



# Louisiana

## Genetic Testing for Limb-Girdle Muscular Dystrophies

**Policy #** 00489

**Original Effective Date:** 01/22/2016

**Current Effective Date:** 07/11/2018

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

*Note: Genetic Testing for Facioscapulohumeral Muscular Dystrophy is addressed separately in medical policy 00392.*

*Note: Genetic Testing for Duchenne and Becker Muscular Dystrophy is addressed separately in medical policy 00471.*

### **When Services May Be Eligible for Coverage**

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

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

Based on review of available data, the Company may consider genetic testing for genes associated with limb-girdle muscular dystrophy (LGMD) to confirm a diagnosis of LGMD when signs and symptoms of LGMD are present but a definitive diagnosis cannot be made without genetic testing to be **eligible for coverage**.

*Note: The most common genes associated with LGMD may include CAPN3 (81406), DYSF (81408), SGCA, SGCB, SGCD, SGCG (81405), FKRP (81404), CAV3 (81404), and LMNA (81406).*

### Patient Selection Criteria

Coverage eligibility for genetic testing for genes associated with LGMD to confirm a diagnosis of LGMD when signs and symptoms of LGMD are present but a definitive diagnosis cannot be made without genetic testing will be considered when at least one of the following criteria are met:

- Results of testing may lead to changes in clinical management that improve outcomes (e.g., confirming or excluding the need for cardiac surveillance); OR
- Genetic testing will allow the affected patient to avoid invasive testing, including muscle biopsy.

Targeted genetic testing for a known familial variant associated with LGMD in an asymptomatic individual to determine future risk of disease may be considered **eligible for coverage** when the following criteria are met:

- The individual has a close (i.e., first- or second-degree) relative with a known familial variant consistent with LGMD;  
AND
- Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance).

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Genetic testing for genes associated with LGMD in an asymptomatic individual to determine future risk of disease may be considered **eligible for coverage** when the following criteria are met:

- The individual has a close (i.e., first- or second-degree) relative diagnosed with LGMD whose genetic status is unavailable;

AND

- Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance).

*Note: The most common genes associated with LGMD may include CAPN3 (81406), DYSF (81408), SGCA, SGCB, SGCD, SGCG (81405), FKR1P (81404), CAV3 (81404), and LMNA (81406).*

### **When Services Are Considered Investigational**

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

Based on review of available data, the Company considers genetic testing for mutations associated with LGMD in all other situations to be **investigational**.\*

The use of genetic testing for mutations associated with LGMD when patient selection criteria are not met is considered to be **investigational**.\*

### **Background/Overview**

#### **MUSCULAR DYSTROPHIES**

Muscular dystrophies are a group of inherited disorders characterized by progressive weakness and degeneration of skeletal muscle, cardiac muscle, or both, which may be associated with respiratory muscle involvement or dysphagia and dysarthria. Muscular dystrophies are associated with a wide spectrum of phenotypes, which may range from rapidly progressive weakness leading to death in the second or third decade of life to clinically asymptomatic disease with elevated creatine kinase (CK) levels. Muscular dystrophies have been classified by clinical presentation and genetic etiology. The most common are the dystrophinopathies, Duchenne (DMD) and Becker (BMD) muscular dystrophies, which are characterized by pathogenic variants in the dystrophin gene. Other muscular dystrophies are characterized by the location of onset of clinical weakness and include the LGMDs, facioscapulohumeral muscular dystrophy, oculopharyngeal muscular dystrophy, distal muscular dystrophy, and humeroperoneal muscular dystrophy (also known as Emery-Dreifuss muscular dystrophy). Congenital muscular dystrophy is a genetically heterogeneous group of disorders, which historically included infants with hypotonia and weakness at birth and findings of muscular dystrophy on biopsy. Finally, myotonic dystrophy is a multisystem disorder characterized by skeletal muscle weakness and myotonia in association with cardiac abnormalities, cognitive impairment, endocrinopathies, and dysphagia.

