Genetic Testing for Muscular Dystrophies

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.
<table>
<thead>
<tr>
<th>Test</th>
<th>Medical Necessity</th>
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| Duchenne (DMD) and Becker (BMD) muscular dystrophies | **Genetic testing for the DMD gene variants may be considered medically necessary when any of the following criteria 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: delay 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 muscles 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**) (see **Note** below for definition of “at-risk”) 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 (see **Note** below for definition of “at-risk”) 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.  
  **Index patient:** The first affected family member who seeks medical care for a genetic disorder. This person may also be called the proband.  

**Genetic testing for the DMD gene variants is considered investigational when the above criteria are not met.**
<table>
<thead>
<tr>
<th>Test</th>
<th>Medical Necessity</th>
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| **Facioscapulohumeral muscular dystrophy (FSHD)** | Genetic testing for FSHD gene variants may be considered medically necessary in a patient with signs and symptoms* of the muscle disease and results of testing will confirm the diagnosis.  

*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.  

Genetic testing for FSHD gene variants is considered investigational when the above criteria are not met. |
| **Limb-girdle muscular dystrophy (LGMD)** | Genetic testing for LGMD gene variants may be considered medically necessary when the following criteria are met:  

- The patient has signs or symptoms* of LGMD and results of testing will confirm the diagnosis  

*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.  

AND  

- At least one of the following criteria is met:  
  - Results of testing may lead to changes in medical management that improves outcomes (eg, confirming or excluding the need to monitor heart function)  
  - Genetic testing will allow the affected patient to avoid invasive testing, including muscle biopsy  

Genetic testing for LGMD gene variants may be considered medically necessary for reproductive planning when:  

- There is a diagnosis of LGMD in one or both of the parents  

AND  

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

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
Test | Medical Necessity
---|---
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 improve outcomes (eg, 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.**

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**Documentation Requirements**

The medical records submitted for review should document that medical necessity criteria are met, including:

• Detailed history and physical supporting that patient has signs and symptoms or is at direct risk of inheriting the genetic disease in question

AND

• Documentation that the result of the test will be used in confirming the diagnosis and guide the treatment plan or for reproductive planning

AND

• For patients without symptoms, also include interpretation of family and medical histories to assess the probability of disease occurrence or recurrence

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**Coding**
<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</td>
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<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, 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 (eg, 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 (eg, 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 (eg, analysis of &gt;50 exons in a single gene by DNA sequence analysis) - includes DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy), full gene sequence</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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Note:  CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

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 (see Table 1). The Society’s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.
Table 1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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>
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</table>

Table 2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<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>

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding of risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
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 or 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.

<table>
<thead>
<tr>
<th>First-degree relatives</th>
<th>Parents, children, brothers and sisters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-degree relatives</td>
<td>Grandparents, aunts, uncles, nieces, nephews, grandchildren, and half brothers and sisters</td>
</tr>
<tr>
<td>Third-degree relatives</td>
<td>Great grandparents, great aunts, great uncles, great grandchildren, and first cousins</td>
</tr>
</tbody>
</table>


**Duchenne and Becker muscular dystrophies:** These are two related genetic diseases, both affecting skeletal muscles causing leg and other muscle weaknesses. 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, those surrounding the shoulder blades, and the 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.

**Benefit Application**

Some plans may have contract or benefit exclusions for genetic testing.
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 dystrophy (FSHD), oculopharyngeal muscular dystrophy, distal muscular dystrophy, and humeroperoneal muscular dystrophy (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.

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 and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less from more severe forms, as well as identify female carriers at risk.
**Facioscapulohumeral muscular dystrophy (FSHD)**

FSHD is an autosomal dominant disease that typically presents before the age of 20 years with the weakness of the facial muscles and the scapular stabilizer muscles. The usual clinical course is a slowly progressive weakness, although the severity is highly variable, and atypical presentations occur. Genetic testing for FSHD has been evaluated as a tool to confirm the diagnosis.

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

The limb-girdle muscular dystrophies (LGMDs) are a genetically heterogeneous group of muscular dystrophies characterized by predominantly proximal muscle weakness (pelvic and shoulder girdles). A large number of genetic variants have been associated with LGMDs.

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. Based on its inheritance pattern and genetic cause, LGMD is classified 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.

LGMDs have an estimated prevalence ranging from 2.27 to 4 per 100,000 in the general population, constituting the fourth most prevalent muscular dystrophy type after the dystrophinopathies (DMD and BMD), facioscapulohumeral muscular dystrophy, and myotonic dystrophy. The prevalence of specific types increases in populations with founder pathogenic variants (eg, Finland, Brazil).

