for breast cancer. *Clin Cancer Res.* 2009;15(1):1521. doi: 10.1158/10780432.

CCR082006.

12.EGAPP: 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 Dec;9(12):81925.

13. Flockhart DA, O'Kane D, Williams MS, et al. ACMG Working Group on Pharmacogenetic Testing of CYP2C9, VKORC1 Alleles for Warfarin Use. Pharmacogenetic testing of CYP2C9 and VKORC1 alleles for warfarin. *Genet Med.* 2008 Feb;10(2):13950. doi: 10.1097/GIM.0b013e318163c35f.

14. Gong L, Thorn CF, Bertagnolli MM, Grosser T, Altman RB, Klein TE. Celecoxib pathways: pharmacokinetics and pharmacodynamics. *Pharmacogenet Genomics.* 2012 Apr;22(4):3108. doi: 10.1097/FPC.0b013e32834f94cb.

15. Guay DR. Tetrabenazine, a monoaminedepleting drug used in the treatment of hyperkinetic movement disorders. *Am J Geriatr Pharmacother.* 2010;8(4):33173. doi: 10.1016/j.amjopharm.2010.08.006.

16. Herbild L, Andersen SE, Werge T, Rasmussen HB, Jürgens G. Does Pharmacogenetic Testing for CYP450 2D6 and 2C19 Among Patients with Diagnoses within the Schizophrenic Spectrum Reduce Treatment Costs? *Basic Clin Pharmacol Toxicol.* 2013 Oct;113(4):266-72. doi: 10.1111/bcpt.12093

17. Hicks JK, Swen JJ, Thorn CF, et al.; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants. *Clin Pharmacol Ther.* 2013;93(5):4028.doi: 10.1038/clpt.2013.2.

18. Huang SW, Chen HS, Wang XQ, et al. Validation of VKORC1 and CYP2C9 genotypes on interindividual warfarin maintenance dose: a prospective study in Chinese patients. Pharmacogenet Genomics. 2009 Mar;19(3):226-34.

19. Johnson JA, Gong L, Whirl-Carillo, et al. Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. *Clin Pharmacol Ther.* 2011 Oct;90(4):6259. doi: 10.1038/clpt.2011.185.

20. Jonas DE, Evans JP, McLeod HL, et al. Impact of genotype-guided dosing on anticoagulation visits for adults starting warfarin: a randomized controlled trial. *Pharmacogenomics.* 2013 Oct;14(13):1593-603. doi: 10.2217/pgs.13.145. PubMed PMID: 24088130.

21. Jorgensen AL, FitzGerald RJ, Oyee J, Pirmohamed M, Williamson PR. Influence of CYP2C9 and VKORC1 on patient response to warfarin: a systematic review and metaanalysis. *PLoS One.* 2012;7(8):e44064. doi: 10.1371/journal.pone.0044064. Epub 2012 Aug 29.

22. Jürgens G, Rasmussen HB, Werge T, Dalhoff K, Nordentoft M, Andersen SE. Does the medication pattern reflect the CYP2D6 genotype in patients with diagnoses within the schizophrenic spectrum? *J Clin Psychopharmacol.* 2012 Feb;32(1):1005.

23. Kadian-Dodov DL, van der Zee SA, Scott SA, Peter I, Martis S, Doheny DO, Rothlauf EB, Lubitz SA, Desnick RJ, Halperin JL. Warfarin pharmacogenetics: a controlled dose-response study in healthy subjects. Vasc Med. 2013 Oct; 18(5):290-7.

24. Klimkowicz-Mrowiec A, Wolkow P, Sado M, et al. Influence of rs1080985 single nucleotide polymorphism of the CYP2D6 gene on response to treatment with donepezil in patients with alzheimer's disease. *Neuropsychiatr Dis Treat.* 2013;9:1029-33. doi: 10.2147/NDT.S46689. Epub 2013 Jul 29. PubMed PMID: 23950644; PubMed Central PMCID: PMC3742350.

25. Kringen MK, Haug KB, Grimholt RM, et al. Genetic variation of VKORC1 and CYP4F2 genes related to warfarin maintenance dose in patients with myocardial infarction. J Biomed Biotechnol. 2011;2011:739-751.

26. Lum DW, Perel P, Hingorani AD, Holmes MV. CYP2D6 Genotype and Tamoxifen Response for Breast Cancer: A Systematic Review and Meta-Analysis. *PLoS One.* 2013 Oct 2;8(10):e76648. doi: 10.1371/journal.pone.0076648. PubMed PMID: 24098545; PubMed Central PMCID: PMC3788742.