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### Limb-Girdle Muscular Dystrophies

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) that may be included in the differential diagnosis of DMD and BMD. Onset can be in childhood or adulthood. 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 elevated CK levels.

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 (e.g., Finland, Brazil).

### 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 1. Summary of Genetic Basis of LGMD**

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
<b>Autosomal dominant</b>						
1A	<i>MYOT</i>	Myotilin	Adulthood	Slow	Yes	
1B <sup>a</sup>	<i>LMNA</i>	Lamin A/C	Adolescence or variable	Slow	Yes	
1C <sup>a</sup>	<i>CAV3</i>	Caveolin-3	Variable	Slow	Yes	
1D	<i>DNAJB6</i>	DNAJ/Hsp40 homolog	Adulthood	Slow	No	
1E	<i>DES</i>	Desmin	Adulthood	Slow	Yes	
1F	<i>TNPO3</i>	Transportin3	Variable	Slow	No	
1G	<i>HNRPDL</i>	Heterogeneous nuclear ribonucleoprotein D-like protein	Adulthood	Slow	No	
1H			Variable	Slow	No	
<b>Autosomal recessive</b>						
2A	<i>CAPN3</i>	Calpain 3	Adolescence to adulthood	Moderate	Rare	≈10% to ≈40%
2B	<i>DYSF</i>	Dysferlin	Adolescence to adulthood	Slow	Yes	≈5% to ≈25%
2C	<i>SGCG</i>	γ-sarcoglycan	Early childhood	Rapid	Yes	68% with childhood
2D	<i>SGCA</i>	α-sarcoglycan	Early childhood	Rapid	Yes	childhood

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LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
2E	<i>SGCB</i>	$\beta$ -sarcoglycan	Early childhood	Rapid	Yes	onset; $\approx$ 10% with adult onset
2F	<i>SGCD</i>	$\delta$ -sarcoglycan	Early childhood	Rapid	Yes	
2G	<i>TCAP</i>	Telethonin	Adolescence	Slow	Yes	3%
2H	<i>TRIM32</i>	Tripartite motif containing 32	Adulthood	Slow	No	6%
2I	<i>FKRP</i>	Fukutin-related protein	<ul style="list-style-type: none"> <li><math>&lt;</math>10 to <math>&gt;</math>40 y</li> <li>Late childhood or variable</li> </ul>	Moderate	Yes	
2J	<i>TTN</i>	Titin	Young adulthood	Rapid	No	25% in U.K.
2K	<i>POMT1</i>	Protein-O-mannosyltransferase 1	Childhood	Slow	No	
2L	<i>ANO5</i>	Anoctamin-5	Variable	Slow	No	25% in U.K.
2M	<i>FKTN</i>	Fukutin	Early childhood	Slow/moderate	Yes	
2N	<i>POMT2</i>	Protein-O-mannosyltransferase 2	Early childhood	Slow/moderate	Rare	25% in U.K.
2O	<i>POMGnT1</i>	Protein O-linked mannosyltransferase 2	Late childhood	Moderate	No	
2P	<i>DAG1</i>	Dystroglycan	Early childhood	Moderate	No	25% in U.K.
2Q	<i>PLEC1</i>	Plectin	Early childhood	Slow	No	
2R	<i>DES</i>	Desmin	Young adulthood		Yes <sup>b</sup>	25% in U.K.
2S	<i>TRAPPC11</i>	Transport protein particle complex 11	Young adulthood	Slow	No	
2T	<i>GMPPB</i>	GDP-mannose pyrophosphorylase B	Early childhood to young adulthood		Yes	25% in U.K.
2U	<i>ISPD</i>	Isoprenoid synthase domain containing	Variable	Moderate/rapid	Yes	
2V	<i>GAA</i>	Glucosidase, $\alpha$ -1	Variable	Variable	Yes	25% in U.K.
2W	<i>LIMS2</i>	Lim and senescent cell antigen-like domains 2	Childhood		Yes	

Adapted from Norwood et al (2007), Mahmood and Jiang (2014), Nigro and Savarese al (2011), Nigro et al (2014), Pegoraro and Hoffman (2012).