Evaluation and diagnosis of LGMD should be carried out by providers with expertise in neuromuscular disorders. The 2014 guidelines from the American Academy of Neurology (AAN) and American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) on treatment of LGMD recommend that “clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (eg, physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and
Background

Dystrophinopathies

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine kinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, the disease is classified as Duchenne (DMD) or Becker muscular dystrophy (BMD); when the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

Duchenne (DMD) and Becker (BMD) Muscular Dystrophies

Duchenne Muscular Dystrophy

DMD, the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene. According to a 2014 systematic review, the incidence of DMD ranges from 1 in 3600 to 1 in 9300 male births. Approximately one-third of DMD cases arise from de novo variants and have no known family history. Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool, from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child’s motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. Most patients will be wheelchair bound by ages 9 to 12 years, but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (eg, decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe
complications commonly appear in the second decade of life and eventually lead to death.\(^1\) Few individuals with DMD survive beyond the third decade.

**Becker Muscular Dystrophy**

BMD is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s.\(^3\)

**Female Carriers**

Females heterozygous for a DMD disease-associated variant can manifest symptoms of the disease.\(^4\) An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from a mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy.\(^5\) Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous women do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated DMD gene in the affected X chromosome.\(^6\) In some cases, this compensation can be reversed by a nonrandom or skewed inactivation of X chromosome, resulting in greater expression of the affected X chromosome and some degree of myopathic features.\(^7\) Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the DMD gene and complete or partial absence of the X chromosome (Turner syndrome).\(^4\)

**Clinical Diagnosis**

**Duchenne Muscular Dystrophy**

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or detection of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties rising from the floor or tip-toe walking, and pseudo hypertrophy of the calves. A clinical examination may reveal
decreased or lost muscle reflexes and, commonly, a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5000 IU/L and 150,000 IU/L), is nonspecific to DMD but is always present in affected patients.1 Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests are may not be necessary for assessment of DMD.8 An open skeletal muscle biopsy is needed when a test for deletions or duplications of the DMD gene is negative. The biopsy will provide general signs of muscular dystrophy, including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

**Becker Muscular Dystrophy**

BMD is clinically similar to DMD but is milder and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5-100 times the normal level).

**Molecular Diagnosis**

DMD is the only gene of which variants are known to cause DMD, BMD, and DMD-associated cardiomyopathy. Molecular genetic testing of DMD can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males. The gene that codes for dystrophin is the largest known human gene.1 A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5000 reported disease-associated variants, as well as a high spontaneous de novo variant rate.9

**Treatment**

There is no cure for DMD or BMD. Treatment is aimed at controlling symptoms to improve quality of life. However, the natural history of the disease can be changed by strategies such as
corticosteroid therapy, proper nutrition, or rehabilitative interventions. Glucocorticoids were shown in a 1991 randomized controlled trial to prolong the period of independent ambulation by 3 years.\textsuperscript{10} The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways.\textsuperscript{1} Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at 2 to 5 years of age, although there has been no demonstrated benefit of therapy before 5 years of age.\textsuperscript{1}

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants.\textsuperscript{11} Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient’s phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials and an exon-skipping therapy using antisense oligonucleotides (eteplirsen [Exondys 51]) has been approved for treatment for patients who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping.\textsuperscript{12}

**Facioscapulohumeral Muscular Dystrophy**

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy and involves progressive weakness and wasting of the facial muscles (facio) as well as shoulder and upper arm (scapulohumeral) muscles. The weakness is often most evident in muscles of the face, resulting in difficulty smiling, whistling, and reduced facial expression. The weakness in the shoulder muscles causes the scapula to protrude from the back (“w wings of the scapula”). The muscles are typically affected asymmetrically, and with progression, the lower extremities, both proximal and distal, become involved.\textsuperscript{1} 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 for mobility. Nonmuscular manifestations include retinal vascular abnormalities that can result in significant loss of vision; however, only about 1% of patients with FSHD experience visual acuity loss.\textsuperscript{1} Most people with FSHD eventually develop high-frequency hearing loss, which is usually not noticeable and only detected by an audiogram. FSHD usually presents between the ages of 6 and 20 years, and life expectancy is not shortened. It is estimated that 4 to 5 people per 100,000 population have FSHD. FSHD affects males and females equally.
FSHD Diagnosis

FSHD has a characteristic distribution of muscle involvement that often can lead to targeted genetic testing without the need for a muscle biopsy.\(^2\) However, atypical presentations have been reported, which include scapulohumeral dystrophy with facial sparing.\(^3,4\) A 2012 retrospective review of an academic center database for the period 1996 to 2011 determined that, of 139 genetically confirmed FSHD cases, 7 had atypical disease, including late age of onset of disease, focal weakness, and dyspnea.\(^5\)

Electromyography and muscle biopsy to confirm the clinical diagnosis of FSHD have largely been supplanted by genetic testing. Electromyography usually shows mild myopathic changes, and muscle biopsy most often shows nonspecific chronic myopathic changes.

