Genetic Testing for Dilated Cardiomyopathy

Policy # 00409
Original Effective Date: 03/19/2014
Current Effective Date: 07/10/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Predisposition to Inherited Hypertrophic Cardiomyopathy is addressed separately in medical policy 00270.

Note: Genetic Testing for Cardiac Ion Channelopathies is addressed separately in medical policy 00408.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider comprehensive genetic testing for individuals with signs or symptoms of dilated cardiomyopathy which is considered idiopathic after a negative workup for secondary causes to be eligible for coverage** (See Policy Guidelines).

Based on review of available data, the Company may consider targeted genetic testing for asymptomatic individuals with a first-degree relative who has dilated cardiomyopathy and a known familial variant to be eligible for coverage.**

Note:
If there is an evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage.
When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for dilated cardiomyopathy in all other situations to be investigational.*

Policy Guidelines

Standard Workup for Patients With Signs or Symptoms of Dilated Cardiomyopathy

The standard workup for patients with signs or symptoms of dilated cardiomyopathy (DCM) includes a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for vitamin B1 deficiency and coronary artery disease as warranted by risk factors. An extensive workup including cardiac magnetic resonance imaging, exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical review updates starting in 2017 (Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organisation, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.
Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Background/Overview
Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is defined as the presence of left ventricular enlargement and dilatation in conjunction with significant systolic dysfunction. Dilated cardiomyopathy has an estimated prevalence of 1 in 2700 in the United States. The age of onset for DCM varies, ranging from infancy to the eighth decade, with most individuals developing symptoms in the fourth through sixth decades.

Idiopathic Dilated Cardiomyopathy
When a patient presents with DCM, a workup is performed to identify underlying causes, especially those treatable. The standard workup consists of a clinical exam, blood pressure monitoring, electrocardiography, echocardiography, and workup for coronary artery disease as warranted by risk factors. An extensive workup including cardiac magnetic resonance imaging (MRI), exercise testing, right-sided catheterization with biopsy, and 24-hour electrocardiography monitoring will uncover only a small number of additional etiologies for DCM. Approximately 35% to 40% of DCM cases are thus determined to be idiopathic after a negative workup for the secondary causes listed above. This has traditionally been termed idiopathic dilated cardiomyopathy (IDC).

Clustering of IDC within families has been reported, leading to the conclusion that at least some cases of DCM have a genetic basis. Familial DCM is diagnosed when 2 closely related family members have IDC in the absence of underlying causes. Penetrance of familial DCM is variable and age-dependent, often leading to a lack of appreciation of the familial component.

Genetic Dilated Cardiomyopathy
Genetic DCM has been proposed as a newer classification that includes both familial DCM and some cases of sporadic IDC. The percentage of patients with sporadic DCM that has a genetic basis is not well characterized. Most disease-associated variants are inherited in an autosomal dominant fashion, but some autosomal recessive, X-linked, and mitochondrial patterns of inheritance also are present. Expanded numbers of genotyped individuals facilitate genotype-phenotype correlations and studies of natural disease history. Recognition of high-risk variant carriers is important as these individuals would be expected to have the most to gain from pre-emptive interventions.
In general, genotype-phenotype correlations in the inherited cardiomyopathies are either not present or not well characterized. There have been some purported correlations between certain disease-associated variants and the presence of arrhythmias. For example, patients with conduction system disease and/or a family history of sudden cardiac death may be more likely to have disease-associated variants in the lamin A/C (LM), SCN5A, and desmin genes. Kayvanpour et al (2017) performed a meta-analysis of genotype-phenotype associations in DCM. The analysis included 48 studies (N=8097 patients) and found a higher prevalence of sudden cardiac death, cardiac transplantation, and ventricular arrhythmias in the LM and phospholamban (PLN) disease-associated variant carriers and increasing penetrance with age of DCM phenotype in subjects with titin (TTN)-truncating variants.

There may be interactions between genetic and environmental factors that lead to the clinical manifestations of DCM. A genetic variant may not in itself be sufficient to cause DCM but may predispose to developing DCM in the presence of environmental factors such as nutritional deficiencies or viral infections. It also has been suggested that DCM genetics may be more complex than single-gene variants, with low-penetrance variants that are common in the population contributing to a cumulative risk of DCM that includes both genetic and environmental factors.

