Proposed Local Coverage Determination (LCD): MolDX: Pharmacogenomics Testing (DL38294)

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Proposed LCD

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Contractor Information

CONTRACTOR NAME	CONTRACT TYPE	CONTRACT NUMBER	JURISDICTION	STATE(S)
Palmetto GBA	A and B MAC	10111 - MAC A	J - J	Alabama
Palmetto GBA	A and B MAC	10112 - MAC B	J - J	Alabama
Palmetto GBA	A and B MAC	10211 - MAC A	J - J	Georgia
Palmetto GBA	A and B MAC	10212 - MAC B	J - J	Georgia
Palmetto GBA	A and B MAC	10311 - MAC A	J - J	Tennessee
Palmetto GBA	A and B MAC	10312 - MAC B	J - J	Tennessee
Palmetto GBA	A and B and HHH MAC	11201 - MAC A	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11202 - MAC B	J - M	South Carolina
Palmetto GBA	A and B and HHH MAC	11301 - MAC A	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11302 - MAC B	J - M	Virginia
Palmetto GBA	A and B and HHH MAC	11401 - MAC A	J - M	West Virginia
Palmetto GBA	A and B and HHH MAC	11402 - MAC B	J - M	West Virginia
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CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA), §1801, which prohibits the Medicare program from exercising supervision of the practice of medicine.

Title XVIII of the Social Security Act (SSA), §1862(a)(1)(A), states that no Medicare payment shall be made for

items or services that are not 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 lacking the necessary documentation to process the claim.

42 Code of Federal Regulations (CFR) §410.32 Diagnostic x-ray tests, diagnostic laboratory tests, and other diagnostic tests: Conditions.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 15, §§80.0, 80.1.1, 80.2. Clinical Laboratory services.

CMS On-Line Manual, Publication 100-02, Medicare Benefit Policy Manual, Chapter 16, §180. Services Related to and Required as a Result of Services Which Are Not Covered Under Medicare.

Coverage Guidance

Coverage Indications, Limitations, and/or Medical Necessity

Unless otherwise specifically noted, the coverage information in this LCD is effective for dates of service on or after the date that the LCD is made final.

This is a limited coverage policy for CYP2D6, CYP2C19, CYP2C9, HLA-B*15:02, HLA-A*31:01, multi-gene panels, and combinatorial pharmacogenomics tests. These tests are generally covered (with a few exceptions) as described in further detail below to increase safety in the use of specific medications by avoiding potentially harmful medications or doses.

Pharmacogenomics testing is considered reasonable and necessary in limited circumstances as described in this Local Coverage Determination (LCD) as an adjunctive personalized medicine decision-making tool once a treating clinician has narrowed treatment possibilities to ~~a small group of specific medications~~ based on other considerations including the patient's diagnosis, the patient's other medical conditions, other medications, professional judgment, clinical science and basic science pertinent to the drug, and the patient's preferences and values.

Pharmacogenomics testing is not considered reasonable and necessary merely on the basis of a patient having a particular diagnosis. Additionally, if the record does reflect that the treating clinician has already considered non-genetic factors to make a preliminary prescribing decision, pharmacogenomics testing is not considered reasonable and necessary. Rather such testing may be considered reasonable and necessary if a particular treatment is being considered for the patient's diagnosis, and there is a significant gene-drug interaction of concern.

This LCD does not address (provides neither coverage nor non-coverage criteria) pharmacogenomic testing for anticoagulation dosing, which is addressed by National Coverage Determination (NCD) 90.1. The primary focus of this LCD is pharmacogenomics in psychiatric and neurologic conditions, though coverage of pharmacogenomic testing is addressed for other indications as well.

Definitions

For the purpose of this LCD, the following terms are defined as follows:

Gene – the term "gene" in this document will be used as a term to encapsulate all of the following: gene, ~~pseudogene,~~ and genetic locus.

Single-gene test - a laboratory test to detect genetic variants of 1 gene. If two or more different single genes are ordered individually but simultaneously, this is not a panel but rather a couple of or multiple single gene tests.

Multi-gene panel – a laboratory test to detect genetic variants of at least 2 genes, wherein the clinician does not individually order genes, but orders a panel with a specified list of genes.

Actionable use – A test is considered to have an actionable use, when the genotype information may lead to selection of or avoidance of a specific therapy or modification of dosage of a therapy. The selection, avoidance, or dose change must be based on the FDA-label for the drug, an FDA warning or safety concern, or a CPIC level A or B gene-drug interaction. An intended change in therapy based on the result of a genotyping test that is not supported by one of these sources is not considered an actionable use for the purposes of this LCD.

Medication selection – The decision(s) of whether to use a particular medication, whether to avoid that medication, or how to dose that medication

General coverage information:

For any single-gene test or multi-gene panel the record must clearly show the clinician's intent in ordering that test (including the type of test and specific genes and/ or variants of interest) and the specific management decision that the test will help to make. This must include the consideration of using a particular drug which has an interaction with the gene being tested. If the record does not indicate the relevant intent and the relevant diagnostic or treatment considerations underlying that intent at the time that the test was ordered, then the test is not considered reasonable and necessary.

If a treating clinician orders a single gene test or a test for a particular allele(s), but as a matter of operational practicality, the laboratory tests that single gene or allele on a platform that looks for variants in other genes / alleles as well, that particular test done in that particular instance is considered a single gene / allele test for coverage purposes.

A multi-gene panel is considered reasonable and necessary if any two single genes on that panel would be considered reasonable and necessary. A multi-gene panel is not considered reasonable and necessary if only a single gene on the panel is considered reasonable and necessary.

If two or more single genes are tested, rather than a multi-gene panel, then the record must reflect that a clinician individually ordered each gene, and each single gene must individually be reasonable and necessary.

Genotyping a specific gene is reasonable and necessary only once per lifetime per patient, unless repeat testing is for variants with an actionable use that have not previously been tested in that gene.

The ordering provider of a pharmacogenomics test is restricted to providers who have the licensure, qualifications, and necessary experience/training to both diagnose the condition being treated and also to prescribe medications (the provider must be able to do both) for the condition either independently or in an arrangement as required by all the applicable state laws.

Specific Coverage Information

This is a limited coverage policy for CYP2D6, CYP2C19, CYP2C9, HLA-B*15:02, and HLA-A*31:01.

A. Clinical Indications

Single gene testing for CYP2D6 is considered reasonable and necessary when the following conditions are met:

1. The patient has a diagnosis for which a provider is considering treatment with an antidepressant, anxiolytic, mood stabilizer (including affective diseases associated with neurodegenerative conditions), a medication treating nociception or pain, an anti-emetic, or a neuroleptic, and the patient is open to treatment with such a medication. The patient's record must reflect this.
2. There must be a specific actionable use (where "actionable use" is defined above) for the result of a CYP2D6 genotype in at least one medication that the provider and patient are considering.

Single gene testing for CYP2C19 is considered reasonable and necessary when the following conditions are met:

1. The patient has a diagnosis for which a provider is considering treatment with an antidepressant, anxiolytic, mood stabilizer, or clopidogrel, and the patient is open to treatment with such a medication. The patient's record must reflect this.
2. There must be a specific actionable use (where "actionable use" is defined above) for the result of a CYP2C19 genotype in at least one medication that the provider and patient are considering.

Single gene testing for CYP2C9 is considered reasonable and necessary when the following conditions are met:

1. The patient has a diagnosis for which a provider is considering treatment with ~~an antidepressant, anxiolytic, mood stabilizer,~~ or Mayzent, and the patient is open to treatment with such a medication. The patient's record must reflect this.

   For patients who receive CYP2C9 testing for Mayzent, coverage will be effective starting with dates of service of 3/26/2019, the approval date for Mayzent.

2. There must be a specific actionable use (where "actionable use" is defined above) for the result of a CYP2C9 genotype in at least one medication that the provider and patient are considering.

Single gene testing for HLA-B*15:02 is considered reasonable and necessary when the following conditions are met:

1. The patient has a diagnosis for which a provider is considering treatment with carbamazepine, oxcarbazepine, or phenytoin and the patient is open to treatment with such a medication. The patient's record must reflect this.
2. There must be a specific actionable use (where "actionable use" is defined above) for the result of a HLA-B*15:02 genotype in at least one medication that the provider and patient are considering.

Single gene testing for HLA-A*31:01 is considered reasonable and necessary when the following conditions are met:

1. The patient has a diagnosis for which a provider is considering treatment with carbamazepine or

oxcarbazepine, and the patient is open to treatment with such a medication. The patient's record must reflect this.
2. There must be a specific actionable use (where "actionable use" is defined above) for the result of a HLA-A*31:01 genotype in at least one medication that the provider and patient are considering.

B. Technical requirements

There are no specific reporting requirements regarding the phenotypic significance of alleles identified. However, the treating clinician receiving the report must be able to use the genetic information presented to guide treatment. As such, while either the lab or the treating clinician may make decisions regarding the clinical significance or phenotypic interpretation of a particular genotype, this interpretation must be done in order for the test to be considered reasonable and necessary. If the laboratory reports clinical significance or phenotypes based on genotype, the phenotypic information reported must be based on empirical data or a validated phenotype prediction method.

A lab may test for a reference allele as a matter of exclusion (e.g. report that a patient has a reference allele when alternate alleles are not found). However, in such cases the report must identify which allele is the reference allele and that the reference allele is reported as a matter of exclusion.

Tests with minimum allele criteria for coverage: CYP2D6, CYP 2C19, and CYP2C9

Below is a list of alleles for particular genes that must be tested for a test of that gene to be considered reasonable and necessary. The test may look for all variants simultaneously, or it may use a stepwise approach composed of multiple assays.

