Introduction

Muscular Dystrophies (MDs) are a group of inherited (genetic) diseases that affect muscle tissues throughout the body. The diseases cause the affected muscles to waste away (atrophy) and become weaker (myopathy) resulting in progressive disability that can range from mild to severe. This policy explains when genetic testing may be covered to help guide medical management and reproductive decision-making for four common muscular dystrophies: Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD, a variant of DMD), Facioscapulohumeral muscular dystrophy (FSHD) and Limb-girdle muscular dystrophy (LGMD).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Test</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne (DMD) and Becker (BMD) muscular</td>
<td>Genetic testing for the DMD gene variants may be considered medically necessary when the following criteria</td>
</tr>
</tbody>
</table>
### Test

**dystrophies (variant of DMD)**

### Medical Necessity

**are met:**

- In a male patient with signs and symptoms of a muscle disease (dystrophinopathy) and results of testing will confirm the diagnosis and guide the treatment plan

**Note:** Signs and symptoms may include late in learning to walk, as the disease gradually weakens the skeletal or voluntary muscles of the arms, legs, and trunk. Toddlers can easily fall over and have trouble getting up; enlarged calf muscle may be seen. Heart and respiratory muscles are affected as the disease progresses. Onset of symptoms for DMD is as early as 3 years of age; BMD is usually in the teens or early adulthood.

- In at-risk female relatives of the affected male (index patient) when:
  - Results of testing will confirm or exclude the need for monitoring heart function (cardiac surveillance)

  **AND/OR**

  Results of testing prior to conception (preconception testing) will provide information about the possibility of passing the gene variant to a child

- In at-risk, asymptomatic male offspring when:
  - Results of testing will confirm or exclude the need for monitoring medical status and heart function

**Note:** Females that are carriers of the trait with the variant in 1-copy of the gene (heterozygous) are at an increased risk for heart muscle disease (cardiomyopathy) and need routine follow-up and treatment.

At-risk females are first- and second-degree female relatives of the index patient (i.e., the index patient’s mother, female siblings, female offspring, maternal grandmother, and maternal aunts).

At-risk males are the offspring of a female carrier or male sibling (brother) of a patient with a DMD-associated dystrophinopathy.

*Genetic testing for the DMD gene variant is considered investigational when the above criteria are not met.*

<p>| Facioscapulohumeral | Genetic testing for FSHD gene variants may be considered |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td>muscular dystrophy (FSHD)</td>
<td>medically necessary in a patient with signs and symptoms of the muscle disease and results of testing will confirm the diagnosis.</td>
</tr>
<tr>
<td></td>
<td>Note: Signs and symptoms may include facial, shoulder blade, or upper arm weakness, and often weakness in the muscles on top of the foot that help with walking. Onset of symptoms is usually between 6-20 years of age.</td>
</tr>
<tr>
<td></td>
<td>Genetic testing for FSHD gene variants is considered investigational when the above criteria are not met.</td>
</tr>
<tr>
<td>Limb-girdle muscular dystrophy (LGMD)</td>
<td>Genetic testing for LGMD gene variants may be considered medically necessary when the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>• The patient has signs and symptoms of LGMD and results of testing will confirm the diagnosis</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>• At least one of the following criteria are met:</td>
</tr>
<tr>
<td></td>
<td>o Results of testing may lead to changes in medical management that improves outcomes (e.g., confirming or excluding the need to monitor heart function)</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>o Genetic testing will allow the affected patient to avoid invasive testing, including muscle biopsy</td>
</tr>
<tr>
<td></td>
<td>Note: Signs and symptoms may include walking with a broad-based stance due to weak hip/leg muscles, trouble getting up from a seated position or from the floor, trouble climbing stairs, difficulty reaching overhead, combing hair, or using a computer keyboard. Onset can begin between childhood and young adulthood.</td>
</tr>
<tr>
<td></td>
<td>Genetic testing for LGMD gene variants may be considered medically necessary for reproductive planning when:</td>
</tr>
<tr>
<td></td>
<td>• There is a diagnosis of LGMD in one or both of the parents</td>
</tr>
<tr>
<td></td>
<td>AND</td>
</tr>
<tr>
<td></td>
<td>• Results of testing prior to conception will provide information about the possibility of passing the gene variant to a child</td>
</tr>
</tbody>
</table>
Genetic testing for LGMD gene variants may be considered medically necessary in a patient without symptoms to determine future risk of disease when the following criteria are met:

- One first- or second-degree relative has a known variant consistent with LGMD (see Definition of Terms).