FSHD Genetics

FSHD is likely to be caused by inappropriate expression of the DUX4 gene in muscle cells. DUX4 is a double homeobox-containing gene (a homeobox gene being one in a large family of genes that direct the formation of many body structures during early embryonic development). DUX4 lies in the macrosatellite repeat D4Z4, which is on chromosome 4q35. D4Z4 has a length of 11 to 100 repeat units on normal alleles. The most common form of FSHD (95%) is designated FSHD type 1 (FSHD1), and individuals with FSHD1 have a D4Z4 allele of between 1 and 10 repeat units.\(^3\) There is no absolute linear and inverse correlation between residual repeat size, disease severity, and onset; however, patients with repeat arrays of 1 to 3 units usually have an infantile onset and rapid progression.\(^1\)

The remaining 5% of patients who do not have FSHD1 are designated as FSHD2, which is clinically indistinguishable from FSHD1. Patients with FSHD2 show loss of DNA methylation and heterochromatin markers at the D4Z4 repeat that are similar to patients with D4Z4 contractions (FSHD1), suggesting that a change in D4Z4 chromatin structure unifies FSHD1 and FSHD2. Variants in the SMCHD1 gene on chromosome 18, which encodes a protein known as structural maintenance of chromosomes flexible hinge domain containing 1, have been associated with FSHD2. Reductions in SMCHD1 gene product levels have been associated with D4Z4 contraction-independent DUX4 expression, suggesting that SMCHD1 acts as an epigenetic modifier of the D4Z4 allele.\(^6\) SMCHD1 has also been identified as a possible modifier of disease severity in patients with FSHD1.\(^7\)
FSHD is inherited in an autosomal dominant manner. Approximately 70% to 90% of individuals inherit the disease-causing deletion from a parent, and 10% to 30% have FSHD as a result of a de novo deletion. On average, de novo variants are associated with larger contractions of D4Z4 compared with the degree of D4Z4 contraction variants observed segregating in families, and individuals with de novo variants tend to have findings at the more severe end of the phenotypic spectrum.3

**FSHD Treatment**

There is currently no treatment or preventive therapy to control symptoms of FSHD. Clinical management is directed at surveillance to identify possible FSHD-related complications, such as hearing loss, and to improve quality of life (eg, assist devices, physical therapy, orthoses to improve mobility and prevent falls).

**Commercially Available Testing for FSHD**

The methodology for testing for FSHD1 uses pulsed-field gel electrophoresis and Southern blot to detect deletions on chromosome 4q35. Laboratories that offer FSHD1 testing include Athena Diagnostics and the University of Iowa Diagnostic Laboratories.

At least 1 commercial laboratory (Prevention Genetics, Marshfield, WI) was identified that offers testing for FSHD2 through sequencing of the SMCHD1 gene via bidirectional Sanger sequencing. Prevention Genetics also offers testing for FSHD2 through next-generation sequencing of the SMCHD1 gene as part of a panel test for limb-girdle muscular dystrophy.

**Testing Strategy**

Because 95% of cases of FSHD are FSHD type 1 (FSHD1), genetic testing for FSHD should begin with testing for contraction in the macrosatellite repeat D4Z4 on chromosome 4q35 using Southern blot analysis. Depending on the index of suspicion for FSHD, if FSHD1 testing is negative, testing for FSHD2, including D4Z4 methylation analysis and testing of the SMCHD1 gene, could be considered.
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 (ie, 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, genetic testing may have potential clinical utility. Having confirmed a specific genetic diagnosis of LGMD may allow the provider to guide medical management and decide whether routine cardiac and/or respiratory monitoring would be appropriate, based on whether the specific gene that was found is associated with these complications. The provider may also avoid therapies not known to be effective for LGMD, potentially avoid invasive testing, and allow informed reproductive planning. For at risk relatives of a proband, genetic testing may help to identify the need for routine cardiac surveillance and allow informed reproductive planning. There is no direct evidence about the impact of genetic testing on outcomes. However, an indirect chain of evidence indicates that genetic testing in general may help patients avoid invasive testing and/or the initiation of appropriate therapies. Establishing a specific genetic diagnosis can also allow increased surveillance for cardiac dysfunction, for which there are effective medical- and device-based therapies.

Doing 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.