The minimum list is based on common variants in the United States with clinical significance. However, labs should be familiar with the populations that they are testing, and the common variants in that population. If clinically significant variants (clinically significant for the indications the test is intended for) not listed below exist in the population whom a lab is testing, the lab should include those variants as well.

CYP2D6

- The following null alleles must be included: *3, *4, *5, *6,*7, *10, *17, and *41
- The following duplications must be tested: *1xN and *2xN

CYP2C19

- The following alleles must be included at a minimum: *2,*3,*17

CYP2C9

- The following alleles must be included at a minimum: *2, *3, *5, *6

Other genes

Pharmacogenomics testing to aid in the treatment of psychiatric or neurologic conditions not described as covered

above (*i.e.* gene or indication not covered above) will generally be considered not reasonable and necessary. However, individual consideration may be given to exceptional cases upon appeal.

Noncovered Indications

Pharmagenomics testing is not covered if a treating clinician is not considering treatment with a medication that has an actionable drug-gene interaction, or if the medication with a drug-gene interaction that the physician is considering is not reasonable and necessary.

Pharmacogenomics testing is not covered if the treating clinician has not already developed a potential treatment plan to include at least one specific medication based on non-genetic factors.

Special Documentation Requirements

In order for any of the above services to be covered, the patient's medical record must clearly reflect the following:

1. The patient has a diagnosis for which pharmacologic therapy is reasonable and necessary and the drug or drugs that the clinician is considering using must be reasonable and necessary for the treatment of the patient's diagnosis.
2. The clinician has made an initial personalized decision for the patient based on the patient's diagnosis, the patient's other medical conditions, other medications the patient is taking, professional judgment, clinical science and basic science pertinent to the drug (e.g. mechanism of action, side effects, etc…), and the patient's preferences and values.
3. The record must reflect the specific drug-gene interaction(s) of concern. General classes of medications or drug-gene interactions do not meet this requirement.
4. Since pharmageonomics testing is only to be used as a tool for personalized medicine, the record must clearly reflect personalized decisions specific to the patient were made in advance of ordering the test. I f a treating clinician is considering using a number of drugs, an explanation of why that drug was selected in accordance with requirement 2 above must be made for each drug, if the use of that drug is the basis for pharmacogenomics testing.
5. Templated statements to meet the above criteria are not personalized decisions and do not meet these documentation requirements. (Though this LCD does not prohibit their presence in the record)

Summary of Evidence

Background

With improvements in genetic sequencing technology and the recognition that inter-individual genetic differences may affect how patients metabolize or physiologically respond to pharmacologically active substances, pharmacogenomic testing has been proposed as a way to personalize medication selection or dose based on a patient's individual genes.[1] The genes encoding the CYP2C19 and CYP2D6 genes emerged as genes of potential important in the response (therapeutic or adverse) to numerous medications[2-4]. In addition combinatorial pharmacogenomics panels have emerged, which find polymorphisms in a number of genes associated with pharmacologically important proteins.[5,6]

With the advance of ~~sequencing~~ technology, there is little question that such testing is now technically feasible, but

for a test to be reasonable and necessary there must be sufficient evidence that it provides incremental information that changes physician management recommendations in a way that improves patient outcomes.

Pharmacogenomic Testing in Psychiatric Disease

Clinical Need and Bioplausibility

In 2017, 17.3 million adults (7.1%) had at least one major depressive episode (MDE) in the past year, with 11.0 million of those adults having an MDE with severe impairment in the past year.[7]

Depression is common among older adults, and is associated with disability as well as significantly decreased quality of life, and evidence regarding the treatment of depression in later life is still not well developed.[8] Treatment using antidepressant medications is a well-accepted treatment approach, though existing research suggests that many patients may not respond to treatment,[9,10] and a review of clinical practice guidelines for the treatment of depression following failed initial treatment noted a common theme of trial of an alternative agent, though there was little consistency regarding how to select such an agent or dose it.[11]

Evidence has emerged that variants in CYP genes and transporters genes may explain some of the physiologic interactions between a patient and a medication, with the most evidence for polymorphisms in CYP2D6 and CYP2C19, which has suggested that genetic information could potentially be able to guide treatment.[3] The rest of this summary will address studies and key expert opinions that address the relationship between the empirical findings and this plausible potential.

Single Gene testing indications as well as alleles and variants of specific genes

An abundance of research on particular alleles and variants has been published. To identify alleles and variants of importance, we reviewed FDA-approval documents, guidelines, and subject matter expert input.

A review of PharmGKB's database of annotations regarding 102 drugs from 3 guidelines[12], shows that the majority of neurologic or psychiatric medications for which dosing guidelines are available have guidelines for CYP2D6 and / or CYP2C19. A common source of guidelines from the Clinical Pharmacogenetic Implemetnation Consoritum (CPIC).

The Clinical Pharmacogenetic Implemetnation Consoritum (CPIC) was described by Dr. Annette Taylor as follows:

> *CPIC is an NIH-funded organization with a membership of more than 300 clinicians, scientists, laboratorians, and others knowledgeable about pharmacogenetics with the purpose of facilitating the use of pharmacogenetic test results for patient care. One barrier to implementing pharmacogenetic testing in the clinic is the difficulty of translating genetic laboratory test results into actionable prescribing decisions for affected drugs. CPIC's goal is to address this barrier by creating freely available, peer-reviewed, evidence-based, and updatable gene/drug clinical practice guidelines. A CPIC Overview Presentation can be found at https://cpicpgx.org/resources/.*
>
> *CPIC uses a rigorous and systematic system to grade levels of evidence, and only gene/drug groupings with strong evidence for actionable prescribing are selected for guideline development. CPIC level A is the designation for gene/drugs for which genetic information should be used to change prescribing of the affected drug. CPIC levels are subject to change as more information is gained from publications. Each guideline adheres to standardized terminology and formatting, and includes one or more tables showing phenotypes from genetic test results and accompanying therapy recommendations, with strength of evidence for the recommendations shown.*

CPIC guidelines help clinicians understand how to use available genetic test results to guide prescribing. There are currently 23 such guidelines, including medications relevant to many areas of medical practice (see below). Following peer review, guidelines are published in a leading journal (Clinical Pharmacology and Therapeutics) and posted on www.cpicpgx.org, where they meet strict inclusion criteria according to www.guidelines.gov and are regularly updated. The guidelines are indexed in PubMed as clinical guidelines, endorsed by ASHP and ASCPT, and referenced in ClinGen and PharmGKB. Additionally, the College of American Pathologists (CAP) has stated: "CAP applauds and supports the objectives, processes and work completed as of December 2018 by the Clinical Pharmacogenetics Implementation Consortium (CPIC®)"

At present, CPIC has a number of guidelines for the dosing of drugs based on gene-drug interactions.[13] The gene-drug interactions have been assigned a level A or B by CPIC are given in the table below. This list does not include all drugs, but is limited to drugs that are or can be used to treat psychiatric or neurologic conditions in addition to clopidogrel.

Gene	**Drug**
CYP2C19	amitriptyline
CYP2C19	citalopram
CYP2C19	clopidogrel
CYP2C19	escitalopram
CYP2C19	clomipramine
CYP2C19	doxepin
CYP2C19	imipramine
CYP2C19	sertraline
CYP2C19	trimipramine
CYP2C9	phenytoin
CYP2D6	amitriptyline
CYP2D6	atomoxetine
CYP2D6	codeine

CYP2D6	fluvoxamine
CYP2D6	nortriptyline
CYP2D6	ondansetron
CYP2D6	oxycodone
CYP2D6	paroxetine
CYP2D6	tramadol
CYP2D6	aripiprazole
CYP2D6	brexpiprazole
CYP2D6	clomipramine
CYP2D6	desipramine
CYP2D6	dextromethorphan
CYP2D6	doxepin
CYP2D6	imipramine
CYP2D6	methylphenidate
CYP2D6	mirtazapine
CYP2D6	pimozide
CYP2D6	protriptyline
CYP2D6	quinidine
CYP2D6	risperidone
CYP2D6	sertraline
CYP2D6	trimipramine

CYP2D6	venlafaxine
CYP2D6	vortioxetine
HLA-B*15:02	carbamazepine
HLA-B*15:02	oxcarbazepine
HLA-B*15:02	phenytoin
HLA-A*31:01	carbamazepine
HLA-A*31:01	oxcarbazepine

The prominence of CYP2D6 in drug metabolism pathways indicates that, as the recent evidence appraisal notes[14], CYP2D6 may be an appropriate comparator for control groups in comparative studies evaluating the benefit of combinatorial pharmacogenomics tests.

The following gene-drug interactions have a level A rating by the Clinical Pharmacogenetic ~~Implemetnation Consoritum~~ (CPIC):

Cytochrome P450 (CYP) testing can be done for specific alleles or variants. A commonly used nomenclature is the star nomenclature, in which alleles that have been identified are given a name as an asterisk followed by a number, for example "*1" or "*2." When a patient has multiple copies of an allele it is expressed in the form "xN," where "N" is the copy number, for example "*2x2." Typically the reference allele is assigned the name "*1." A patient may be reported to have this allele only because another variant was not found; as such, the probability of a patient being identified as having a reference allele goes down as the number of other alleles tested increases. This means, that tests may disagree on whether a given patient has a reference allele on each chromosome because of the other alleles tested.