OR

- One first- or second-degree relative has a diagnosis of LGMD and their genetic variant status is unavailable (see Definition of Terms).

AND

- Results of testing will lead to changes in medical management that improves outcomes (e.g., confirming or excluding the need to monitor heart function).

Genetic testing for LGMD gene variants is considered investigational when the above criteria are not met.

**Coding**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, scanning or duplication/deletion variant of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
<tr>
<td>81408</td>
<td>Molecular pathology procedure, Level 9 (e.g., analysis of &gt;50 exons in a single gene by DNA sequence analysis) - includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy)</td>
</tr>
</tbody>
</table>
Definition of Terms

**Analytic Validity:** This refers to the technical accuracy of the test in detecting the presence or absence of a gene variant (such as a DNA sequence variant, chromosomal deletion, or biochemical indicator).

**At-risk females:** This refers to a first and second-degree female relative of the index patient (proband) and includes the index patient’s mother, sisters, daughters, maternal grandmother, and maternal aunts.

**At-risk:** This refers to having a greater chance (probability) of inheriting a specific gene variant based on family relationship. (See degrees of relationship definition)

**Carrier testing:** This test tells a patient if they “carry” a genetic change that can cause a disease. Carriers often do not show signs of the disorder but can pass the genetic variation to their children, who may develop the disorder or become carriers.

**Clinical Utility:** This refers to how the results of the diagnostic test will be used to change medical management and whether these changes lead to clinically important improvements in health outcomes. Clinical utility refers to the risks and benefits resulting from genetic test use.

**Clinical Validity:** This refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) to identify a particular clinical condition.

**Creatine kinase (CK) test:** CK is a muscle enzyme found in the brain, skeletal muscles and heart. An elevation in the CK level in the blood indicates muscle has been damaged, for example by a heart attack or a disorder such as a muscular dystrophy.

**Degrees of relationship:** This refers to close blood relatives on the same side of the family (mother or father). (see table below)
First-degree relatives | Parents, children, brothers and sisters
---|---
Second-degree relatives | Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half brothers and sisters
Third-degree relatives | Great grandparents, great aunts, great uncles, great grandchildren, and first cousins


**Duchenne and Becker muscular dystrophies:** These are two related genetic diseases, both affecting skeletal muscles causing leg and other weakness. While DMD often begins to show symptoms between age 2 to 5, Becker muscular dystrophy typically begins to show symptoms in the teen years. Both types of dystrophy may affect breathing muscles. Becker dystrophy also may affect the heart muscle whereas DMD does not. Both diseases cause the affected muscles to waste away (atrophy) and become weaker (myopathy). These two diseases occur more often in males than in females.

**Duchenne muscular dystrophy (DMD) gene:** This gene provides instructions for making a protein called dystrophin. (See dystrophin definition)

**Dystrophin:** A protein found in the sarcolemma of muscle cells that helps the cells remain intact. Genetic mutations may cause problems with dystrophin production, which can result in various muscular dystrophies including DMD and Becker muscular dystrophy.

**Dystrophinopathy:** A muscle disease resulting in progressive muscle degeneration and weakness caused by changes in the DMD gene that tells the body to make the protein dystrophin.

**Facioscapulohumeral muscular dystrophy:** This refers to a group of genetic diseases that affect the muscles in the face, the shoulder blades, and upper arms. The disease causes the affected muscles to waste away (atrophy) and become weaker (myopathy). Unlike some other forms of muscular dystrophy, this one typically does not affect the heart and breathing functions. It usually occurs in adolescence and early adulthood.

**Index case/patient:** The first affected family member who seeks medical care for a genetic disorder. This person may also be called the proband.

**Limb-girdle muscular dystrophy (LGMD):** A group of genetic diseases that primarily affect the voluntary muscles of the shoulders, upper arms, pelvic area and thighs. The disease causes muscles to waste away (atrophy) and become weaker. There are at least 19 forms of LGMD.