**Diagnosis of Dilated Cardiomyopathy**

Primary clinical manifestations of DCM are heart failure and arrhythmias. Symptoms of heart failure, such as dyspnea on exertion and peripheral edema, are the most common presentations of DCM. These symptoms are generally gradual in onset and slowly progressive over time. Progressive myocardial dysfunction also may lead to electrical instability and arrhythmias. Symptoms of arrhythmias may include light-headedness, syncope, or sudden cardiac arrest.

Many underlying conditions can cause DCM, including:

- Ischemic coronary artery disease
- Toxins
- Metabolic conditions
- Endocrine disorders
- Inflammatory and infectious diseases
- Infiltrative disorders
- Tachycardia-mediated cardiomyopathy.
Genetic Testing for Dilated Cardiomyopathy

Treatment of Dilated Cardiomyopathy

Treatment of DCM is similar to that for other causes of heart failure. This includes medications to reduce fluid overload and relieve strain on the heart and lifestyle modifications such as salt restriction. Patients with clinically significant arrhythmias also may be treated with antiarrhythmic medications, pacemaker implantation, and/or an automatic implantable cardiac defibrillator. Automatic implantable cardiac defibrillator placement for primary prevention also may be performed if criteria for low ejection fraction and/or other clinical symptoms are present. End-stage DCM can be treated with cardiac transplantation.

Genetic Testing for Dilated Cardiomyopathy

Approximately 30% to 40% of patients with DCM referred for genetic testing will have a disease-associated variant identified. Disease-associated variants linked to DCM have been identified in more than 40 genes of various types and locations. The most common genes involved are those that code for TTN, myosin heavy chain (MYH7), troponin T (TNNT2), and alpha-tropomyosin (TPM1). These 4 genes account for approximately 30% of disease-associated variants identified in cohorts of patients with DCM. A high proportion of the identified disease-associated variants are rare, or novel, variants, thus creating challenges in assigning the pathogenicity of discovered variants. Some individuals with DCM will have more than 1 DCM-associated variant. The frequency of multiple disease-associated variants is uncertain, as is the clinical significance.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice.
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practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Dilated cardiomyopathy (DCM) is characterized by progressive left ventricular enlargement and systolic dysfunction, leading to clinical manifestations of heart failure. There are a variety of causes of DCM, including genetic and nongenetic conditions. Genetic forms of DCM are heterogeneous in their molecular basis and clinical expression. Genetic testing for DCM has potential utility for confirming a diagnosis of genetic DCM and as a prognostic test in family members when familial DCM is present.

Summary of Evidence
For individuals who have signs and/or symptoms of dilated cardiomyopathy (DCM) who receive comprehensive genetic testing, the evidence includes large case series reporting clinical validity and prospective observational studies reporting clinical utility. Relevant outcomes are overall survival, test validity, symptoms, change in disease status, functional outcomes, quality of life, and treatment-related morbidity. The percentage of patients with idiopathic DCM who have a genetic variant (clinical sensitivity) is relatively low, in the range of 10% to 40%. Additional studies assessed clinical outcomes of patients with DCM and at least 1 known variant compared with patients with DCM and no known variants. The studies reported that patients with DCM and known variants experienced lower event-free survival, earlier onset of symptoms, lower transplant-free survival, and more life-threatening arrhythmias compared with patients with DCM and no known variants. A prospective observational study has reported that patients with DCM and known variants experienced high rates of morbidity and mortality during 4 to 8 years of follow-up. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include earlier implantation of cardiac defibrillators or increased surveillance to detect worsening of symptoms, as well as cascade genetic testing of asymptomatic family members. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a first-degree relative who has DCM and a known familial variant who receive targeted genetic testing for a known familial variant, the evidence includes retrospective studies and case series reporting clinical value and a prospective observational study reporting clinical utility. Relevant outcomes are test validity, symptoms, morbid events, functional outcomes, quality of life, and treatment-related morbidity. For an individual at-risk due
to genetic DCM in the family, genetic testing can identify whether a familial variant has been inherited. A prospective observational study with 4 to 8 years of follow-up reported the development of cardiac symptoms among patients initially asymptomatic who had DCM-related variants. While direct evidence of clinical usefulness is lacking, confirming a diagnosis can lead to changes in clinical management, which improve net health outcomes. Changes in management may include periodic clinical and cardiovascular evaluations to detect the earliest signs of disease, as well as genetic counseling. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

**Supplemental Information**

**Practice Guidelines and Position Statements**

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

**American Heart Association**

In 2016, the American Heart Association (AHA) released a scientific statement regarding diagnostic and treatment strategies for specific dilated cardiomyopathy (DCM), the AHA stated: "A significant proportion of idiopathic DCM cases could have genetic causes and could benefit from genetic screening, especially in familial or suspected cases; however, randomized clinical trials that demonstrate an association of genetic testing for specific disorders with disease-specific gene panels and improvement in clinical outcomes are not available, and this awaits future studies." Table 1 summarizes the AHA recommendations regarding genetic testing for patients with DCM.