Genetic Basis and Clinical Correlation

As the genetic basis of the LGMDs has been elucidated, it has been recognized that there is tremendous heterogeneity in genetic variants that cause the LGMD phenotype. LGMDs were initially classified based on a clinical and locus-based system. As of 2015, at least 9 autosomal dominant types (designated LGMD1A through LGMD1H) and at least 23 autosomal recessive types (designated LGMD2A through LGMD2W) have been identified. Subtypes vary in inheritance, pathophysiology, age of onset, and severity. Table 1 summarizes involved gene and
protein, clinical characteristics (if known), and proportions of all cases represented by a specific genotype (if known).

**Table 3. Summary of Genetic Basis of LGMD**

<table>
<thead>
<tr>
<th>LGMD Type</th>
<th>Involved Gene</th>
<th>Involved Protein</th>
<th>Age at Onset</th>
<th>Rate of Progression</th>
<th>Cardiac Involvement?</th>
<th>Percent AR LGMD Cases</th>
</tr>
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<tbody>
<tr>
<td>Autosomal dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1A</td>
<td><em>MYOT</em></td>
<td>Myotilin</td>
<td>Adulthood</td>
<td>Slow</td>
<td>Yes</td>
<td></td>
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<tr>
<td>1B⁺</td>
<td><em>LMNA</em></td>
<td>Lamin A/C</td>
<td>Adolescence or variable</td>
<td>Slow</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>1C⁺</td>
<td><em>CAV3</em></td>
<td>Caveolin-3</td>
<td>Variable</td>
<td>Slow</td>
<td>Yes</td>
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<tr>
<td>1D</td>
<td><em>DNAJB6</em></td>
<td>DNAJ/Hsp40 homolog</td>
<td>Adulthood</td>
<td>Slow</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>1E</td>
<td><em>DES</em></td>
<td>Desmin</td>
<td>Adulthood</td>
<td>Slow</td>
<td>Yes</td>
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</tr>
<tr>
<td>1F</td>
<td><em>TNPO3</em></td>
<td>Transportin3</td>
<td>Variable</td>
<td>Slow</td>
<td>No</td>
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<td>1G</td>
<td><em>HNRPDL</em></td>
<td>Heterogeneous nuclear ribonucleoprotein D-like protein</td>
<td>Adulthood</td>
<td>Slow</td>
<td>No</td>
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<tr>
<td>1H</td>
<td></td>
<td></td>
<td>Variable</td>
<td>Slow</td>
<td>No</td>
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<td>Autosomal recessive</td>
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<td>2A</td>
<td><em>CAPN3</em></td>
<td>Calpain 3</td>
<td>Adolescence to adulthood</td>
<td>Moderate</td>
<td>Rare</td>
<td>≈10% to ≈40%</td>
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<tr>
<td>2B</td>
<td><em>DYSF</em></td>
<td>Dysferlin</td>
<td>Adolescence to adulthood</td>
<td>Slow</td>
<td>Yes</td>
<td>≈5% to ≈25%</td>
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<td>2C</td>
<td><em>SGCG</em></td>
<td>γ-sarcoglycan</td>
<td>Early childhood</td>
<td>Rapid</td>
<td>Yes</td>
<td>68% with childhood onset; ≈10% with adult onset</td>
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<td>2D</td>
<td><em>SGCA</em></td>
<td>α-sarcoglycan</td>
<td>Early childhood</td>
<td>Rapid</td>
<td>Yes</td>
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<td>2E</td>
<td><em>SGCB</em></td>
<td>β-sarcoglycan</td>
<td>Early childhood</td>
<td>Rapid</td>
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<td>2F</td>
<td><em>SGCD</em></td>
<td>δ-sarcoglycan</td>
<td>Early childhood</td>
<td>Rapid</td>
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<td>2G</td>
<td><em>TCAP</em></td>
<td>Telethonin</td>
<td>Adolescence</td>
<td>Slow</td>
<td>Yes</td>
<td>3%</td>
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<td>2H</td>
<td><em>TRIM32</em></td>
<td>Tripartite motif containing 32</td>
<td>Adulthood</td>
<td>Slow</td>
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<tr>
<td>2I</td>
<td><em>FKRP</em></td>
<td>Fukutin-related protein</td>
<td>&lt;10 to &gt;40 y</td>
<td>Moderate</td>
<td>Yes</td>
<td>6%</td>
</tr>
<tr>
<td>LGMD Type</td>
<td>Involved Gene</td>
<td>Involved Protein</td>
<td>Age at Onset</td>
<td>Rate of Progression</td>
<td>Cardiac Involvement?</td>
<td>Percent AR LGMD Cases</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>-----------------</td>
<td>--------------</td>
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<td>----------------------</td>
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<tr>
<td>2J</td>
<td>TTN</td>
<td>Titin</td>
<td>Late childhood or variable</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2K</td>
<td>POMT1</td>
<td>Protein-O-mannosyltransferase 1</td>
<td>Childhood</td>
<td>Slow</td>
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<td></td>
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<td>2L</td>
<td>ANOS5</td>
<td>Anoctamin-5</td>
<td>Variable</td>
<td>Slow</td>
<td>No</td>
<td>25% in U.K.</td>
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<td>2M</td>
<td>FKTN</td>
<td>Fukutin</td>
<td>Early childhood</td>
<td>Slow/moderate</td>
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<tr>
<td>2N</td>
<td>POMT2</td>
<td>Protein-O-mannosyltransferase 2</td>
<td>Early childhood</td>
<td>Slow/moderate</td>
<td>Rare</td>
<td></td>
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<tr>
<td>2O</td>
<td>POMGnT1</td>
<td>Protein O-linked mannose beta1, 2-Nacetyl-glucosaminyl-transferase</td>
<td>Late childhood</td>
<td>Moderate</td>
<td>No</td>
<td></td>
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<tr>
<td>2P</td>
<td>DAG1</td>
<td>Dystroglycan</td>
<td>Early childhood</td>
<td>Moderate</td>
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<td>2Q</td>
<td>PLEC1</td>
<td>Plectin</td>
<td>Early childhood</td>
<td>Slow</td>
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<tr>
<td>2R</td>
<td>DES</td>
<td>Desmin</td>
<td>Young adulthood</td>
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<td>2S</td>
<td>TRAPPC11</td>
<td>Transport protein particle complex 11</td>
<td>Young adulthood</td>
<td>Slow</td>
<td>No</td>
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</tr>
<tr>
<td>2T</td>
<td>GMPPB</td>
<td>GDP-mannose pyrophosphorylase B</td>
<td>Early childhood to young adulthood</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
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<td>2U</td>
<td>ISPD</td>
<td>Isoprenoid synthase domain containing</td>
<td>Variable</td>
<td>Moderate/rapid</td>
<td>Yes</td>
<td></td>
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<tr>
<td>2V</td>
<td>GAA</td>
<td>Glucosidase, α-1</td>
<td>Variable</td>
<td>Variable</td>
<td>Yes</td>
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<tr>
<td>2W</td>
<td>LIMS2</td>
<td>Lim and senescent cell antigen-like domains 2</td>
<td>Childhood</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>