CYP2C9

CYP2C9 has clinical significance in the metabolism of phenytoin with a CPIC A gene-drug interaction that is considered actionable.[13,15] Additionally, the recently FDA-approved drug Mayzent, which is indicated for the treatment of multiple sclerosis requires CYP2C9 genotyping for dosing in accordance with the FDA prescribing information.[16] Since this LCD does not address pharmacogenomics for warfarin dosing, alleles and variants relevant to warfarin are not reviewed here. The following alleles are both common and are believed to have clinical significance for phenytoin dosing: *2, *3, *5, and *6, and a joint recommendation from the Association for Molecular Pathology and the College of American Pathologists has recommended that these variants be included as part of a CYP2C9 test.[17] The *1, *2, and *3 alleles are necessary to safely dose the newly FDA-approved drug Mayzent.[16]

CYP2D6

CYP2D6 is a clinically important enzyme in the metabolism of a large number of mediations is a CPIC level A or B gene-drug interaction and dosing guideline.[13] A number of particular alleles have been recommended for inclusion in a panel as follows: *3, *4, *5, *6,*7, *10, *17, and *41,*1xN, and *2xN. Dr. de Leon recommended a potential list of alleles that included this group, along with some other alleles, though he noted that his list may be too comprehensive to be used as minimum bar.

CYP2C19

CYP2C19 is a clinically important enzyme in the metabolism of a number of selective serotonin reuptake inhibitors as well as tricyclic antidepressants with a CPIC level A or B gene-drug interaction and dosing guideline.[13,15] Recently published recommendations, including a report of the Association of Molecular pathology, recommend the following alleles by included as a minimum based on clinical importance and population frequency: *2,*3,*17.[15,18]

HLA testing

Two specific HLA alleles are recommended for testing.[15] They are HLA-B*15:02 and HLA-A*31:01. Both of these have level A or B gene-drug recommendations from CPIC as noted above.

Subject Matter Panel and Contractor Advisory Committee (CAC) Meeting on June 26th, 2019

A panel of subject matter experts and CAC members from CGS, Wisconsin Physicians Services, Noridian, and Palmetto GBA was convened on June 26th, 2019 over the phone. While only invited experts and CAC members could speak, interested members of the public who registered could listen. The full recording is also available.[19] Subject matter experts on the panel included the list below. Included members may have additional titles and positions to those listed.

Mary Relling, Chair, Pharmaceutical Dept. St. Jude Children's Research Hospital

John Greden, Founder and Executive Director, University of Michigan Comprehensive Depression Center

Annette Taylor, AVP, LabCorp, Co-Business Lead, Pharmacogenomics

Stuart Scott, Associate, Associate Professor, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

The panel generally agreed that pharmacogenomics testing generally speaking has the ability to provide clinically utile information that allows treating clinicians to select and dose particular medications appropriately. Pharmacogenomic testing (presumably for genes associated with pharmacokinetic pathways) was described as being analogous to measuring renal function with a serum creatinine prior to dosing renally cleared medications. The panel generally agreed that single gene testing and multi- gene panels (as defined at the top of this LCD) for particular genes has role in medication dosing and selection. The panel members did not specifically recommend or support the use of any one combinatorial pharmacogenomics test over another. There was general agreement that combinatorial pharmacogenomics tests with a proprietary algorithm not available for public review required independent evidence establishing their validity and utility. Additionally, a comment was made that CYP2C19 and CYP2D6 testing would most likely be the appropriate comparator in a clinical study to determine if a combinatorial pharmacogenomics test

provides information that improves outcomes more than single gene or multi-gene panels. While it was not discussed by the panel, a manuscript submitted by Dr. Black did a retrospective comparison (using statistical modelling rather than a direct comparison) of GeneSight to single gene testing.[20] This study suggested that combinatorial testing predicts poor antidepressant response and outcomes better than single gene testing. Two gene panels were not considered.

A CAC member commented that pharmacogenomics testing is becoming increasingly common, and it should not be restricted by provider type.

Additional Expert Input

In addition to the panel, a number of experts who were unable to attend provided written correspondence. These included the following:

John Logan Black, Co-Director, Personalized Genomics Laboratory, Department of Laboratory Medicine and Pathology, Mayo Clinic

To summarize, Dr. Black's comment generally agreed with the comments of the panel. He indicated support for the use of genetics in guiding pharmacologic treatment, referencing guidelines from CPIC and the FDA. He also provided references to a number of peer-reviewed studies which have been reviewed in this LCD. As regards combinatorial testing, he noted that evidence does support their use, though he also noted that it "is unclear is whether the power of combinatorial pharmacogenomics is driven by a few genes or if it is absolutely due to the combinatorial effects." He indicated that for panel testing, he would recommend a minimum panel in psychiatry consisting of CYP2C9, CYP2C19, CYP2D6, HLA-A*31:01 and HLA-B*15:02.

Jose DeLeon, Professor, Psychiatry, University of Kentucky

Dr. de Leon's comments largely agree with the panel's comments as well, though he specifically noted the clinical utility of HLA-B*15:02 in any patient of Asian ancestry before starting carbamazepine, and for CYP2D6 and CYP2C19 genes for some antidepressants and some antipsychotics. Additionally, Dr. de Leon also indicated his belief that the evidence did not support the use of GeneSight. Notably, he indicated the importance of CYP2D6 and CYP2C19 and questioned the testing of other CYPs. He also noted that the GUIDED study (reviewed above) "further demonstrated that the study results were negative and the authors had to use secondary outcomes to try to demonstrate that a negative study had positive results."

Bruce Cohen - Director of the Program for Neuropsychiatric Research at McLean Hospital and Harvard Medical School

Dr. Cohen's comments are summarized below.

Limitations of pharmacogenomics testing

A number of opinion leaders and experts representing multiple provider types have articulated how pharmacogenomics can be used, and how it might drive prescribing decisions, other thought leaders have called into question the utility of pharmacogenomics or specific tests in pharmacogenomics. Notably, the American Psychiatric Association, which is one of the largest organizations in the country representing treating clinicians with medication prescribing authority has to date published no position statement, guideline, or evidentiary interpretation.

The Food and Drug Administration (FDA) has published a document raising concerns about pharmacogenomics testing.[21] The document notes: "…the relationship between DNA variations and the effectiveness of antidepressant medication has never been established.'' It goes on to state as a recommendation to providers

> *If you are using, or considering using, a genetic test to predict a patient's response to specific medications, be aware that for most medications, the relationship between DNA variations and the medication's effects has not been established.*

However, the document also notes:

> *There are a limited number of cases for which at least some evidence does exist to support a correlation between a genetic variant and drug levels within the body, and this is described in the labeling of FDA cleared or approved genetic tests and FDA approved medications. The FDA authorized labels for these medical products may provide general information on how DNA variations may impact the levels of a medication in a person's body, or they may describe how genetic information can be used in determining therapeutic treatment, depending on the available evidence.*

A manuscript examining the metascience of pharmacogenomics testing and providing an accompanying viewpoint reviewed 10 clinical studies of pharmacogenomics in psychiatry and found that none of them were blinded and used a protocol-based comparison.[22] The authors point to two evidence-based protocols that are freely available and could have been used, STAR*D and the Texas Medication Algorithm Project. As the authors state early on:

> *Simply put, MDD [Major Depressive Disorder] is determined by a large number of genes, and, except in rare cases, no single gene or limited gene set, even those for drug metabolism and drug targets, determines more than a few percent of the risk of illness or course of treatment.*

The STAR*D study included 2,876 subjects with major depressive disorder from multiple institutions.[10,23,24] In this study all participants started with citalopram as the initial treatment and may have advanced through additional levels of treatment up to level 4. If a subject did not respond at a given level, that subject was then advanced to the next level of treatment, which included alternative treatments instead of or in addition to the treatment the patient was on.

Dr. Bruce M. Cohen, the Director of the Program for Neuropsychiatric Research at McLean Hospital and Harvard Medical School, who submitted indicated that current pharmacogenetic tests offer no clear clinical value over freely available and well-established protocols for drug selection with a reference to a number of recent documents.[21,22] He also pointed out that, should a clinician be unsure about drug choice, a psychiatry consultation costs substantially less money than pharmacogenetic testing.

Analysis of Evidence
(Rationale for Determination)

Numerous prior Medicare coverage decisions have considered the evidence in the hierarchical framework of Fryback and Thornbury[25] where Level 2 addresses diagnostic accuracy, sensitivity, and specificity of the test; Level 3 focuses on whether the information produces change in the physician's diagnostic thinking; Level 4 concerns the effect on the patient management plan and Level 5 measures the effect of the diagnostic information on patient outcomes. To apply this same hierarchical framework to analyze an in vitro diagnostic test, we utilized the ACCE Model Process for

Evaluating Genetic Tests.[26] The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

When a physician is treating a patient for a particular diagnosis, there are often many available treatment options. The physician may go through a series of decisions and use numerous sources of information, including evidence, professional judgement, and patient values and preferences to narrow down the treatment approach form an array of potential treatments to the selection of a specific treatment or course of treatment.

Contemporary treatment of psychiatric and neurologic conditions often involves the use of a medication or more than one medication selected from among a large number of potential medications or treatments. The optimal medication for a particular patient is a decision to be made by the physician and patient. Many medications for the treatment of psychiatric and / or neurologic conditions have important interactions with enzymes in a person's body. The evidence clearly suggests that pharmacogenomics has the ability to predict how a patient will metabolize a number of specific drugs, and some evidence indeed suggests that this can be used as a tool for drug selection. The putative clinical utility of pharmcogenomics testing comes from the ability to link genotype to phenotype and then to link phenotype to medication selection (which may include avoidance) or medication dosing. There appears to be general agreement within the scientific community that for some alleles of some genes there is a clear phenotype, and that the phenotype has an established interaction with particular drugs. There also appears to be supporting evidence (including guidelines) that specific medication selection decisions (including dosing and avoidance) may be made based on genotypes and phenotypes.

However, there are a number of remaining uncertainties in the evidence.