AR: autosomal recessive; LGMD: limb-girdle muscular dystrophy.

<sup>a</sup> Rare recessive cases have been described for IB and IC.

<sup>b</sup> Atrioventricular conduction block.

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.

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### ***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, LGMD2C-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 (DCM).

### ***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 ( $\kappa=0.27$ ), 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.

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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 (e.g.,  $\alpha$ -dystroglycan, sarcoglycans, dysferlin, caveolin-3), cytoplasmic proteins (e.g., calpain-3, desmin), or nuclear proteins (e.g., 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 (e.g., contractures, scoliosis). Clinical management guidelines are available from the American Academy of Neurology (AAN) and American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM).

### ***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.

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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. Autologous bone marrow transplant has been investigated for LGMD but is not in general clinical use. 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. 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. 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. 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.

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- 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.
- 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 2.

**Table 2. LGMD Variants Included in Commercial NGS Test Panels**

Gene	GeneDx	Prevention Genetics		Centogene	Athena Diagnostics <sup>b</sup>
		Autosomal Dominant <sup>a</sup>	Autosomal Recessive		
<i>MYOT</i>	X	X		X	X
<i>LMNA</i>	X	X		X	X
<i>CAV3</i>	X	X		X	X
<i>DNAJB6</i>	X	X		X	X
<i>DES</i>	X	X	X		X
<i>TNPO3</i>	X	X			
<i>HNRPDL</i>					
<i>CAPN3</i>	X		X	X	X
<i>DYSF</i>	X		X	X	X
<i>SGCG</i>	X		X	X	X
<i>SGCA</i>	X		X	X	X
<i>SGCB</i>	X		X	X	X
<i>SGCD</i>	X		X	X	X
<i>TCAP</i>	X		X	X	X
<i>TRIM32</i>	X		X	X	X
<i>FKRP</i>	X		X	X	X
<i>TTN</i>	X		X	X	X
<i>POMT1</i>	X			X	X
<i>ANO5</i>	X		X	X	X
<i>FKTN</i>	X			X	X
<i>POMT2</i>	X			X	X
<i>POMGnT1</i>	X			X	X
<i>DAG1</i>				X	X
<i>PLEC1</i>				X	X
<i>TRAPPC11</i>			X		X
<i>GMPPB</i>	X		X		

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ISPD	X
GAA	
LIMS2	X

LGMD: limb-girdle muscular dystrophy; NGS: next-generation sequencing.

<sup>a</sup> This panel also includes testing for *SMCHD1*, which is associated with facioscapulohumeral muscular dystrophy

<sup>b</sup> This panel also includes testing for *PNPLA2*, which is associated with neutral lipid storage disease with myopathy, and *TOR1AIP1*.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

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

#### **Centers for Medicare and Medicaid Services (CMS)**

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

### **Rationale/Source**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

### **TESTING INDIVIDUALS WITH SIGNS OR SYMPTOMS OF LIMB-GIRDLE MUSCULAR DYSTROPHY**

#### **Clinical Context and Test Purpose**

The purpose of genetic testing of individuals with suspected LGMD is to establish the diagnosis of LGMD, direct treatment, and monitor based on a genetic diagnosis. Changes in management may include discontinuation of routine cardiac and/or respiratory surveillance in the absence of a specific genetic diagnosis with specific complications, avoidance of therapies not known to be efficacious for LGMD, potential avoidance of invasive testing, and informing reproductive decision making.

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The question addressed in this evidence review is: In individuals with suspected LGMD, does use of the genetic testing result eliminate or reduce the need for a muscle biopsy, need for cardiac and/or respiratory surveillance, and lead to improved health outcomes?

The following PICOTS were used to select literature to inform this review.

### **Patients**

The relevant population of interest is individuals with signs or symptoms of LGMD.

### **Interventions**

The test being considered is testing of genes associated with LGMD.