27. Mak KH, Bhatt DL, Shao M, et al. Ethnic variation in adverse cardiovascular outcomes and bleeding complications in the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) study. *Am Heart J.* Apr 2009; 157(4):65865. doi: 10.1016/j.ahj.2008.08.031.

28. Markkula A, Hjertberg M, Rose C, Ingvar C, Jernström H. No association found between CYP2D6 genotype and early breast cancer events in tamoxifen-treated patients. *Acta Oncol.* 2013 Oct 14.

29. McClain MR, Palomaki GE, Piper M, Haddow JE. A rapidACCE review of CYP2C9 and VKORC1 alleles testing to inform warfarin dosing in adults at elevated risk for thrombotic events to avoid serious bleeding. *Genet Med.* 2008 Feb;10(2):8998. doi: 10.1097/GIM.0b013e31815bf924.

30. Mega JL, Simon T, Collet JP, et al. Reduced function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a metaanalysis. *JAMA.* Oct 2010;304(16):182130. doi: 10.1001/jama.2010.1543.

31. Mehanna R, Hunter C, Davidson A, JimenezShahed J, Jankovic J. Analysis of CYP2D6 genotype and response to tetrabenazine. *Mov Disord.* 2013;28(2):2105. doi: 10.1002/mds.25278.

32. NCCN Guidelines 2013: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed October 1, 2013.

33. Ned RM. Genetic Testing for CYP450 Polymorphisms to Predict Response to Clopidogrel: Current evidence and test availability. *PLoS Curr.* Sep 2010; RRN1180.doi:10.1371/currents.RRN1180

34. Noetzli M, Guidi M, Ebbing K, et al. Relationship of CYP2D6, CYP3A, POR, and ABCB1 genotypes with galantamine plasma concentrations. *Ther Drug Monit.* 2013 Apr;35(2):2705. doi:10.1097/FTD.0b013e318282ff02.

35. Noetzli M, Eap CB. Pharmacodynamic, pharmacokinetic and pharmacogenetic aspects of drugs used in the treatment of Alzheimer's disease. *Clin Pharmacokinet.* 2013 Apr;52(4):225-41.doi: 10.1007/s4026201300389.

36. Ong FS, Deignan JL, Kuo JZ, Bernstein KE, Rotter JI, Grody WW. Das K. Clinical utility of pharmacogenetic biomarkers in cardiovascular therapeutics: a challenge for clinical implementation. *Pharmacogenomics.* 2012 Mar;13(4):46575. doi: 10.2217/pgs.12.2.Pharmgkb. 20012013: http://www.pharmgkb.org/gene/PA128#tabview=tab0&subtab=31. Accessed October 1, 2013.

37. Ravyn D, Ravyn V, Lowney R, Nasrallah HA. CYP450 pharmacogenetic treatment strategies for antipsychotics: a review of the evidence. *Schizophr Res.* 2013 Sep;149(1-3):1-14. doi: 10.1016/j.schres.2013.06.035.

38. Rieder MJ, Reiner AP, Gage BF, et al. Effect of VKORC1 haplotypes on transcriptional regulation and warfarin dose. New Eng. J. Med. 352: 2285-2293, 2005.

39. Schadel M, Wu D, Otton SV, Kalow W, Sellers EM. Pharmacokinetics of Dextromethorphan and Metabolites in Humans: Influence of the CYP2D6 Phenotype and Quinidine Inhibition. *Journal of Clinical Psychopharmacology.* August 1995 Volume 15 Issue 4 pp 263-269.

40. Scott SA, Sangkuhl K, Stein CM, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for cytochrome P4502C19 (CYP2C19) genotype and clopidogrel therapy: 2013 Update. *Clin Pharmacol Ther.* May 22, 2013. doi: 10.1038/clpt.2013.105.

41. 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):2506. doi: 10.1097/YIC.0b013e32832e5b0d.

42. Shuldiner AR, O'Connell JR, Bliden KP, et al. Association of cytochrome P450 2C19 genotype with the antiplatelet effect and clinical efficacy ofclopidogrel therapy. *JAMA.* Aug 28, 2009;302(8):84957. doi: 10.1001/jama.2009.1232.