While there are some large studies in pharmacogenomics, we are not aware of large high quality studies that used a clear evidence-based prescribing approach in the control arm. As a number of prominent psychiatrists with expertise in the biological underpinnings of mental health have pointed out, it is not clear that pharmacogenomics testing is a better tool for drug selection than using a standardized evidence-based protocol which does not rely on genetics, or a consultation from a knowledgeable provider. We are unaware of any studies that used a clear standardized evidence-based protocol in the control arm. Moreover, psychiatric conditions have significant complexity involving many genes and factors outside of pharmacogenomics. As such, while the evidence does suggest that pharmacogenomics testing can be used to refine the selection of a medication or dose, there is not sufficient evidence to suggest that pharmacogenomics is reasonable and necessary for the initial narrowing or selection of potential medications to treat a patient.

Since the medical necessity for testing a gene in pharmacogenomics can only come from the ability of that test to inform a management decision based on a gene-drug interaction, a test for a specific gene or allele is not reasonable and necessary unless and until a clinician is considering using a drug that has an interaction with a specific gene or allele. Once this initial decision has been made it may reasonable and necessary to test for that allele or that gene. For example, a clinician using a treatment approach based on the STAR*D study, may consider use of citalopram as a first line treatment. Citalopram is considered to have an actionable CYP2C19 gene-drug interaction. We are unaware of an actionable drug-gene interaction for CYP2D6 for citalopram. Alternatively, if the clinician were considering the use of fluvoxamine, this has an actionable drug-gene interaction for CYP2D6 but not for CYP2C19. If a clinician is not considering using a medication with an interaction with a gene being tested, or if the patient who is being tested is unable or unwilling to use a medication interacting with the gene or allele being tested, then there is no benefit to the patient to run a test of that gene or allele.

Since pharmacogenomics testing at present is based on gene-drug interactions, the service can only potentially have clinically utility when a particular drug or a number of particular drugs with known gene-drug interactions are being considered for use in a particular patient. As such, pharmacogenomic testing is only reasonable and necessary when a provider is considering using a drug which has a clinically actionable gene-drug interaction. This clearly requires significant awareness and thoughtfulness on the part of a treating clinician. While it is possible that specialists in mental health or pharmacogenomics are more likely to be aware of a potential gene-drug interaction in medications used to treat mental illness, if a clinician is considering treatment with a drug that has a known gene-drug interaction, and the clinician is ordering a pharmacogenomics test specifically to inform the decision regarding the use of that drug, then actionability is not dependent on provider type. Additionally, peer-reviewed literature suggests that patients do as well when a pharmacogenomic test is ordered by a psychiatrist as by a primary care provider in the treatment of a mood disorder. Finally, the discussion held on June 26th, 2019 indicated a high degree of agreement among those who spoke that there is not a reason to limit the coverage by provider type.

In summary, the present evidence does not clearly demonstrate that routine pharmacogenomics testing for the purpose of aiding in medication selection offers a benefit over selection of medications based on a knowledge of the metabolic pathways for particular drugs and / or contemporary evidence-based medication selection protocols. However, there are clear biological pathways driven by specific genes which may affect concentrations of a drug that patient experiences, including drugs that are components of evidence-based protocols. As such, when a clinician is specifically considering using a drug, because a clear evidence-base or individualized factors make it the one of the most appropriate potential treatments, and that medication has a clinically important drug-gene interaction, the evidence suggests that testing the gene can help refine that initial medication selection by avoiding an unsafe or ineffective medication or leading to a change of dose.

This remains an actively evolving area of medicine, and even experts who express skepticism about the current role of pharmacogenomics also agree that knowledge in the field is rapidly evolving, and genetics likely has a role in the future of psychiatry. As such, MolDX will continue to actively monitor the field, and we suspect that this policy may require frequent revisions to remain current with the pace of development in the field.

Proposed Process Information

Synopsis of Changes

CHANGES	FIELDS CHANGED
Not Applicable	N/A

Associated Information

N/A

Sources of Information

N/A

Bibliography

1. Mancinelli L, Cronin M, Sadée WJAP. Pharmacogenomics: the promise of personalized medicine. 2000;2(1):29-41.
2. Hicks JK, Sangkuhl K, Swen JJ, et al. Clinical pharmacogenetics implementation consortium guideline (CPIC) for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. 2017;102(1):37-44.
3. Altar CA, Hornberger J, Shewade A, Cruz V, Garrison J, Mrazek D. Clinical validity of cytochrome P450 metabolism and serotonin gene variants in psychiatric pharmacotherapy. *Int Rev Psychiatry.* 2013;25(5):509-

533.
4. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee WJJ. Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review. 2001;286(18):2270-2279.
5. Eichelbaum M, Ingelman-Sundberg M, Evans WEJARM. Pharmacogenomics and Individualized Drug Therapy. 2006;57:119-137.
6. Evans WE, Johnson JA, genetics h. Pharmacogenomics: the inherited basis for interindividual differences in drug response. *Annual review of genomics.* 2001;2(1):9-39.
7. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2017 National Survey on Drug Use and Health (HHS Publication No. SMA 18-5068, NSDUH Series H-53). 2018. Accessed July 16, 2019.
8. Valiengo LdCL, Stella F, Forlenza OV. Mood disorders in the elderly: prevalence, functional impact, and management challenges. *Neuropsychiatric disease and treatment.* 2016;12:2105-2114.
9. Gartlehner G, Gaynes BN, Amick HR, et al. *Nonpharmacological Versus Pharmacological Treatments for Adult Patients With Major Depressive Disorder.* Agency for Healthcare Research and Quality;2015.
10. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry.* 2006;163(1):28-40.
11. MacQueen G, Santaguida P, Keshavarz H, et al. Systematic Review of Clinical Practice Guidelines for Failed Antidepressant Treatment Response in Major Depressive Disorder, Dysthymia, and Subthreshold Depression in Adults. *Can J Psychiatry.* 2017;62(1):11-23.
12. Whirl-Carrillo M, McDonagh EM, Hebert J, et al. Pharmacogenomics knowledge for personalized medicine. 2012;92(4):414-417.
13. The Clinical Pharmacogenetics Implementation Consortium. Genes-Drugs. Accessed July 16, 2019.
14. Zeier Z, Carpenter LL, Kalin NH, et al. Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. 2018:appi. ajp. 2018.17111282.
15. Bousman C, Al Maruf A, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. *Current opinion in psychiatry.* 2019;32(1):7-15.
16. Food and Drug Administration. MAYZENT Full Prescribing Information. In: Food and Drug Administration, ed2019.
17. Pratt VM, Cavallari LH, Del Tredici AL, et al. Recommendations for Clinical CYP2C9 Genotyping Allele Selection: A Joint Recommendation of the Association for Molecular Pathology and College of American Pathologists. *J Mol Diagn.* 2019.
18. Pratt VM, Del Tredici AL, Hachad H, et al. Recommendations for clinical CYP2C19 genotyping allele selection: a report of the association for molecular pathology. *The Journal of Molecular Diagnostics.* 2018;20(3):269-276.
19. CGS, Palmetto GBA, Noridian, Wisconsin Physicians Service Insurance Corporation. Pharmacogenomics Carrier Advisory Committee. 2019. Accessed July 16, 2019.
20. Altar C, Carhart J, Allen J, Hall-Flavin D, Dechairo B, Winner J. Clinical validity: combinatorial pharmacogenomics predicts antidepressant responses and healthcare utilizations better than single gene phenotypes. *The pharmacogenomics journal.* 2015;15(5):443.
21. Food and Drug Administration. The FDA Warns Against the use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication. In: Administration FaD, edNovember 1, 2018.
22. Zubenko GS, Sommer BR, Cohen BM. On the marketing and use of pharmacogenetic tests for psychiatric treatment. *JAMA Psychiatry.* 2018;75(8):769-770.
23. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006;163(11):1905-1917.
24. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR* D Project results: a comprehensive review of findings. *Current psychiatry reports.* 2007;9(6):449-459.
25. Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. *Med Decis Making.* 1991;11(2):88-94.
26. Centers for Disease Control and Prevention. ACCE Model List of 44 Targeted Questions Aimed at a Comprehensive Review of Genetic Testing. 2010. Accessed July 16, 2019.

Open Meetings

MEETING DATE	MEETING STATE(S)	MEETING INFORMATION
10/07/2019	South Carolina	Columbia

Contractor Advisory Committee (CAC) Meetings

MEETING DATE	MEETING STATE(S)	MEETING INFORMATION
06/26/2019	Alabama Georgia North Carolina South Carolina Tennessee Virginia West Virginia	Joint contractor web conference

MAC Meeting Information URL(s)

N/A

Proposed LCD Posting Date

08/22/2019

Comment Period Start Date

10/07/2019

Comment Period End Date

11/21/2019

Released to Final LCD Date
Please Note: This is not the LCD Effective Date.

N/A

Reason for Proposed LCD

- Provider Education/Guidance

Proposed Contact

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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)
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)
81227	CYP2C9 (CYTOCHROME P450, FAMILY 2, SUBFAMILY C, POLYPEPTIDE 9) (EG, DRUG METABOLISM), GENE ANALYSIS, COMMON VARIANTS (EG, *2, *3, *5, *6)
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)
0071U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, FULL GENE SEQUENCE (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
0072U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (IE, CYP2D6-2D7 HYBRID GENE) (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY

CODE	DESCRIPTION
	PROCEDURE)
0073U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (IE, CYP2D7-2D6 HYBRID GENE) (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
0074U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (IE, NON-DUPLICATED GENE WHEN DUPLICATION/MULTIPLICATION IS TRANS) (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
0075U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (IE, 5' GENE DUPLICATION/MULTIPLICATION) (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)
0076U	CYP2D6 (CYTOCHROME P450, FAMILY 2, SUBFAMILY D, POLYPEPTIDE 6) (EG, DRUG METABOLISM) GENE ANALYSIS, TARGETED SEQUENCE ANALYSIS (IE, 3' GENE DUPLICATION/ MULTIPLICATION) (LIST SEPARATELY IN ADDITION TO CODE FOR PRIMARY PROCEDURE)

Group 2 Paragraph:

N/A

Group 2 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)

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)

ICD-10 Codes that Support Medical Necessity

Group 1 Paragraph:

The following diagnosis codes are covered for Group 1 CPT®/HCPCS codes if the treatment for the diagnosis involves the treating clinician considering treatment with a medication that makes the service billed from Group 1 reasonable and necessary.