**Table 1. Genetic Testing Recommendations for Dilated Cardiomyopathy by the American Heart Association**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case.</td>
<td>B</td>
</tr>
</tbody>
</table>

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Recommendation | LOE
--- | ---
In patients with familial or idiopathic cardiomyopathy, genetic testing can be useful in conjunction with genetic counseling. | B

Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to facilitate cascade screening within the family, and to help with family planning. | A

**Recommendations for Pediatric DCM** | LOE
--- | ---
Comprehensive or targeted DCM genetic testing (LMNA and SCN5A) is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) or a family history of premature unexpected sudden death. | A

Mutation-specific genetic testing is recommended for family members and appropriate relatives after the identification of a DCM-causative mutation in the index case. | B

Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, facilitate cascade screening within the family, and help with family planning. | A

In pediatric patients with a DCM phenotype, and musculoskeletal symptoms such as hypotonia, a skeletal muscle biopsy may aid in the diagnosis, and genetic testing may be considered. | C

DCM: dilated cardiomyopathy; LOE: level of evidence.

**American College of Medical Genetics and Genomics**

In 2018, the American College of Medical Genetics and Genomics (ACMG) published clinical practice recommendations for the genetic evaluation of cardiomyopathy. The following recommendations were made for all types of cardiomyopathy:

- Genetic testing is recommended for the most clearly affected family member.
- Cascade genetic testing of at-risk family members is recommended for pathogenic and likely pathogenic variants.
- In addition to routine newborn screening tests, specialized evaluation of infants with cardiomyopathy is recommended, and genetic testing should be considered.
The ACMG also provided information on specific variants, noting that \textit{TTRtv} represents the most common genetic variant found in DCM (10\% to 20\% of cases), with \textit{LMNA} being the second most common variant identified (diagnostic yield of 5.5\%).

When a cardiovascular phenotype has been identified, the ACMG recommends family-based genetic evaluations and surveillance screening.

**Heart Rhythm Society and European Heart Rhythm Association**

In 2011, the Heart Rhythm Society and European Heart Rhythm Association issued joint guidelines on genetic testing for cardiac channelopathies and cardiomyopathies.\textsuperscript{59} These guidelines included the following recommendations on genetic testing for DCM and were reaffirmed in 2018 (Table 6).

<table>
<thead>
<tr>
<th>Table 6. Genetic Testing Recommendations for Dilated Cardiomyopathy by the Heart Rhythm Society and European Heart Rhythm Association</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
</tr>
<tr>
<td>“Comprehensive or targeted (\textit{LM} and \textit{SCN5A}) DCM genetic testing is recommended for patients with DCM and significant cardiac conduction disease (ie, first-, second-, or third-degree heart block) and/or with a family history of premature unexpected sudden death.”</td>
</tr>
<tr>
<td>“Mutation-specific [familial variant] testing is recommended for family members and appropriate relatives following the identification of a DCM-causative mutation in the index case.”</td>
</tr>
<tr>
<td>“Genetic testing can be useful for patients with familial DCM to confirm the diagnosis, to recognize those who are highest risk of arrhythmia and syndromic features, to facilitate cascade screening within the family, and to help with family planning.”</td>
</tr>
</tbody>
</table>

COR: class of recommendation (I: recommended; IIa: can be useful); DCM: dilated cardiomyopathy.