43. Simon T, Verstuyft C, MaryKrause M, et al. French Registry of Acute STElevation

44. and NonST-Elevation Myocardial Infarction (FASTMI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med.* Jan 22, 2009; 360(4):36375. doi: 10.1056/NEJMoa0808227.

45. Visvanathan K, Chlebowski RT, Hurley P, et al; American Society of Clinical Oncology Clinical Practice Guideline Update on the Use of Pharmacologic Interventions Including Tamoxifen, Raloxifene, and Aromatase Inhibition for Breast Cancer Risk Reduction, *J Clin Oncol.* 2009; 27(19): 3235–3258. doi: 10.1200/JCO.2008.20.5179 Prescriber information, medication specific.

46. Wegman P, Elingarami S, Carstensen J, Stål O, Nordenskjöld B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. *Breast Cancer Res.* 2007;9(1):R7.

47. Xie X, Ma YT, et al. Personalized antiplatelet therapy according to CYP2C19 genotype after percutaneous coronary intervention: A randomized control trial. *Int J Cardiol.* 2013 Jul 11. pii: S0167-5273(13)01068-1. doi: 10.1016/j.ijcard.2013.06.014.

48. Yang J, Chen Y, Li X, et al. Influence of CYP2C9 and VKORC1 genotypes on the risk of hemorrhagic complications in warfarin-treated patients: A systematic review and meta-analysis. *Int J Cardiol.* 2013 Aug 6. doi:pii: S0167-5273(13)01362-4. 10.1016/j.ijcard.2013.07.151. [Epub ahead of print] PubMed PMID: 23932037.

Bibliography

NA

Revision History Information

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
01/01/2019	R5	LCD is revised to add 0070U per the 2019 HCPCS Code Update. 12/20/2018: 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.	• Creation of Uniform LCDs With Other MAC Jurisdiction • Revisions Due To CPT/HCPCS Code Changes
10/01/2018	R4	09/19/2018: 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. LCD is revised to add ICD-10 F53.0 to Group 2 diagnoses due to 2019 ICD-10 code updates.	• Creation of Uniform LCDs With Other MAC Jurisdiction • Revisions Due To ICD-10-CM Code Changes
10/01/2017	R3	02/06/2018: 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. LCD is revised to remove *Title XVIII of the Social Security Act, §1862(a)(1)(D) items and services related to research and experimentation* from the CMS National Coverage Policy section.	• Creation of Uniform LCDs With Other MAC Jurisdiction
10/01/2017	R2	09/08/2017: 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. Added the following codes under ICD-10 Codes that Support Medical Necessity , Group 1:I25.111, I25.118, I25.119, I25.701, I25.708, I25.709, I25.711, I25.718, I25.719, I25.721, I25.728, I25.729, I25.731, I25.738, I25.739, I25.751, I25.758, I25.759, I25.761, I25.768, I25.769,	• Creation of Uniform LCDs With Other MAC Jurisdiction • Revisions Due To ICD-10-CM Code Changes

REVISION HISTORY DATE	REVISION HISTORY NUMBER	REVISION HISTORY EXPLANATION	REASON(S) FOR CHANGE
		I25.791, I25.798 and I25.799 effective 6/1/2017. Added ICD-10 codes I21.9, I21.A1, I21.A9 due to the 2017 Annual ICD-10 Code Update.	
07/08/2016	R1	Effective 07/08/2016, CPT code 81479 is added to groups 1 & 2 under the "CPT/HCPCS Codes " section, per the MolDX contractor. The Part A LCD (L36309) is retired and Part A contract numbers are added to the Part B LCD so that they will have the same LCD number in the Medicare Coverage Database.	• Creation of Uniform LCDs With Other MAC Jurisdiction • Revisions Due To CPT/HCPCS Code Changes

Associated Documents

Attachments

N/A

Related Local Coverage Documents

Article(s)
A54235
- (MCD Archive Site)A54747
- (MCD Archive Site)

Related National Coverage Documents

N/A

Public Version(s)

Updated on 12/21/2018 with effective dates 01/01/2019 - N/A
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Updated on 02/06/2018 with effective dates 10/01/2017 - 09/30/2018
Updated on 09/09/2017 with effective dates 10/01/2017 - N/A
Some older versions have been archived. Please visit the MCD Archive Site to retrieve them.

Keywords

- genetic

- testing
- MolDx
- genotyping
- pharmacogenetic
- CYP2C19
- CYP2D6
- CYP2C9
- VKORC1
- 81225
- 81479
- 81226
- 81227
- 81355
- 0070U