The prevalence of different variants and LGMD subtypes can differ widely by country, but the autosomal recessive forms are generally more common. Pathogenic variants in CAPN3 represent 20% to 40% of LGMD cases, and LGMD2A is the most frequent LGMD in most countries. DYSF pathogenic variants leading to LGMD2B are the second most common LGMD in many, but not all, areas (15%-25%). Sarcoglycanopathies constitute about 10% to 15% of all LGMDs, but 68% of the severe forms.
In an evaluation of 370 patients with suspected LGMD enrolled in a registry from 6 U.S. university centers, 312 of whom had muscle biopsy test results available, Moore et al (2006) reported on the distribution of LGMD subtypes based on muscle biopsy results as follows: 12% LGMD2A, 18% LGMD2B, 15% LGMD2C-2F, and 1.5% LGMD1C.  

Clinical Variability

Other than presentation with proximal muscle weakness, LGMD subtypes can have considerable clinical variability regarding weakness severity and associated clinical conditions. The sarcoglycanopathies (LGMD2C-2F) cause a clinical picture similar to that of the intermediate forms of DMD and BMD, with the risk of cardiomyopathy in all forms of the disease.

Of particular clinical importance is that fact while most, but not all, LGMD subtypes are associated with an increased risk of cardiomyopathy, arrhythmia, or both, the risk of cardiac disorders varies across subtypes. LGMD1A, LGMD1B, LGMB2C-K, and LGMD2M-P have all been associated with cardiac involvement. Sarcoglycan variants tend to be associated with severe cardiomyopathy. Similarly, patients with the LGMD subtypes of LGMD2I and 2C-2F are at higher risk of respiratory failure.

Many genes associated with LGMD subtypes have allelic disorders, both with neuromuscular disorder phenotypes and clinically unrelated phenotypes. Variants in the lamin A/C proteins, which are caused by splice-site variants in the LMNA gene, are associated with different neuromuscular disorder phenotypes, including Emery-Dreifuss muscular dystrophy, a clinical syndrome characterized by childhood-onset elbow, posterior cervical, and ankle contractures and progressive humeroperoneal weakness, autosomal dominant LGMD (LGMD1B), and congenital muscular dystrophy. All forms have been associated with cardiac involvement, including atrial and ventricular arrhythmias and dilated cardiomyopathy.