Group 1 Codes:

ICD-10 CODE	DESCRIPTION
F01.51	Vascular dementia with behavioral disturbance
F02.81	Dementia in other diseases classified elsewhere with behavioral disturbance
F06.0	Psychotic disorder with hallucinations due to known physiological condition
F06.1	Catatonic disorder due to known physiological condition
F06.2	Psychotic disorder with delusions due to known physiological condition
F06.30	Mood disorder due to known physiological condition, unspecified
F06.31	Mood disorder due to known physiological condition with depressive features
F06.32	Mood disorder due to known physiological condition with major depressive-like episode
F06.33	Mood disorder due to known physiological condition with manic features
F06.34	Mood disorder due to known physiological condition with mixed features
F06.4	Anxiety disorder due to known physiological condition
F06.8	Other specified mental disorders due to known physiological condition
F10.121	Alcohol abuse with intoxication delirium
F10.14	Alcohol abuse with alcohol-induced mood disorder
F10.150	Alcohol abuse with alcohol-induced psychotic disorder with delusions
F10.151	Alcohol abuse with alcohol-induced psychotic disorder with hallucinations
F10.159	Alcohol abuse with alcohol-induced psychotic disorder, unspecified
F10.180	Alcohol abuse with alcohol-induced anxiety disorder
F10.188	Alcohol abuse with other alcohol-induced disorder
F10.221	Alcohol dependence with intoxication delirium
F10.230	Alcohol dependence with withdrawal, uncomplicated
F10.231	Alcohol dependence with withdrawal delirium
F10.232	Alcohol dependence with withdrawal with perceptual disturbance
F10.239	Alcohol dependence with withdrawal, unspecified
F10.24	Alcohol dependence with alcohol-induced mood disorder
F10.250	Alcohol dependence with alcohol-induced psychotic disorder with delusions
F10.251	Alcohol dependence with alcohol-induced psychotic disorder with hallucinations
F10.259	Alcohol dependence with alcohol-induced psychotic disorder, unspecified
F10.280	Alcohol dependence with alcohol-induced anxiety disorder
F10.288	Alcohol dependence with other alcohol-induced disorder

ICD-10 CODE	DESCRIPTION
F10.29	Alcohol dependence with unspecified alcohol-induced disorder
F10.921	Alcohol use, unspecified with intoxication delirium
F10.94	Alcohol use, unspecified with alcohol-induced mood disorder
F10.950	Alcohol use, unspecified with alcohol-induced psychotic disorder with delusions
F10.951	Alcohol use, unspecified with alcohol-induced psychotic disorder with hallucinations
F10.959	Alcohol use, unspecified with alcohol-induced psychotic disorder, unspecified
F10.980	Alcohol use, unspecified with alcohol-induced anxiety disorder
F10.988	Alcohol use, unspecified with other alcohol-induced disorder
F11.121	Opioid abuse with intoxication delirium
F11.14	Opioid abuse with opioid-induced mood disorder
F11.150	Opioid abuse with opioid-induced psychotic disorder with delusions
F11.151	Opioid abuse with opioid-induced psychotic disorder with hallucinations
F11.159	Opioid abuse with opioid-induced psychotic disorder, unspecified
F11.188	Opioid abuse with other opioid-induced disorder
F11.220	Opioid dependence with intoxication, uncomplicated
F11.221	Opioid dependence with intoxication delirium
F11.222	Opioid dependence with intoxication with perceptual disturbance
F11.229	Opioid dependence with intoxication, unspecified
F11.23	Opioid dependence with withdrawal
F11.24	Opioid dependence with opioid-induced mood disorder
F11.250	Opioid dependence with opioid-induced psychotic disorder with delusions
F11.251	Opioid dependence with opioid-induced psychotic disorder with hallucinations
F11.259	Opioid dependence with opioid-induced psychotic disorder, unspecified
F11.288	Opioid dependence with other opioid-induced disorder
F11.921	Opioid use, unspecified with intoxication delirium
F11.922	Opioid use, unspecified with intoxication with perceptual disturbance
F11.94	Opioid use, unspecified with opioid-induced mood disorder
F11.950	Opioid use, unspecified with opioid-induced psychotic disorder with delusions
F11.951	Opioid use, unspecified with opioid-induced psychotic disorder with hallucinations
F11.959	Opioid use, unspecified with opioid-induced psychotic disorder, unspecified
F11.988	Opioid use, unspecified with other opioid-induced disorder
F12.121	Cannabis abuse with intoxication delirium

ICD-10 CODE	DESCRIPTION
F12.122	Cannabis abuse with intoxication with perceptual disturbance
F12.150	Cannabis abuse with psychotic disorder with delusions
F12.151	Cannabis abuse with psychotic disorder with hallucinations
F12.159	Cannabis abuse with psychotic disorder, unspecified
F12.180	Cannabis abuse with cannabis-induced anxiety disorder
F12.188	Cannabis abuse with other cannabis-induced disorder
F12.221	Cannabis dependence with intoxication delirium
F12.222	Cannabis dependence with intoxication with perceptual disturbance
F12.23	Cannabis dependence with withdrawal
F12.250	Cannabis dependence with psychotic disorder with delusions
F12.251	Cannabis dependence with psychotic disorder with hallucinations
F12.259	Cannabis dependence with psychotic disorder, unspecified
F12.280	Cannabis dependence with cannabis-induced anxiety disorder
F12.288	Cannabis dependence with other cannabis-induced disorder
F12.921	Cannabis use, unspecified with intoxication delirium
F12.922	Cannabis use, unspecified with intoxication with perceptual disturbance
F12.93	Cannabis use, unspecified with withdrawal
F12.950	Cannabis use, unspecified with psychotic disorder with delusions
F12.951	Cannabis use, unspecified with psychotic disorder with hallucinations
F12.959	Cannabis use, unspecified with psychotic disorder, unspecified
F12.980	Cannabis use, unspecified with anxiety disorder
F12.988	Cannabis use, unspecified with other cannabis-induced disorder
F13.121	Sedative, hypnotic or anxiolytic abuse with intoxication delirium
F13.14	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced mood disorder
F13.150	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced psychotic disorder with delusions
F13.151	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced psychotic disorder with hallucinations
F13.159	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced psychotic disorder, unspecified
F13.180	Sedative, hypnotic or anxiolytic abuse with sedative, hypnotic or anxiolytic-induced anxiety disorder

ICD-10 CODE	DESCRIPTION
F13.188	Sedative, hypnotic or anxiolytic abuse with other sedative, hypnotic or anxiolytic-induced disorder
F13.220	Sedative, hypnotic or anxiolytic dependence with intoxication, uncomplicated
F13.221	Sedative, hypnotic or anxiolytic dependence with intoxication delirium
F13.229	Sedative, hypnotic or anxiolytic dependence with intoxication, unspecified
F13.230	Sedative, hypnotic or anxiolytic dependence with withdrawal, uncomplicated
F13.231	Sedative, hypnotic or anxiolytic dependence with withdrawal delirium
F13.232	Sedative, hypnotic or anxiolytic dependence with withdrawal with perceptual disturbance
F13.239	Sedative, hypnotic or anxiolytic dependence with withdrawal, unspecified
F13.24	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced mood disorder
F13.250	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced psychotic disorder with delusions
F13.251	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced psychotic disorder with hallucinations
ICD-10 CODE	DESCRIPTION
F13.259	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced psychotic disorder, unspecified
F13.26	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced persisting amnestic disorder
F13.27	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced persisting dementia
F13.280	Sedative, hypnotic or anxiolytic dependence with sedative, hypnotic or anxiolytic-induced anxiety disorder
F13.288	Sedative, hypnotic or anxiolytic dependence with other sedative, hypnotic or anxiolytic-induced disorder
F13.921	Sedative, hypnotic or anxiolytic use, unspecified with intoxication delirium
F13.94	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced mood disorder
F13.950	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced psychotic disorder with delusions
F13.951	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced psychotic disorder with hallucinations
F13.959	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced psychotic disorder, unspecified

ICD-10 CODE	DESCRIPTION
F13.980	Sedative, hypnotic or anxiolytic use, unspecified with sedative, hypnotic or anxiolytic-induced anxiety disorder
F13.988	Sedative, hypnotic or anxiolytic use, unspecified with other sedative, hypnotic or anxiolytic-induced disorder
F14.121	Cocaine abuse with intoxication with delirium
F14.122	Cocaine abuse with intoxication with perceptual disturbance
F14.14	Cocaine abuse with cocaine-induced mood disorder
F14.150	Cocaine abuse with cocaine-induced psychotic disorder with delusions
F14.151	Cocaine abuse with cocaine-induced psychotic disorder with hallucinations
F14.159	Cocaine abuse with cocaine-induced psychotic disorder, unspecified
F14.180	Cocaine abuse with cocaine-induced anxiety disorder
F14.188	Cocaine abuse with other cocaine-induced disorder
F14.220	Cocaine dependence with intoxication, uncomplicated
F14.221	Cocaine dependence with intoxication delirium
F14.222	Cocaine dependence with intoxication with perceptual disturbance
F14.229	Cocaine dependence with intoxication, unspecified
F14.23	Cocaine dependence with withdrawal
F14.24	Cocaine dependence with cocaine-induced mood disorder
F14.250	Cocaine dependence with cocaine-induced psychotic disorder with delusions
F14.251	Cocaine dependence with cocaine-induced psychotic disorder with hallucinations
F14.259	Cocaine dependence with cocaine-induced psychotic disorder, unspecified
F14.280	Cocaine dependence with cocaine-induced anxiety disorder
F14.288	Cocaine dependence with other cocaine-induced disorder
F14.921	Cocaine use, unspecified with intoxication delirium
F14.922	Cocaine use, unspecified with intoxication with perceptual disturbance
F14.94	Cocaine use, unspecified with cocaine-induced mood disorder
F14.950	Cocaine use, unspecified with cocaine-induced psychotic disorder with delusions
F14.951	Cocaine use, unspecified with cocaine-induced psychotic disorder with hallucinations
F14.959	Cocaine use, unspecified with cocaine-induced psychotic disorder, unspecified
F14.980	Cocaine use, unspecified with cocaine-induced anxiety disorder
F14.988	Cocaine use, unspecified with other cocaine-induced disorder
F15.121	Other stimulant abuse with intoxication delirium