**Proband:** The first affected family member who seeks medical care for a genetic disorder. This person may also be called the index case.
Description

Muscular Dystrophies overview

Muscular dystrophies (MD) are a group of inherited muscle disorders with physical characteristics of progressive weakness and degeneration of skeletal muscle, cardiac muscle, or both; there may be respiratory muscle involvement or problems swallowing (dysphagia) and problems speaking (dysarthria) when facial muscles are affected. MDs are associated with a wide range of observable traits (phenotypes) that go from rapidly progressive weakness leading to death in the second or third decade of life to no clinical symptoms of the disease (asymptomatic disease) with an elevated blood level of creatine kinase (CK) as the main indicator. MDs have been classified based on signs and symptoms of the disorder and the genetic cause (etiology). The most common MDs are the dystrophinopathies (Duchenne (DMD) and Becker (BMD) muscular dystrophies) that are identified by variants in the dystrophin (DMD) gene.

Other MDs are differentiated by the location of muscle weakness in the body and include the limb-girdle muscular dystrophies (LGMD), facioscapulohumeral muscular dystrophies (FSHD), oculopharyngeal muscular dystrophies, distal muscular dystrophies, and humeroperoneal muscular dystrophies (also known as Emery-Dreifuss muscular dystrophy). The congenital muscular dystrophies are a genetically heterogeneous group of disorders, which historically included infants with weak muscle tone (hypotonia) at birth and findings of MD on biopsy. Finally, myotonic dystrophy is a multisystem disorder characterized by skeletal muscle weakness and muscle contraction/spasm (myotonia) in association with cardiac abnormalities, cognitive impairment, hormone gland disorder (endocrinopathies), and difficulty swallowing (dysphagia). This policy will focus on three common MDs.

Background

Duchenne (DMD) and Becker (BMD) muscular dystrophies

Variants in the DMD gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases, including the progressive diseases DMD and BMD. When the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure). Genetic testing can confirm a diagnosis and distinguish the less and more severe forms, as well as identify female carriers at risk for heart muscle disease.
Virtually all males with DMD or BMD have detectable DMD variants, indicating a high clinical sensitivity for genetic testing. Clinical utility of DMD gene testing can be established for the proband/index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between DMD and the less severe BMD. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

Direct evidence on the clinical utility of DMD gene testing in at-risk female relatives is lacking, but an indirect chain of evidence exists, as female carriers are at increased risk for dilated cardiomyopathy. Confirmation or exclusion of the variant helps with decisions about the need for routine follow-up of cardiac health status and can indicate the likelihood of a woman considering pregnancy to have a baby with the gene variant. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Facioscapulohumeral muscular dystrophy (FSHD)**

FSHD is an autosomal dominant disease that typically presents between the ages of 6 and 20 years. It is the third most common muscular dystrophy and involves progressive weakness and wasting of the facial muscles (facio), and shoulder and upper arm (scapulohumeral) muscles. The severity of the disease is highly variable, ranging from mildly affected, asymptomatic individuals to severely affected individuals, with approximately 20% of patients eventually requiring a wheelchair. FSHD affects males and females equally.

There is no direct evidence for the clinical utility of genetic testing for patients with suspected FSHD, as no studies were identified that described how a molecular diagnosis of FSHD changed patient management. However, a chain of evidence supports the use of D4Z4 contraction variant testing for suspected FSHD to establish a diagnosis, initiate therapies consistent with appropriate guidelines, and avoid a muscle biopsy in most cases.

**Limb-girdle muscular dystrophy (LGMD)**

The term limb-girdle muscular dystrophy is a clinical descriptor for a group of muscular dystrophies characterized by predominantly proximal muscle weakness (pelvic and shoulder girdles) which may be included in the differential diagnosis of DMD and BMD. Onset can be in childhood or adulthood. LGMD is classified based on its inheritance pattern and genetic cause into more than 31 different types. The degree of disability depends on the location and degree
of weakness. Some LGMD subtypes are characterized by only mild, slowly progressive weakness, while others are associated with early-onset, severe disease with loss of ambulation. LGMDs may be associated with cardiac dysfunction, cardiomyopathy (dilated or hypertrophic), respiratory depression, and dysphagia or dysarthria. Of particular note is the risk of cardiac complications, which is a feature of many but not all LGMDs. Most patients have an elevated creatine kinase (CK) level.