Clinical Diagnosis

A diagnosis of LGMD is suspected in patients who have myopathy in the proximal musculature in the shoulder and pelvic girdles, but the distribution of weakness and the degree of involvement of distal muscles varies, particularly early in the disease course. Certain LGMD subtypes may be suspected by family history, patterns of weakness, CK levels, and associated clinical findings. However, there is considerable clinical heterogeneity and overlap across the LGMD subtypes.
Without genetic testing, diagnostic evaluation can typically lead to a general diagnosis of an LGMD, with limited ability to determine the subcategory. Most cases of LGMD will have elevated CK levels, with some variation in the degree of elevation based on subtype. Muscle imaging with computed tomography or magnetic resonance imaging may be obtained to assess areas of involvement and guide muscle biopsy. Magnetic resonance imaging or computed tomography may be used to evaluate patterns of muscle involvement. At least for calpainopathy (LGMD2A) and dysferlinopathy (LGMD2B), magnetic resonance imaging may show patterns distinct from other neuromuscular disorders, including hyaline body myopathy and myotonic dystrophy. In a study (2012) that evaluated muscle computed tomography in 118 patients with LGMD and 32 controls, there was generally poor overall interobserver agreement (κ=0.27), and low sensitivity (40%) and specificity (58%) for LGMD.

Electromyography has limited value in LGMD, although it may have clinical utility if there is a clinical concern for type III spinal muscular atrophy. Electromyography typically shows myopathic changes with small polyphasic potentials.

A muscle biopsy may be used in suspected LGMD to rule out other, treatable causes of weakness (in some cases), and to attempt to identify an LGMD subtype. All LGMD subtypes are characterized on muscle biopsy by dystrophic features, with degeneration and regeneration of muscle fibers, variation in fiber size, fiber splitting, increased numbers of central nuclei, and endomysial fibrosis. Certain subtypes, particularly in dysferlin deficiency (LGMD2B), may show inflammatory infiltrates, which may lead to an inaccurate diagnosis of polymyositis.

Following standard histologic analysis, immunohistochemistry and immunoblotting are typically used to evaluate myocyte protein components, which may include sarcolemma-related proteins (eg, α-dystroglycan, sarcoglycans, dysferlin, caveolin-3), cytoplasmic proteins (eg, calpain-3, desmin), or nuclear proteins (eg, lamin A/C). Characteristic findings on muscle biopsy immunostaining or immunoblotting can be seen for calpainopathy (LGMD2A), sarcoglycanopathies (LGMD2C-2F), dysferlinopathy (LGMD2B), and O-linked glycosylation defects (dystroglycanopathies; LGMD2I, LGMD2K, LGMD2M, LGMD2O, LGMD2N). However, muscle biopsy is imperfect: secondary deficiencies in protein expression can be seen in some LGMD. In the 2006 Moore study (previously described), 9% of all muscle biopsy samples had reduced expression of more than 1 protein tested. In some variants, muscle immunohistochemistry results may be misleading because the variant leads to normal protein amounts but abnormal function. For example, Western blot analysis for calpain-3, with loss of all calpain-3 bands, may be diagnostic of LGMD2A, but the test is specific but not sensitive, because some LGMD2A patients may retain normal amounts of nonfunctional protein.
A blood-based dysferlin protein assay, which evaluates dysferlin levels in peripheral blood CD14-positive monocytes, has been evaluated in a sample of 77 individuals with suspected dysferlinopathy. However, the test is not yet in widespread use.

**Treatment**

At present, no therapies have been clearly shown to slow the progression of muscle weakness for the LGMDs. Treatment is focused on supportive care to improve muscle strength, slow decline in strength, preserve ambulation and treat and prevent musculoskeletal complications that may result from skeletal muscle weakness (eg, contractures, scoliosis). Clinical management guidelines are available from the American Academy of Neurology and Association of Neuromuscular & Electrodiagnostic Medicine (see Practice Guidelines and Position Statements section).

**Monitoring for Complications**

Different genetic variants associated with clinical LGMD are associated with different rates of complications and the speed and extent of disease progression.

Monitoring for respiratory depression and cardiac dysfunction is indicated for LGMD subtypes associated with respiratory or cardiac involvement because patients are often asymptomatic until they have significant organ involvement. When respiratory depression is present, patients may be candidates for invasive or noninvasive mechanical ventilation. Treatments for cardiac dysfunction potentially include medical or device-based therapies for heart failure or conduction abnormalities.

Patients may need monitoring and treatment for swallowing dysfunction if it is present, along with physical and occupation therapy and bracing for management of weakness.