ICD-10 CODE	DESCRIPTION
F15.122	Other stimulant abuse with intoxication with perceptual disturbance
F15.14	Other stimulant abuse with stimulant-induced mood disorder
F15.150	Other stimulant abuse with stimulant-induced psychotic disorder with delusions
F15.151	Other stimulant abuse with stimulant-induced psychotic disorder with hallucinations
F15.159	Other stimulant abuse with stimulant-induced psychotic disorder, unspecified
F15.180	Other stimulant abuse with stimulant-induced anxiety disorder
F15.188	Other stimulant abuse with other stimulant-induced disorder
F15.220	Other stimulant dependence with intoxication, uncomplicated
F15.221	Other stimulant dependence with intoxication delirium
F15.222	Other stimulant dependence with intoxication with perceptual disturbance
F15.229	Other stimulant dependence with intoxication, unspecified
F15.23	Other stimulant dependence with withdrawal
F15.24	Other stimulant dependence with stimulant-induced mood disorder
F15.250	Other stimulant dependence with stimulant-induced psychotic disorder with delusions
F15.251	Other stimulant dependence with stimulant-induced psychotic disorder with hallucinations
F15.259	Other stimulant dependence with stimulant-induced psychotic disorder, unspecified
F15.280	Other stimulant dependence with stimulant-induced anxiety disorder
F15.288	Other stimulant dependence with other stimulant-induced disorder
F15.921	Other stimulant use, unspecified with intoxication delirium
F15.922	Other stimulant use, unspecified with intoxication with perceptual disturbance
F15.94	Other stimulant use, unspecified with stimulant-induced mood disorder
F15.950	Other stimulant use, unspecified with stimulant-induced psychotic disorder with delusions
F15.951	Other stimulant use, unspecified with stimulant-induced psychotic disorder with hallucinations
F15.959	Other stimulant use, unspecified with stimulant-induced psychotic disorder, unspecified
F15.980	Other stimulant use, unspecified with stimulant-induced anxiety disorder
F15.988	Other stimulant use, unspecified with other stimulant-induced disorder
F16.121	Hallucinogen abuse with intoxication with delirium
F16.122	Hallucinogen abuse with intoxication with perceptual disturbance

ICD-10 CODE	DESCRIPTION
F16.14	Hallucinogen abuse with hallucinogen-induced mood disorder
F16.150	Hallucinogen abuse with hallucinogen-induced psychotic disorder with delusions
F16.151	Hallucinogen abuse with hallucinogen-induced psychotic disorder with hallucinations
F16.159	Hallucinogen abuse with hallucinogen-induced psychotic disorder, unspecified
F16.180	Hallucinogen abuse with hallucinogen-induced anxiety disorder
F16.183	Hallucinogen abuse with hallucinogen persisting perception disorder (flashbacks)
F16.188	Hallucinogen abuse with other hallucinogen-induced disorder
F16.221	Hallucinogen dependence with intoxication with delirium
F16.24	Hallucinogen dependence with hallucinogen-induced mood disorder
F16.250	Hallucinogen dependence with hallucinogen-induced psychotic disorder with delusions
F16.251	Hallucinogen dependence with hallucinogen-induced psychotic disorder with hallucinations
F16.259	Hallucinogen dependence with hallucinogen-induced psychotic disorder, unspecified
F16.280	Hallucinogen dependence with hallucinogen-induced anxiety disorder
F16.283	Hallucinogen dependence with hallucinogen persisting perception disorder (flashbacks)
F16.288	Hallucinogen dependence with other hallucinogen-induced disorder
F16.921	Hallucinogen use, unspecified with intoxication with delirium
F16.94	Hallucinogen use, unspecified with hallucinogen-induced mood disorder
F16.950	Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder with delusions
F16.951	Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder with hallucinations
F16.959	Hallucinogen use, unspecified with hallucinogen-induced psychotic disorder, unspecified
F16.980	Hallucinogen use, unspecified with hallucinogen-induced anxiety disorder
F16.983	Hallucinogen use, unspecified with hallucinogen persisting perception disorder (flashbacks)
F16.988	Hallucinogen use, unspecified with other hallucinogen-induced disorder
F17.208	Nicotine dependence, unspecified, with other nicotine-induced disorders
F17.218	Nicotine dependence, cigarettes, with other nicotine-induced disorders
F17.228	Nicotine dependence, chewing tobacco, with other nicotine-induced disorders
F17.298	Nicotine dependence, other tobacco product, with other nicotine-induced disorders

ICD-10 CODE	DESCRIPTION
F18.121	Inhalant abuse with intoxication delirium
F18.14	Inhalant abuse with inhalant-induced mood disorder
F18.150	Inhalant abuse with inhalant-induced psychotic disorder with delusions
F18.151	Inhalant abuse with inhalant-induced psychotic disorder with hallucinations
F18.159	Inhalant abuse with inhalant-induced psychotic disorder, unspecified
ICD-10 CODE	DESCRIPTION
F18.180	Inhalant abuse with inhalant-induced anxiety disorder
F18.188	Inhalant abuse with other inhalant-induced disorder
F18.220	Inhalant dependence with intoxication, uncomplicated
F18.221	Inhalant dependence with intoxication delirium
F18.229	Inhalant dependence with intoxication, unspecified
F18.24	Inhalant dependence with inhalant-induced mood disorder
F18.250	Inhalant dependence with inhalant-induced psychotic disorder with delusions
F18.251	Inhalant dependence with inhalant-induced psychotic disorder with hallucinations
F18.259	Inhalant dependence with inhalant-induced psychotic disorder, unspecified
F18.27	Inhalant dependence with inhalant-induced dementia
F18.280	Inhalant dependence with inhalant-induced anxiety disorder
F18.288	Inhalant dependence with other inhalant-induced disorder
F18.921	Inhalant use, unspecified with intoxication with delirium
F18.94	Inhalant use, unspecified with inhalant-induced mood disorder
F18.950	Inhalant use, unspecified with inhalant-induced psychotic disorder with delusions
F18.951	Inhalant use, unspecified with inhalant-induced psychotic disorder with hallucinations
F18.959	Inhalant use, unspecified with inhalant-induced psychotic disorder, unspecified
F18.980	Inhalant use, unspecified with inhalant-induced anxiety disorder
F18.988	Inhalant use, unspecified with other inhalant-induced disorder
F19.121	Other psychoactive substance abuse with intoxication delirium
F19.122	Other psychoactive substance abuse with intoxication with perceptual disturbances
F19.14	Other psychoactive substance abuse with psychoactive substance-induced mood disorder
F19.150	Other psychoactive substance abuse with psychoactive substance-induced psychotic disorder with delusions
F19.151	Other psychoactive substance abuse with psychoactive substance-induced psychotic

ICD-10 CODE	DESCRIPTION
	disorder with hallucinations
F19.159	Other psychoactive substance abuse with psychoactive substance-induced psychotic disorder, unspecified
F19.180	Other psychoactive substance abuse with psychoactive substance-induced anxiety disorder
F19.188	Other psychoactive substance abuse with other psychoactive substance-induced disorder
F19.220	Other psychoactive substance dependence with intoxication, uncomplicated
F19.221	Other psychoactive substance dependence with intoxication delirium
F19.222	Other psychoactive substance dependence with intoxication with perceptual disturbance
F19.229	Other psychoactive substance dependence with intoxication, unspecified
F19.230	Other psychoactive substance dependence with withdrawal, uncomplicated
F19.231	Other psychoactive substance dependence with withdrawal delirium
F19.232	Other psychoactive substance dependence with withdrawal with perceptual disturbance
F19.239	Other psychoactive substance dependence with withdrawal, unspecified
F19.24	Other psychoactive substance dependence with psychoactive substance-induced mood disorder
F19.250	Other psychoactive substance dependence with psychoactive substance-induced psychotic disorder with delusions
F19.251	Other psychoactive substance dependence with psychoactive substance-induced psychotic disorder with hallucinations
F19.259	Other psychoactive substance dependence with psychoactive substance-induced psychotic disorder, unspecified
F19.26	Other psychoactive substance dependence with psychoactive substance-induced persisting amnestic disorder
F19.27	Other psychoactive substance dependence with psychoactive substance-induced persisting dementia
F19.280	Other psychoactive substance dependence with psychoactive substance-induced anxiety disorder
F19.288	Other psychoactive substance dependence with other psychoactive substance-induced disorder
F19.921	Other psychoactive substance use, unspecified with intoxication with delirium
F19.922	Other psychoactive substance use, unspecified with intoxication with perceptual disturbance