### **Comparators**

The following practice is currently being used: standard diagnostic workup without genetic testing.

### **Outcomes**

The potential beneficial outcomes of primary interest would be reductions in muscle biopsies to confirm the diagnosis of LGMD and whether changes in management are initiated based on confirming a genetic diagnosis of LGMD.

Potential harmful outcomes are those resulting from false-positive or false-negative test results. False-positive test results can lead to the inappropriate initiation of treatments or psychological harm after receiving positive test results. False-negative test results can lead to lack of cardiac and/or respiratory surveillance.

### **Timing**

The time frame for outcomes measures varies from short-term changes in disease status or changes in cardiac and/or respiratory surveillance to long-term changes in outcomes.

### **Setting**

Patients suspected of LGMD are actively managed by neurologists. Genetic testing is used to confirm a diagnosis of LGMD. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### **Simplifying Test Terms**

There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

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Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

### Technically Reliable

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

For LGMD, clinical validity may refer to the overall yield of testing for any LGMD-associated variant in patients with the clinically suspected disease, or the testing yield for specific variants. The genetic test is generally considered the criterion standard for determining a specific LGMD subtype.

### Unselected LGMD Populations

One potential role for genetic testing in LGMD is an assessment of patients with clinically suspected LGMD, but who do not necessarily have results of a muscle biopsy available.

The AAN and AANEM published joint guidelines (2014) on the diagnosis and treatment of limb-girdle and distal dystrophies, which included a systematic review of studies that assessed the yield of genetic testing for LGMD in patients who present with suspected muscular dystrophy. The types of studies available, and the study size and population included (if described), are summarized in Table 3.

**Table 3. Genetic Testing Yield in Patients With Suspected LGMD**

LGMD Type	Involved Protein	Evidence Base <sup>a</sup>	Population	Variant Detection Frequency
LGMD1A	Myotilin	1 class I study	1105 patients with genetic muscle disorders; 68 with LGMD	No myotilin variants among patients with LGMD
		3 class III studies	Not described	<1% to 1.7%

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LGMD Type	Involved Protein	Evidence Base <sup>a</sup>	Population	Variant Detection Frequency
LGMD1B	Lamin A/C	1 class I study	1105 patients with genetic muscle disorders; 68 with LGMD	8.8% of all muscle disorder cases
		9 class III studies	Patients with clinical LGMD	0.9%-4%
		3 class III studies	Not described	1.3%-2.6%
LGMD1C	Caveolin-3	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	26.5% of all LGMD cases
LGMD2A	Calpain-3	2 class I studies	84 patients with unknown MD	46.4%
		19 class III studies	Not described	6%-57%; most series reporting 18.5%-35%
LGMD2B	Dysferlin	1 class I study	1105 patients with genetic muscle disorders; 68 with LGMD	5.9% of LGMD cases
		11 class III studies	Not described	0.6%-33% of LGMD
LGMD2C	γ-sarcoglycan	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	5.9% of all muscle disorder cases
			204 patients with dystrophy on muscle biopsy and normal dystrophin	2%
		16 class III studies	Not described	1.3%-13.2%
	α-sarcoglycan	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	0.07 per 100,000
			204 patients with dystrophy on muscle biopsy and normal dystrophin	3.4%
		14 class III studies	Not described	3.3%-15%
	β-sarcoglycan	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	2.9% of all muscle disorder cases
			204 patients with dystrophy on muscle biopsy and normal dystrophin	1%
		13 class III studies	Not described	0%-23%
	δ-sarcoglycan	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	None
			204 patients with dystrophy on muscle biopsy and normal dystrophin	None
		12 class III studies	Not described	0%-14%
LGMD2G	Telethonin	2 class III studies	63 patients with myofibrillar myopathy	None
			140 patients with LGMD from 40 families	4.2%
LGMD2I	Fukutin-related protein	1 class I study	1105 patients with genetic muscle disorders; 68 with LGMD	19.1% of LGMD cases
		1 class II study	102 patients with persistent hyper-CK-emia	5.1%
		12 class III studies	Not described	4%-30%
LGMD2J	Titin	1 class III study	25 families and 25 sporadic cases; primarily distal myopathy	16% of familial cases; none in sporadic cases
LGMD2K	POMT1	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative <i>FKRP</i> variant testing	8%
LGMD2L	Anoctamin-5	2 class III studies	64 patients with LGMD or Miyoshi myopathy without dysferlin variants	31.3%
			101 patients with undetermined LGMD, distal myopathy, or elevated CK levels	24.8%
LGMD2M	Fukutin	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative <i>FKRP</i> variant testing	6.5%