**Investigational Therapies**

A number of therapies are under investigation for LGMD. Glucocorticoids have been reported to have some benefit in certain subtypes (LGMD2D, LGMD2I, LGMD2L). However, a small (N=25) randomized, double-blind, placebo-controlled trial (2013) of the glucocorticoid deflazacort in patients with genetically confirmed LGMD2B (dysferlinopathy) showed no benefit and a trend toward worsening strength associated with deflazacort therapy.12 Autologous bone marrow
transplant has been investigated for LGMD but is not in general clinical use.13 Adeno-associated virus-mediated gene transfer to the extensor digitorum brevis muscle has been investigated in LGMD2D, and in a phase 1 trial in LGMD2C.14 Exon-skipping therapies have been investigated as a treatment for dysferlin gene variants (LGMD2B) given the gene’s large size.

**Molecular Diagnosis**

Because most variants leading to LGMD are single nucleotide variants, the primary method of variant detection is gene sequencing using Sanger sequencing or next-generation sequencing (NGS) methods. In cases in which an LGMD is suspected, but gene sequencing is normal, deletion and duplication analysis through targeted comparative genomic hybridization or multiplex ligation-dependent probe amplification may also be obtained.

A number of laboratories offer panels of tests for LGMD that rely on Sanger sequencing or NGS. The following list is not exhaustive.

- **GeneDx** offers the Limb-Girdle Muscular Dystrophy Panel.15 This panel uses NGS and reports only on panel genes, with concurrent targeted array comparative genomic hybridization (aCGH) analysis to evaluate for deletions and duplications for most genes (exceptions, GMPPB and TNPO3). Multiplex polymerase chain reaction assay is performed to assess for the presence of the 3 untranslated region insertion in the FKTN gene. All reported sequence variants are confirmed by conventional di-deoxy DNA sequence analysis, quantitative polymerase chain reaction, multiplex ligation-dependent probe amplification, repeat polymerase chain reaction analysis, or another appropriate method.

- **Prevention Genetics** offers several LGMD tests.16,17 They include an autosomal dominant LGMD Sanger sequencing panel, which includes MYOT, LMNA, DNAJB6, and CAV3 sequencing either individually or as a panel, followed by aCGH for deletions and duplications. The company also offers an autosomal recessive LGMD Sanger sequencing panel, which includes sequencing of SGCG, SGCA, SGCB, SGCD, TRIM32, CAPN3, DYSF, FKRP, TTN, TCAP, GMPPB, ANO5, and TRAPPC11, either individually or as a panel, followed by aCGH for deletions/duplications. Also, Prevention Genetics offers 2 NGS panels for LGMD, which involve NGS followed by aCGH if the variant analysis is negative. Additional Sanger sequencing is performed for any regions not captured or with an insufficient number of sequence reads. All pathogenic, undocumented and questionable variant calls are confirmed by Sanger sequencing.

  - **Counsyl** offers a Foresight™ Carrier Screen, which includes testing for multiple diseases that may require early intervention or cause shortened life or intellectual disability and is designed as a carrier test for reproductive planning. Testing for LGMD2D and LGMD2E
may be added to the panel. Testing is conducted by NGS, without evaluation for large duplications or deletions.

- Centogene (Rostock) offers an NGS panel for LGMD, which includes sequencing of the included variants (with hot spot testing for *TTN*), followed by deletion and duplication testing by multiplex ligation–dependent probe amplification (if ordered), with whole exome sequencing if no variants are identified.18
- Athena Diagnostics offers NGS testing for *FKRP*, *LMNA*, *DYSF*, *CAV3*, and *CAPN3* (NGS followed by dosage analysis), along with an NGS panel, with deletion and duplication testing for SGCA, SGCG, and *CAPN3*.

Variants included in some of the currently available NGS testing panels are summarized in Table 4.

Table 4. LGMD Variants Included in Commercial NGS Test Panels

<table>
<thead>
<tr>
<th>Gene</th>
<th>GeneDx</th>
<th>Prevention Genetics</th>
<th>Centogene</th>
<th>Athena Diagnostics&lt;sup&gt;b&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Autosomal Dominant&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Autosomal Recessive</td>
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LGMD: limb-girdle muscular dystrophy; NGS: next-generation sequencing.\(^a\) This panel also includes testing for \(SMCHD1\), which is associated with facioscapulohumeral muscular dystrophy.\(^b\) This panel also includes testing for \(PNPLA2\), which is associated with neutral lipid storage disease with myopathy, and \(TOR1AIP1\).