The genes involved with known forms of LGMD\textsuperscript{43-46} are either autosomal dominant or autosomal recessive and include the following:

**Autosomal dominant genes:** MYOT, LMNA, CAV3, DNAJB6, DES, TNPO3, HNRPDL

**Autosomal recessive genes:** CAPN3, DYSF, SGCG, SGCA, SGCB, SGCD, TCAP, TRIM32, FKR, TTN, POMT1, ANO5, FKTN, POMT2, POMGnT1, DAG1, PLEC1, DES, TRAPP11, GMPPB, ISP1, GAA, LIMS2

The clinical utility of testing for variants associated with LGMD for a patient with clinically suspected LGMD (index case) includes:

- Confirming the diagnosis of LGMD and initiating/directing treatment of the disease, including evaluation by a cardiologist/cardiac testing, respiratory function testing/monitoring, and prevention of secondary complications (e.g., through immunizations, physical therapy/bracing, fracture risk reduction).

- Avoidance of treatments that might be initiated for other neuromuscular disorders not known to be efficacious for LGMD, such as glucocorticoids for suspected dystrophinopathy or immunosuppressants for suspected myositis.

- Potential discontinuation of routine cardiac and respiratory surveillance in patients who have an identified variant not known to be associated with cardiac or respiratory dysfunction.

- Potential avoidance of invasive testing (e.g., muscle biopsy).

- Reproductive planning.

The clinical utility of testing for variants associated with LGMD for an at-risk family member (i.e., first- or second-degree relative of the index case) includes:

- Confirming or excluding the need for cardiac surveillance.

- Reproductive planning and decision-making prior to pregnancy, when results of testing will provide information about the possibility of passing the gene variant to a child.
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.

Benefit Application

Some plans may have contract or benefit exclusions for genetic testing.

Evidence Review

Duchenne (DMD) and Becker (BMD) muscular dystrophies

For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for DMD gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of Duchenne (DMD) and Becker muscular dystrophy (BMD). Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published studies of analytic validity are lacking, however, for deletion/duplication analysis by chromosomal microarray analysis and single nucleotide variants (SNVs) by full gene sequencing, analytic validity has been reported to be high (98%-99%), with false positives being rare. Virtually all males with DMD or BMD have identifiable DMD pathogenic variants, indicating a high clinical sensitivity for genetic testing. Clinical utility of DMD gene testing can be established for the index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between DMD and the less severe BMD. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.
For individuals who are female and are a relative of a patient with a DMD-associated dystrophinopathy who receive targeted DMD testing for a known familial variant to determine carrier status, the direct evidence is lacking. The primary outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for the analytic and clinical validity for testing for a known familial variant are lacking, but the validity is expected to be high. Direct evidence on the clinical utility of DMD gene testing in at-risk female relatives is lacking. However, the chain of evidence is strong, because determination of carrier status in a female for a DMD familial variant necessitates or eliminates the need for routine cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic male offspring of a female DMD familial variant carrier or asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy, the direct evidence is lacking. The primary outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for the analytic and clinical validity for testing for a known familial variant are lacking, but the validity is expected to be high. Direct evidence on the clinical utility of DMD gene testing in asymptomatic male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy is lacking. However, the chain of evidence is strong, because detection of the DMD familial variant necessitates or eliminates the need for increased medical monitoring or cardiac surveillance.1-20

Facioscapulohumeral Muscular Dystrophy

For individuals who get genetic testing for FSHD, the evidence supporting improved outcomes is generally lacking. Relevant outcomes are test accuracy, test validity, morbid events, functional outcomes, quality of life, and resource utilization. Test accuracy and validity have been reported to be high. A definitive diagnosis may end the need for additional testing in the etiologic workup, avoid the need for a muscle biopsy, as well as initiate and direct clinical management changes that can result in improved health outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.21-36
Limb-Girdle Muscular Dystrophies

The analytic validity of genetic testing for variants associated with limb-girdle muscular dystrophy (LGMD) is likely to be high. The true clinical sensitivity and specificity of genetic testing for LGMD in general cannot be determined. While the yield of genetic testing in patients with clinically suspected LGMD varies depending on the population characteristics (i.e., patients with only clinical symptoms versus patients with biopsy findings suggestive of LGMD), the available body of evidence suggests that the yield of testing is reasonably high. Genetic testing is generally considered the criterion standard for diagnosis of a specific LGMD subtype.