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LGMD Type	Involved Protein	Evidence Base <sup>a</sup>	Population	Variant Detection Frequency
LGMD2N	POMT2	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative <i>FKRP</i> variant testing	9.7%
LGMD2O	POMGNT1	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative <i>FKRP</i> variant testing	7.6%

Adapted From Narayanaswami et al (2014).

CK: creatine kinase; LGMD: limb-girdle muscular dystrophy; MD: muscular dystrophy.

<sup>a</sup> Class I studies include statistical, population-based samples of patients studied at a uniform point in time (usually early) during the course of the condition, with all patients undergoing the intervention of interest, and with outcomes determined in an evaluation that is masked to patients' clinical presentations. Class II studies are similar to class I, but the patient population is a non-referral-clinic-based sample, and most, not all, patients undergo the intervention of interest. Class III studies include samples of patients studied during the course of the condition, some of whom undergo the intervention of interest, and in whom the outcome is determined by someone other than the treating physician.

The studies included in the AAN and AANEM systematic review on the prevalence of variants in various populations were heterogeneous regarding patient populations used. Representative studies are detailed next.

Norwood et al (2009) reported on the prevalence of genetic variants in a large population of patients with genetic muscle disorders (included in the AAN and AANEM systematic review). The population included 1105 cases with various inherited muscle diseases diagnosed and treated by at a single neuromuscular clinic, which was considered the only neuromuscular disorders referral center for northern England. Of the total patient population, 75.7% (n=836) had a confirmed genetic diagnosis. Myotonic dystrophy was the most commonly represented single diagnosis, representing 28.1% of the total sample, while 22.9% had a dystrophinopathy. Sixty-eight patients had a clinical diagnosis of LGMD, of whom 43 (6.15%) had positive genetic testing for a gene associated with LGMD. Of patients with a clinical diagnosis of LGMD, 72.1% had positive genetic testing, most commonly for LGMD2A (26.5%; 95% confidence interval, 16.0% to 37.0%).

### Variable Gene Expression

For some LGMD subtypes, there is variable expressivity for a given gene variant, which has been characterized in several retrospective analyses of the clinical features of patients with a specific gene variant. Maggi et al (2014) conducted a retrospective cohort analysis to characterize the clinical phenotypes of myopathic patients (n=78) and nonmyopathic patients with *LMNA* variants (n=78). Of the 78 myopathic patients, 37 (47%) had an LGMD phenotype (*LGMD1B*), 18 (23%) had congenital muscular dystrophy, 17 (22%) had autosomal dominant Emery-Dreifuss muscular dystrophy, and 6 (8%) had an atypical myopathy. Of the myopathic patients, 54 (69.2%) had cardiac involvement, and 41 (52.6%) received an implantable cardioverter defibrillator. Among 30 family members without myopathy but with *LMNA* variants, 20 (66.7%) had cardiac involvement, and 35% underwent implantable cardioverter defibrillator placement. Among all patients, frameshift variants were associated with a higher risk of heart involvement.