**Summary of Evidence**

**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 DMD or BMD. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Virtually all males with DMD or BMD have identifiable \(DMD\) disease-associated variants, indicating a high clinical sensitivity for genetic testing. The 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 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 evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or BMD. Relevant 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 clinical validity for testing for a known familial variant are lacking, but 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 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 an asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy who receive targeted DMD testing for a known familial variant to determine DMD status, the evidence includes case series and database entries. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for clinical validity of testing for a known familial variant are lacking, but 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 surveillance or cardiac surveillance in an asymptomatic male of a female carrier or the asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Facioscapulohumeral Muscular Dystrophy (FSHD)**

For individuals who have clinical signs of FSHD who receive genetic testing for FSHD, the evidence supporting improved outcomes is generally lacking. Relevant outcomes are test accuracy and 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, and initiate and direct clinical management changes that can result in improved health.
outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have signs or symptoms of an LGMD who receive genetic testing for LGMD-associated genes, the evidence includes systematic reviews, case series, and genotype-phenotype correlations evaluating the clinical validity and genetic testing yield. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The true clinical sensitivity and specificity of genetic testing for LGMD, in general, cannot be determined. While the genetic testing yield in patients with clinically suspected LGMD varies by population characteristics (ie, patients with only clinical symptoms vs patients with biopsy findings suggestive of LGMD), the available body of evidence suggests that testing yield is reasonably high. Genetic testing is generally considered the criterion standard for diagnosis of specific LGMD subtypes. For patients with clinically suspected LGMD, there is clinical utility in genetic testing to confirm a diagnosis of LGMD and direct treatment 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), to avoid therapies not known to be efficacious for LGMD, potentially to avoid invasive testing, and to allow reproductive planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with a first- or second-degree relative with an LGMD and a known familial variant who receive targeted familial variant testing, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. Published data on the clinical validity for testing for a known familial variant are lacking, but is expected to be high. Direct evidence on the clinical utility of LGMD-associated familial variant testing in asymptomatic relatives is lacking. However, the chain of evidence is strong, because determination of carrier status for an LGMD 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 that the technology results in a meaningful improvement in the net health outcome.

For individuals who are asymptomatic with a first- or second-degree relative with an LGMD whose genetic status is unknown who receive genetic testing for LGMD-associated genes, the evidence is limited. Relevant outcomes are overall survival, test accuracy and validity, changes in
reproductive decision making, change in disease status, and morbid events. Published data on the clinical validity of testing for a known familial variant are lacking, but is expected to be high. Direct evidence on the clinical utility of genetic testing for LGMD-associated genes in asymptomatic relatives is lacking. However, the chain of evidence is strong, because determination of carrier status for an LGMD pathogenic 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 that the technology results in a meaningful improvement in the net health outcome.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov found some trials that may relate to this policy listed in Table 5.

Table 5. Clinical Trials for Muscular Dystrophies

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td></td>
<td><strong>FSHD</strong></td>
<td></td>
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<tr>
<td>NCT01437345a</td>
<td>A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy</td>
<td>53</td>
<td>Aug 2017 (completed)</td>
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<tr>
<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 (unknown)</td>
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<td></td>
<td><strong>LGMD</strong></td>
<td></td>
<td></td>
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<tr>
<td>NCT02810028</td>
<td>Acceptance and Commitment Therapy for Muscle Disease</td>
<td>154</td>
<td>Jul 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

*a Denotes industry-sponsored or cosponsored trial.
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 in 2010 for the molecular diagnosis of DMD/BMD.\(^{11}\) 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.

**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 was stated that when a physician suspects FSHD based on clinical findings, the odds favor a diagnosis of FSHD, and genetic testing is the preferred diagnostic choice.\(^{13}\)

**LGMD**

**American Academy of Neurology**

In 2014, the American Academy of Neurology and the Practices Issues review Panel of the American Association of Neuromuscular and Electrodiagnostic Medicine issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies, with the following recommendations\(^{37}\):

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 obligatory 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 (eg, 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). Genetic testing for FSHD is available under the auspices of the Clinical Laboratory Improvement Amendments. Tests from laboratories such as GeneDx, Prevention Genetics, Centogene, Counsyl, and Athena Diagnostics are offered under the auspices of the Clinical Laboratory Improvement Amendments. 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


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<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>
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<td>09/01/15</td>
<td>Update Related Policies. Add 12.04.132.</td>
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<th>Comments</th>
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<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>
</tr>
<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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<tr>
<td>11/01/17</td>
<td>Minor update, policy statements were reformatted for clarity.</td>
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<tr>
<td>06/01/18</td>
<td>Annual Review, approved May 3, 2018. Policy updated with literature review through January 2018; References 2, 10, 12 and 23 were added; references 8, 13-22 were deleted. Policy statements unchanged.</td>
</tr>
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</table>

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