For patients with clinically suspected LGMD, there is the potential for clinical utility in genetic testing to confirm a diagnosis of LGMD and guide medical management and monitoring on the basis of a specific genetic diagnosis (including discontinuation of routine cardiac and/or respiratory surveillance if a specific genetic diagnosis not associated with these complications can be made), avoid therapies not known to be effective for LGMD, potentially avoid invasive testing, and allow reproductive planning. For at risk relatives of a proband, there is potential for clinical utility in genetic testing to identify the need for routine cardiac surveillance and allow reproductive planning. There is no direct evidence about the impact of genetic testing on outcomes, however an indirect chain of evidence indicates that the use of genetic testing in general may help patients avoid invasive testing and/or initiation of appropriate therapies, and the establishment of a specific genetic diagnosis can allow increased surveillance for cardiac dysfunction, for which there are effective medical- and device-based therapies.

The use of genetic testing for variants associated with LGMD may be considered medically necessary to confirm a diagnosis of LGMD in a patient with symptoms suspicious for the disease. In addition, testing for variants associated with LGMD may be considered medically necessary to identify a variant in an at-risk family member of a proband/index case when the results of testing may confirm or exclude the need for cardiac surveillance or inform reproductive decision making.37-70

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov found some trials that may relate to this policy listed in Table 1.
Table 1. Clinical trials for muscular dystrophies

<table>
<thead>
<tr>
<th>Genetic disorder</th>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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</thead>
<tbody>
<tr>
<td>DMD/BMD</td>
<td>NCT02780492</td>
<td>Developing Tools for Assessing the Natural History of Ambulant and Non-ambulant DMD Individuals to Assist in Antisense-oligomer Clinical Trials</td>
<td>80</td>
<td>Dec 2019</td>
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<tr>
<td>FSHD</td>
<td>NCT01437345</td>
<td>A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy</td>
<td>50</td>
<td>Aug 2018</td>
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<tr>
<td></td>
<td>NCT01970735</td>
<td>Clinical, Genetic and Epigenetic Characterization of Patients With FSHD Type 1/FSHD Type 2</td>
<td>100</td>
<td>Oct 2016</td>
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<tr>
<td>LGMD</td>
<td>NCT02810028</td>
<td>Acceptance and Commitment Therapy for Muscle Disease</td>
<td>154</td>
<td>Jul 2018</td>
</tr>
</tbody>
</table>

**Practice Guidelines and Position Statements**

*DMD/BMD*

**Consensus Best Practice Guidelines for Diagnosis of DMD/BMD**

A meeting of 29 senior scientists from the United States, Europe, India, and Australia established consensus Best Practice Guidelines for the molecular diagnosis of DMD/BMD. Recommendations for testing are:

- If there is a clinical suspicion of a dystrophinopathy, first screen for deletions and duplications.
• If no deletion or duplication is detected, but the clinical diagnosis is verified, screening for point variants should be performed.⁸

Recommendations from consensus Best Practice Guidelines for molecular diagnosis of DMD/BMD indicate that testing of an affected male (the index case) be performed so that carrier testing in female relatives at risk can focus on the variant found in the affected family member.

**FSHD**

**European Neuromuscular Centre International**

In a report from the 171st European Neuromuscular Centre International Workshop Standards of Care and Management of FSHD held in January 2010, it is stated that when a physician concludes facioscapulohumeral syndrome based on clinical findings, the odds are in favor of FSHD, and genetic testing is the preferred diagnostic choice.⁹

**American Academy of Neurology**

In 2015, the American Academy of Neurology published an evidence-based guideline summary for evaluation, diagnosis and management of facioscapulohumeral muscular dystrophy. ³⁴ They made the statement that at present, commercial genetic testing in FSHD is limited to FSHD1 testing and available genetic testing for FSHD type 1 is highly sensitive and specific. Their recommendations include the following:

• When clinical presentation of FSHD is typical and the inheritance pattern is consistent with autosomal dominant inheritance, clinical diagnosis is usually straightforward. If, in such circumstances, the diagnosis is genetically confirmed in a first-degree relative, genetic testing is not necessary for each affected individual.