ICD-10 CODE	DESCRIPTION
F19.94	Other psychoactive substance use, unspecified with psychoactive substance-induced mood disorder
F19.950	Other psychoactive substance use, unspecified with psychoactive substance-induced psychotic disorder with delusions
F19.951	Other psychoactive substance use, unspecified with psychoactive substance-induced psychotic disorder with hallucinations
F19.959	Other psychoactive substance use, unspecified with psychoactive substance-induced psychotic disorder, unspecified
F19.980	Other psychoactive substance use, unspecified with psychoactive substance-induced anxiety disorder
F19.988	Other psychoactive substance use, unspecified with other psychoactive substance-induced disorder
F20.0	Paranoid schizophrenia
F20.1	Disorganized schizophrenia
F20.2	Catatonic schizophrenia
F20.3	Undifferentiated schizophrenia
F20.81	Schizophreniform disorder
F20.9	Schizophrenia, unspecified
F22	Delusional disorders
F23	Brief psychotic disorder
F24	Shared psychotic disorder
F25.0	Schizoaffective disorder, bipolar type
F25.1	Schizoaffective disorder, depressive type
F25.8	Other schizoaffective disorders
F25.9	Schizoaffective disorder, unspecified
F28	Other psychotic disorder not due to a substance or known physiological condition
F29	Unspecified psychosis not due to a substance or known physiological condition
F30.13	Manic episode, severe, without psychotic symptoms
F30.2	Manic episode, severe with psychotic symptoms
F30.3	Manic episode in partial remission
F31.13	Bipolar disorder, current episode manic without psychotic features, severe
F31.2	Bipolar disorder, current episode manic severe with psychotic features
F31.4	Bipolar disorder, current episode depressed, severe, without psychotic features

ICD-10 CODE	DESCRIPTION
F31.5	Bipolar disorder, current episode depressed, severe, with psychotic features
F31.63	Bipolar disorder, current episode mixed, severe, without psychotic features
F31.64	Bipolar disorder, current episode mixed, severe, with psychotic features
F31.71	Bipolar disorder, in partial remission, most recent episode hypomanic
F31.73	Bipolar disorder, in partial remission, most recent episode manic
F31.75	Bipolar disorder, in partial remission, most recent episode depressed
F31.77	Bipolar disorder, in partial remission, most recent episode mixed
F31.81	Bipolar II disorder
F31.9	Bipolar disorder, unspecified
F32.2	Major depressive disorder, single episode, severe without psychotic features
F32.3	Major depressive disorder, single episode, severe with psychotic features
F32.4	Major depressive disorder, single episode, in partial remission
F32.89	Other specified depressive episodes
F33.2	Major depressive disorder, recurrent severe without psychotic features
F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms
F33.41	Major depressive disorder, recurrent, in partial remission
F40.01	Agoraphobia with panic disorder
F41.0	Panic disorder [episodic paroxysmal anxiety]
F42.2	Mixed obsessional thoughts and acts
F42.4	Excoriation (skin-picking) disorder
F42.8	Other obsessive-compulsive disorder
F42.9	Obsessive-compulsive disorder, unspecified
F43.0	Acute stress reaction
F43.11	Post-traumatic stress disorder, acute
F43.12	Post-traumatic stress disorder, chronic
F43.21	Adjustment disorder with depressed mood
F43.22	Adjustment disorder with anxiety
F43.23	Adjustment disorder with mixed anxiety and depressed mood
ICD-10 CODE	DESCRIPTION
F43.24	Adjustment disorder with disturbance of conduct
F43.25	Adjustment disorder with mixed disturbance of emotions and conduct
F50.01	Anorexia nervosa, restricting type

ICD-10 CODE	DESCRIPTION
F50.02	Anorexia nervosa, binge eating/purging type
F50.2	Bulimia nervosa
F50.82	Avoidant/restrictive food intake disorder
F50.89	Other specified eating disorder
F53.0	Postpartum depression
F53.1	Puerperal psychosis
F60.3	Borderline personality disorder
F63.81	Intermittent explosive disorder
F84.0	Autistic disorder
F84.3	Other childhood disintegrative disorder
F84.5	Asperger's syndrome
F84.8	Other pervasive developmental disorders
F84.9	Pervasive developmental disorder, unspecified
R40.0	Somnolence
R40.1	Stupor
R45.851	Suicidal ideations

Group 2 Paragraph:

The following diagnosis codes are covered for 81225 if the treatment for the diagnosis involves the treating clinician considering treatment with a medication that makes the service described by 81225 reasonable and necessary.

Group 2 Codes:

ICD-10 CODE	DESCRIPTION
G45.0	Vertebro-basilar artery syndrome
G45.1	Carotid artery syndrome (hemispheric)
G45.2	Multiple and bilateral precerebral artery syndromes
G45.3	Amaurosis fugax
G45.4	Transient global amnesia
G45.8	Other transient cerebral ischemic attacks and related syndromes
G45.9	Transient cerebral ischemic attack, unspecified
I20.0	Unstable angina
I21.01	ST elevation (STEMI) myocardial infarction involving left main coronary artery
I21.02	ST elevation (STEMI) myocardial infarction involving left anterior descending

ICD-10 CODE	DESCRIPTION
	coronary artery
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
I21.21	ST elevation (STEMI) myocardial infarction involving left circumflex coronary artery
I21.29	ST elevation (STEMI) myocardial infarction involving other sites
I21.3	ST elevation (STEMI) myocardial infarction of unspecified site
I22.0	Subsequent ST elevation (STEMI) myocardial infarction of anterior wall
I22.1	Subsequent ST elevation (STEMI) myocardial infarction of inferior wall
I22.8	Subsequent ST elevation (STEMI) myocardial infarction of other sites
I22.9	Subsequent ST elevation (STEMI) myocardial infarction of unspecified site
I24.0	Acute coronary thrombosis not resulting in myocardial infarction
I24.8	Other forms of acute ischemic heart disease
I63.011	Cerebral infarction due to thrombosis of right vertebral artery
I63.012	Cerebral infarction due to thrombosis of left vertebral artery
I63.019	Cerebral infarction due to thrombosis of unspecified vertebral artery
I63.02	Cerebral infarction due to thrombosis of basilar artery
I63.031	Cerebral infarction due to thrombosis of right carotid artery
I63.032	Cerebral infarction due to thrombosis of left carotid artery
I63.039	Cerebral infarction due to thrombosis of unspecified carotid artery
I63.10	Cerebral infarction due to embolism of unspecified precerebral artery
I63.111	Cerebral infarction due to embolism of right vertebral artery
I63.112	Cerebral infarction due to embolism of left vertebral artery
I63.119	Cerebral infarction due to embolism of unspecified vertebral artery
I63.12	Cerebral infarction due to embolism of basilar artery
I63.131	Cerebral infarction due to embolism of right carotid artery
I63.132	Cerebral infarction due to embolism of left carotid artery
I63.19	Cerebral infarction due to embolism of other precerebral artery
I63.20	Cerebral infarction due to unspecified occlusion or stenosis of unspecified precerebral arteries
I63.211	Cerebral infarction due to unspecified occlusion or stenosis of right vertebral artery

ICD-10 CODE	DESCRIPTION
I63.212	Cerebral infarction due to unspecified occlusion or stenosis of left vertebral artery
I63.219	Cerebral infarction due to unspecified occlusion or stenosis of unspecified vertebral artery
I63.22	Cerebral infarction due to unspecified occlusion or stenosis of basilar artery
I63.231	Cerebral infarction due to unspecified occlusion or stenosis of right carotid arteries
I63.232	Cerebral infarction due to unspecified occlusion or stenosis of left carotid arteries
I63.239	Cerebral infarction due to unspecified occlusion or stenosis of unspecified carotid artery
I63.29	Cerebral infarction due to unspecified occlusion or stenosis of other precerebral arteries
I63.30	Cerebral infarction due to thrombosis of unspecified cerebral artery
I63.311	Cerebral infarction due to thrombosis of right middle cerebral artery
I63.312	Cerebral infarction due to thrombosis of left middle cerebral artery
I63.319	Cerebral infarction due to thrombosis of unspecified middle cerebral artery
I63.321	Cerebral infarction due to thrombosis of right anterior cerebral artery
I63.322	Cerebral infarction due to thrombosis of left anterior cerebral artery
I63.329	Cerebral infarction due to thrombosis of unspecified anterior cerebral artery
I63.331	Cerebral infarction due to thrombosis of right posterior cerebral artery
I63.332	Cerebral infarction due to thrombosis of left posterior cerebral artery
I63.339	Cerebral infarction due to thrombosis of unspecified posterior cerebral artery
I63.341	Cerebral infarction due to thrombosis of right cerebellar artery
I63.342	Cerebral infarction due to thrombosis of left cerebellar artery
I63.349	Cerebral infarction due to thrombosis of unspecified cerebellar artery
I63.39	Cerebral infarction due to thrombosis of other cerebral artery
I63.40	Cerebral infarction due to embolism of unspecified cerebral artery
I63.411	Cerebral infarction due to embolism of right middle cerebral artery
I63.412	Cerebral infarction due to embolism of left middle cerebral artery
I63.419	Cerebral infarction due to embolism of unspecified middle cerebral artery
I63.421	Cerebral infarction due to embolism of right anterior cerebral artery
I63.422	Cerebral infarction due to embolism of left anterior cerebral artery
I63.431	Cerebral infarction due to embolism of right posterior cerebral artery
I63.432	Cerebral infarction due to embolism of left posterior cerebral artery
I63.439	Cerebral infarction due to embolism of unspecified posterior cerebral artery