The 2011 Heart Rhythm Society and European Heart Rhythm Association consensus statement also noted that prophylactic implantable cardioverter-defibrillator can be considered in patients with known arrhythmia and/or conduction system disease (\textit{LM} or Desmin [DES]).
Heart Failure Society of America
In 2018, the Heart Failure Society of America published practice guidelines on the genetic evaluation of cardiomyopathy. The following recommendations for genetic testing for cardiomyopathy (including DCM) were made:

- “Evaluation, genetic counseling, and genetic testing of cardiomyopathy patients are complex processes. Referral to centers expert in genetic evaluation and family-based management should be considered (Level of Evidence B).”
- “Genetic testing should be considered for the one most clearly affected person in a family to facilitate screening and management.”
- “Genetic and family counseling is recommended for all patients and families with cardiomyopathy (Level of Evidence A).”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03037632</td>
<td>Precision Medicine for Dilated Cardiomyopathy in European and African Ancestry</td>
<td>6500</td>
<td>Apr 2023</td>
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<tr>
<td>NCT04572893</td>
<td>Open-Label Exploratory Study of Oral MYK-491 in Stable Ambulatory Patients With Primary Dilated</td>
<td>24</td>
<td>Jan 2025</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study Description</th>
<th>NCT No.</th>
<th>Protocol Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01736566</td>
<td>The MedSeq Project Pilot Study: Integrating Whole</td>
<td>213</td>
<td>Aug 2022</td>
</tr>
<tr>
<td></td>
<td>Genome Sequencing Into the Practice of Clinical Medicine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT03860454</td>
<td>The Deep Phenotype of Lamin A/C Cardiomyopathy - A Proof-of-Principle Relax-omic Pipeline</td>
<td>150</td>
<td>Feb 2025</td>
</tr>
<tr>
<td>NCT03843255</td>
<td>Defining the Genetics, Biomarkers and Outcomes for Dilated Cardiomyopathy: a Prospective Multicentre Observational Study</td>
<td>2000</td>
<td>Jul 2027</td>
</tr>
<tr>
<td>NCT02148926</td>
<td>Clinical and Genetic Examinations of Dilated Cardiomyopathy</td>
<td>4554</td>
<td>Jun 2018 (unknown)</td>
</tr>
<tr>
<td>NCT03572569</td>
<td>Risk Stratification in Children and Adolescents with Primary Cardiomyopathy</td>
<td>200</td>
<td>Dec 2020 (unknown)</td>
</tr>
<tr>
<td>NCT01857856</td>
<td>PHOspholamban RELated CArdiomyopathy STudy - Intervention (Efficacy Study of Eplerenone in Presymptomatic PLN-R14del Carriers)</td>
<td>84</td>
<td>Oct 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
* Denotes industry-sponsored or cosponsored trial.

References
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59. Ackerman MJ, Priori SG, Willems S, et al. HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies this document was developed as a partnership between the Heart Rhythm Society (HRS) and the European Heart Rhythm Association (EHRA). Heart Rhythm. Aug 2011; 8(8): 1308-39. PMID 21787999


Policy History
Original Effective Date:  03/19/2014
Current Effective Date:  07/10/2023
03/06/2014  Medical Policy Committee review
03/19/2014  Medical Policy Implementation Committee approval. New policy.
01/01/2015  Coding Update
03/05/2015  Medical Policy Committee review
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03/20/2015  Medical Policy Implementation Committee approval. No change to coverage.
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/03/2016  Medical Policy Committee review
03/16/2016  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes and CPT coding update
03/02/2017  Medical Policy Committee review
03/15/2017  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/01/2018  Medical Policy Committee review
03/21/2018  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019  Medical Policy Committee review
06/19/2019  Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for Dilated Cardiomyopathy” to “Genetic Testing for Idiopathic Dilated Cardiomyopathy”. Policy statements changed from investigational to medically necessary. Added a Note after the second eligible for coverage statement as follows: “If there is evidence that previous genetic testing for dilated cardiomyopathy was completed, repeated testing is not necessary and is not eligible for coverage. Added vitamin B1 deficiency to workup for patients with signs and symptoms of dilated cardiomyopathy in the Policy Guidelines.
06/04/2020  Medical Policy Committee review
06/10/2020  Medical Policy Implementation Committee approval. Title changed from “Genetic Testing for Idiopathic Dilated Cardiomyopathy” to “Genetic Testing for Dilated Cardiomyopathy”. Coverage eligibility unchanged.
06/03/2021  Medical Policy Committee review
06/09/2021  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/02/2022  Medical Policy Committee review
06/08/2022  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/01/2023  Medical Policy Committee review
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06/14/2023 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 06/2024

Coding
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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>81403, 81405, 81406, 81407, 81439, 81479</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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</tbody>
</table>

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
   1. Consultation with technology evaluation center(s);
   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.
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NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.