Sarkozy et al (2013) evaluated the prevalence of *ANO5* variants and associated clinical features among 205 patients without a genetic diagnosis but with a clinical suspicion of *ANO5* variant (or LGMD2L), who

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were evaluated at a single European center. A clinical suspicion of the *ANO5* variant (anoctaminopathy) could have been based on clinical examination, muscle assessment, and clinical evaluations including CK analysis, electromyography, muscle magnetic resonance imaging, and/or muscle biopsy. *ANO5* gene sequence variants were identified in 90 (44%) unrelated individuals and 5 affected relatives. Sixty-one percent of variants were a c.191dupA allelic variant, which is a founder mutation (pathogenic variant) found in most British and German LGMD2L patients. Age of onset was variable, ranging from teens to late 70s, with a lower-limb predominance of symptoms. Three individuals with *ANO5* variants had very mild clinical disease, and 1 patient was asymptomatic, but no specific genotype-phenotype correlations were demonstrated.

### *Panel Testing*

Ghosh and Zhou (2012) described the yield of a LGMD panel, which included testing for genes associated with lamin A/C (LGMD1B), caveolin-3 (LGMD1C), calpain-3 (LGMD2A), dysferlin (LGMD2B), the sarcoglycans (LGMD2C-2F), and Fukutin-related protein (LGMD2I), among 27 patients with a clinical suspicion of LGMD seen at a single center. Ten (37%) patients had positive testing, most commonly for LGMD2A (n=4). The testing yield was higher among children (3/6 [50%] patients tested), although the sample was very small.

### **LGMD Patients With Muscle Biopsy Results**

A smaller number of studies have evaluated the yield of genetic variant testing for LGMD in patients suspected of having a particular LGMD subtype on the basis of muscle biopsy.

Fanin et al (2009) evaluated the yield of molecular diagnostics among 550 cases with specific LGMD-related phenotypes, including severe childhood-onset LGMD, adult-onset LGMD, distoproximal myopathy, and asymptomatic hyper-CK-emia, who had undergone muscle biopsy with multiple protein screening. Before muscle biopsy, testing of all patients had excluded recent physical exercise or toxic or endocrinologic causes of myopathy. Dystrophinopathy was also excluded in all cases. Muscle biopsy samples underwent a systematic evaluation of calpain-3 (for LGMD2A), dysferlin (for LGMD2B), and  $\alpha$ -sarcoglycan (for LGMD2D) by immunoblotting and of caveolin-3 (for LGMD1C) by immunohistochemistry. Calpain-3 autolytic activity was also evaluated using a functional in vitro assay. Genetic testing of *DYSF*, *CAPN3*, sarcoglycans, *FKRP*, and *LMNA* was conducted single-strand conformational variant or denaturing high-performance liquid chromatography analysis, which are older methods of gene variant analysis. Of the 550 cases with muscle biopsies, 122 had childhood-onset LGMD, 186 had adult-onset LGMD, 38 had distoproximal myopathy, and 204 had asymptomatic hyper-CK-emia. In the entire cohort, a molecular diagnosis (positive genetic testing) was made in 234 (42.5%) cases, most commonly a calpain-3 variant, consistent with LGMD2A. Excluding patients with asymptomatic hyper-CK-emia, a molecular diagnosis was made in 205 (59.2%) of 346 cases with an LGMD phenotype. Patients with childhood-onset LGMD were more likely to have a molecular diagnosis (94/122 [77.0%]). Of the 226 patients with a protein abnormality on muscle biopsy, 193 (85.4%) had a genetic diagnosis.

In an earlier, smaller study, Guglieri et al (2008) reported on results from molecular diagnostic testing for a series of 181 patients (155 families) with clinical signs of LGMD and muscle biopsy with dystrophic features.

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The genetic testing yield varied by muscle biopsy protein (Western blotting and immunohistochemistry) findings: among 72 subjects with calpain-3 deficiency on protein testing, the variant detection rate was 61%, compared with 93.5% of the 31 subjects with dysferlin deficiency, 87% (for any sarcoglycan gene variant) of the 32 subjects with sarcoglycan deficiency, and 100% of the 52 subjects with caveolin-3 deficiency. The frequency of LGMD subtypes was as follows: LGMD1C (caveolin-3) 1.3%; LGMD2A (calpain-3) 28.4%; LGMD2B (dysferlin) 18.7%; LGMD2C ( $\gamma$ -sarcoglycan) 4.5%; LGMD2D ( $\alpha$ -sarcoglycan) 8.4%; LGMD2E ( $\beta$ -sarcoglycan) 4.5%; LGMD2F ( $\delta$ -sarcoglycan) 0.7%; LGMD2I (Fukutin-related protein) 6.4%; and undetermined 27.1%.