ICD-10 CODE	DESCRIPTION
I63.441	Cerebral infarction due to embolism of right cerebellar artery
I63.442	Cerebral infarction due to embolism of left cerebellar artery
I63.449	Cerebral infarction due to embolism of unspecified cerebellar artery
I63.49	Cerebral infarction due to embolism of other cerebral artery
I63.50	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebral artery
I63.511	Cerebral infarction due to unspecified occlusion or stenosis of right middle cerebral artery
I63.512	Cerebral infarction due to unspecified occlusion or stenosis of left middle cerebral artery
I63.519	Cerebral infarction due to unspecified occlusion or stenosis of unspecified middle cerebral artery
I63.521	Cerebral infarction due to unspecified occlusion or stenosis of right anterior cerebral artery
I63.522	Cerebral infarction due to unspecified occlusion or stenosis of left anterior cerebral artery
I63.529	Cerebral infarction due to unspecified occlusion or stenosis of unspecified anterior cerebral artery
I63.531	Cerebral infarction due to unspecified occlusion or stenosis of right posterior cerebral artery
I63.532	Cerebral infarction due to unspecified occlusion or stenosis of left posterior cerebral artery
I63.539	Cerebral infarction due to unspecified occlusion or stenosis of unspecified posterior cerebral artery
I63.541	Cerebral infarction due to unspecified occlusion or stenosis of right cerebellar artery
I63.542	Cerebral infarction due to unspecified occlusion or stenosis of left cerebellar artery
I63.549	Cerebral infarction due to unspecified occlusion or stenosis of unspecified cerebellar artery
I63.59	Cerebral infarction due to unspecified occlusion or stenosis of other cerebral artery
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.9	Cerebral infarction, unspecified
I65.01	Occlusion and stenosis of right vertebral artery
I65.02	Occlusion and stenosis of left vertebral artery
I65.03	Occlusion and stenosis of bilateral vertebral arteries
I65.09	Occlusion and stenosis of unspecified vertebral artery

ICD-10 CODE	DESCRIPTION
I65.1	Occlusion and stenosis of basilar artery
I65.21	Occlusion and stenosis of right carotid artery
I65.22	Occlusion and stenosis of left carotid artery
I65.23	Occlusion and stenosis of bilateral carotid arteries
I65.29	Occlusion and stenosis of unspecified carotid artery
I65.8	Occlusion and stenosis of other precerebral arteries
I65.9	Occlusion and stenosis of unspecified precerebral artery
I66.01	Occlusion and stenosis of right middle cerebral artery
ICD-10 CODE	DESCRIPTION
I66.02	Occlusion and stenosis of left middle cerebral artery
I66.03	Occlusion and stenosis of bilateral middle cerebral arteries
I66.09	Occlusion and stenosis of unspecified middle cerebral artery
I66.11	Occlusion and stenosis of right anterior cerebral artery
I66.12	Occlusion and stenosis of left anterior cerebral artery
I66.13	Occlusion and stenosis of bilateral anterior cerebral arteries
I66.19	Occlusion and stenosis of unspecified anterior cerebral artery
I66.21	Occlusion and stenosis of right posterior cerebral artery
I66.22	Occlusion and stenosis of left posterior cerebral artery
I66.23	Occlusion and stenosis of bilateral posterior cerebral arteries
I66.29	Occlusion and stenosis of unspecified posterior cerebral artery
I66.3	Occlusion and stenosis of cerebellar arteries
I66.8	Occlusion and stenosis of other cerebral arteries
I66.9	Occlusion and stenosis of unspecified cerebral artery
I67.2	Cerebral atherosclerosis
I67.81	Acute cerebrovascular insufficiency
I67.82	Cerebral ischemia
I67.83	Posterior reversible encephalopathy syndrome
I67.841	Reversible cerebrovascular vasoconstriction syndrome
I67.848	Other cerebrovascular vasospasm and vasoconstriction
I67.89	Other cerebrovascular disease
I70.201	Unspecified atherosclerosis of native arteries of extremities, right leg
I70.202	Unspecified atherosclerosis of native arteries of extremities, left leg

ICD-10 CODE	DESCRIPTION
I70.203	Unspecified atherosclerosis of native arteries of extremities, bilateral legs
I70.208	Unspecified atherosclerosis of native arteries of extremities, other extremity
I70.209	Unspecified atherosclerosis of native arteries of extremities, unspecified extremity
I70.211	Atherosclerosis of native arteries of extremities with intermittent claudication, right leg
I70.212	Atherosclerosis of native arteries of extremities with intermittent claudication, left leg
I70.213	Atherosclerosis of native arteries of extremities with intermittent claudication, bilateral legs
I70.218	Atherosclerosis of native arteries of extremities with intermittent claudication, other extremity
I70.219	Atherosclerosis of native arteries of extremities with intermittent claudication, unspecified extremity
I70.221	Atherosclerosis of native arteries of extremities with rest pain, right leg
I70.222	Atherosclerosis of native arteries of extremities with rest pain, left leg
I70.223	Atherosclerosis of native arteries of extremities with rest pain, bilateral legs
I70.228	Atherosclerosis of native arteries of extremities with rest pain, other extremity
I70.229	Atherosclerosis of native arteries of extremities with rest pain, unspecified extremity
I70.231	Atherosclerosis of native arteries of right leg with ulceration of thigh
I70.232	Atherosclerosis of native arteries of right leg with ulceration of calf
I70.233	Atherosclerosis of native arteries of right leg with ulceration of ankle
I70.234	Atherosclerosis of native arteries of right leg with ulceration of heel and midfoot
I70.235	Atherosclerosis of native arteries of right leg with ulceration of other part of foot
I70.238	Atherosclerosis of native arteries of right leg with ulceration of other part of lower leg
I70.239	Atherosclerosis of native arteries of right leg with ulceration of unspecified site
I70.241	Atherosclerosis of native arteries of left leg with ulceration of thigh
I70.242	Atherosclerosis of native arteries of left leg with ulceration of calf
I70.243	Atherosclerosis of native arteries of left leg with ulceration of ankle
I70.244	Atherosclerosis of native arteries of left leg with ulceration of heel and midfoot
I70.245	Atherosclerosis of native arteries of left leg with ulceration of other part of foot
I70.248	Atherosclerosis of native arteries of left leg with ulceration of other part of lower leg
I70.249	Atherosclerosis of native arteries of left leg with ulceration of unspecified site

ICD-10 CODE	DESCRIPTION
I70.25	Atherosclerosis of native arteries of other extremities with ulceration
I70.261	Atherosclerosis of native arteries of extremities with gangrene, right leg
I70.262	Atherosclerosis of native arteries of extremities with gangrene, left leg
I70.263	Atherosclerosis of native arteries of extremities with gangrene, bilateral legs
I70.268	Atherosclerosis of native arteries of extremities with gangrene, other extremity
I70.269	Atherosclerosis of native arteries of extremities with gangrene, unspecified extremity

Group 3 Paragraph:

The following diagnosis codes are covered for 81227 if the treatment for the diagnosis involves the treating clinician considering treatment with Mayzent.

Group 3 Codes:

ICD-10 CODE	DESCRIPTION
G35	Multiple sclerosis
G40.001	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, with status epilepticus
G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, not intractable, without status epilepticus
G40.011	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, with status epilepticus
G40.019	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset, intractable, without status epilepticus
G40.101	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, with status epilepticus
G40.109	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus
G40.111	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, with status epilepticus
G40.119	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, intractable, without status epilepticus
G40.201	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, with status epilepticus
G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus
G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus

ICD-10 CODE	DESCRIPTION
G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
G40.301	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.309	Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.311	Generalized idiopathic epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.319	Generalized idiopathic epilepsy and epileptic syndromes, intractable, without status epilepticus
G40.A01	Absence epileptic syndrome, not intractable, with status epilepticus
G40.A09	Absence epileptic syndrome, not intractable, without status epilepticus
G40.A11	Absence epileptic syndrome, intractable, with status epilepticus
G40.A19	Absence epileptic syndrome, intractable, without status epilepticus
G40.B01	Juvenile myoclonic epilepsy, not intractable, with status epilepticus
G40.B09	Juvenile myoclonic epilepsy, not intractable, without status epilepticus
G40.B11	Juvenile myoclonic epilepsy, intractable, with status epilepticus
G40.B19	Juvenile myoclonic epilepsy, intractable, without status epilepticus
G40.401	Other generalized epilepsy and epileptic syndromes, not intractable, with status epilepticus
G40.409	Other generalized epilepsy and epileptic syndromes, not intractable, without status epilepticus
G40.411	Other generalized epilepsy and epileptic syndromes, intractable, with status epilepticus
G40.419	Other generalized epilepsy and epileptic syndromes, intractable, without status epilepticus
G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
G40.509	Epileptic seizures related to external causes, not intractable, without status epilepticus
G40.801	Other epilepsy, not intractable, with status epilepticus
G40.802	Other epilepsy, not intractable, without status epilepticus
G40.803	Other epilepsy, intractable, with status epilepticus
G40.804	Other epilepsy, intractable, without status epilepticus
G40.811	Lennox-Gastaut syndrome, not intractable, with status epilepticus
G40.812	Lennox-Gastaut syndrome, not intractable, without status epilepticus

ICD-10 CODE	DESCRIPTION
G40.813	Lennox-Gastaut syndrome, intractable, with status epilepticus
G40.814	Lennox-Gastaut syndrome, intractable, without status epilepticus
G40.821	Epileptic spasms, not intractable, with status epilepticus
G40.822	Epileptic spasms, not intractable, without status epilepticus
G40.823	Epileptic spasms, intractable, with status epilepticus
G40.824	Epileptic spasms, intractable, without status epilepticus
G40.89	Other seizures
G40.901	Epilepsy, unspecified, not intractable, with status epilepticus
G40.909	Epilepsy, unspecified, not intractable, without status epilepticus
G40.911	Epilepsy, unspecified, intractable, with status epilepticus
G40.919	Epilepsy, unspecified, intractable, without status epilepticus

ICD-10 Codes that DO NOT Support Medical Necessity

N/A

Additional ICD-10 Information

N/A

Associated Documents

Attachments

N/A

Related Local Coverage Documents

N/A

Related National Coverage Documents

N/A

Keywords

- Pharmacogenomics