• In the setting of atypical or sporadic cases, genetic confirmation is important for genetic counseling, especially with the recent discovery of two genetically distinct forms of FSHD.
  
  o Clinicians should obtain genetic confirmation of FSHD1 in patients with atypical presentations and no first-degree relatives with genetic confirmation of the disease (Level B).
For the diagnosis of LGMD:

- For patients with suspected muscular dystrophy, it is recommended that clinicians use a clinical approach to guide genetic diagnosis based on the clinical phenotype, including the pattern of muscle involvement, inheritance pattern, age at onset, and associated manifestations (e.g., early contractures, cardiac or respiratory involvement) (Level B recommendation).

- For patients with suspected muscular dystrophy when the initial clinically directed genetic testing does not provide a diagnosis, the recommendation is that clinicians obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole genome screening, or next-generation sequencing to identify the genetic abnormality (Level C recommendation).

For the management of cardiac complications in LGMD:

- Clinicians should refer newly diagnosed patients with (1) LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C–K, LGMD2M–P or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including ECG and structural evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management (Level B recommendation).

- If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management (Level B recommendation).

- Clinicians should refer muscular dystrophy patients with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation (Level B).
- It is not obligatory for clinicians to refer patients with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms (Level B recommendation).

For the management of respiratory complications in LGMD:

- Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course (Level B recommendation).

- In patients with a known high risk of respiratory failure (e.g., those with LGMD2I), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency (Level B recommendation).

- It is not mandatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic (Level C recommendation).

- Clinicians should refer muscular dystrophy patients with excessive daytime somnolence, nonrestorative sleep (e.g., frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life (Level B recommendation).

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be
licensed by 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.

References


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/13/14</td>
<td>Annual Review. Policy updated with literature review through January 29, 2014. No change to policy statement. References 11, 14, 17, and 18 added.</td>
</tr>
<tr>
<td>05/27/15</td>
<td>Annual Review. Policy updated with literature review through February 23, 2015; references 19-21 added; reference 19 deleted. Policy statements unchanged. Language added to Benefit Application regarding testing index patient/case. Phrase “index patient” substituted for “proband.” ICD-9 diagnosis codes 783.9 and V26.31 removed; they are not specific to the policy.</td>
</tr>
<tr>
<td>09/01/15</td>
<td>Update Related Policies. Add 12.04.132.</td>
</tr>
<tr>
<td>01/01/17</td>
<td>Interim Update, approved December 13, 2016. Combined content from policies 12.04.86, 12.04.105, 12.04.132 into this one policy document. Title changed. Genetic testing for the muscular dystrophies detailed in this policy may be considered medically necessary when criteria are met. No change to policy statements. References older than 2006 were removed. Removed CPT code 81161. Moved policy to new format.</td>
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<tr>
<td>05/01/17</td>
<td>Annual review, approved April 11, 2017. Policy statement added for DMD testing for male offspring of female carriers and asymptomatic brothers of affected siblings. Policy updated with literature review through January 2017; reference 21 added. The policy is revised with genetics nomenclature, “mutations” changed to “variants” when applicable.</td>
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</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

阿拉伯 (Arabic):
يعيد هذا الإشعار المعلومات المهمة. قد يعطي هذا الإشعار معلومات هامة لمراقبة طبي. قد تكون هناك تراخيص للعذاب. Premera Blue Cross قبل أن تصدر هذه المعلومات والمساعدة بناءً على متطلبات أحد تراخيصه. إذاً، لحوالي تطور هذه المعلومات والمساعدة بناءً على متطلبات أحد تراخيصه. إتصل 800-722-1471 (TTY: 800-842-5357) للعذاب.

中文 (Chinese):
本通知有重要的讯息。本通知可能有关於您透过 Premera Blue Cross 提交的申索或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前采取行动，以保留您的健康保险或者费用补贴。您有权利免费以您的母语得到本讯息和帮助。请拨电话 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalini nga adda ket naglaon iti napateg nga impormasion maipanggpe ngiaplaksyon wu wow coverage babaen ti Premera Blue Cross. Daytoy ket mabalini dagiti importante a pelta iti daytoy a pakdaar. Mabalini nga adda rumbeng nga aramindegi nga adda sakbay dagiti partikular a naituding nga adaw tapno mapagtalaineyo ti coverage ti salun-atyo wu wow coverage babaen iti pakdaar. Adda barbaa tagi a mangala ti daytoy nga impormasion ken tung bangdayo a pagasao nga awan ti bayadan. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).