In another small study, Fanin et al (1997) reported on rates of sarcoglycan gene variants among 18 subjects with muscular dystrophy and  $\alpha$ -sarcoglycan deficiency assessed using immunohistochemistry and immunoblotting of muscle biopsy samples. Pathogenic variants in 1 gene involved in the sarcoglycan complex were identified in 13 patients.

Krahn et al (2009) evaluated the testing yield for *DYSF* variants in a cohort of 134 patients who had a clinical phenotype consistent with LGMD2B, loss or strong reduction of dysferlin protein expression on muscle biopsy Western blot and/or immunohistochemistry, or both. *DYSF* variants known to be associated with myopathy were detected in 89 (66%) patients. Bartoli et al (2014) reported on results of whole exome sequencing in a follow-up analysis of 37 patients who had negative targeted *DYSF* variant testing. In 5 (13.5%) cases, molecular diagnosis could be made directly by identification of compound heterozygous or homozygous variants previously associated with LGMD on whole exome sequencing, including 2 *CAPN3* variants, 1 *ANO5* variant, 1 *GNE* variant, and 1 *DYSF* variant, with 1 additional case requiring additional Sanger sequencing for complete identification.

### **Section Summary: Clinically Valid**

Estimates of the testing yield for variants associated with LGMD vary by the variants included and the characteristics of the patient populations tested. The true clinical sensitivity and specificity of genetic testing for LGMD variants, in general, cannot be determined because there is no criterion standard test for diagnosing LGMD. Studies have reported testing yields ranging from 37% to greater than 70% in patients with clinically suspected LGMD. The criterion standard for diagnosing an LGMD subtype is the genetic test. The specificity of a positive LGMD genetic test result in predicting the clinical phenotype of LGMD is not well-defined. However, there is evidence to support a finding that some variants associated with LGMD predict the presence of cardiac complications.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

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### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified addressing the clinical utility of managing patients with genetic testing. In the absence of direct evidence of clinical utility, a chain of evidence must be assessed to determine the potential clinical utility of a test.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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

- Confirming the diagnosis of LGMD and initiating and directing treatment of the disease, including evaluation by a cardiologist with cardiac testing, respiratory function testing and monitoring, and prevention of secondary complications (e.g., through immunizations, physical therapy or 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 a proband) includes:

- Confirming or excluding the need for cardiac surveillance.
- Reproductive planning in individuals considering offspring who would alter reproductive decision making based on test results.

### **Management of Cardiac Complications**

Similar to DMDs and BMDs, patients with LGMD are at higher risk of cardiac abnormalities, including DCM and various arrhythmias. Specific LGMD subtypes are more likely to be associated with cardiac disorders. Potential device-based therapies for patients at-risk of arrhythmias include cardiac pacing and an implantable cardioverter defibrillator. Guidelines from the American College of Cardiology, American Heart Association, and Heart Rhythm Society on the use of device-based therapy of cardiac rhythm abnormalities published in 2008 recommended that indications for a permanent pacemaker address the presence of

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muscular dystrophy. These guidelines have recommended considering implantation of a permanent pacemaker for patients with LGMD with *any* degree of atrioventricular block (class IIb recommendation; level of evidence: B), or bifascicular block or any fascicular block (class IIb recommendation; level of evidence: C), with or without symptoms, because there may be unpredictable progression of atrioventricular conduction disease.

Certain LGMD subtypes are more strongly associated with cardiac disorders than others. LGMD types 2C through 2F and 2I are associated with a primary DCM, with conduction disorders occurring as a secondary phenomenon. Other LGMD subtypes are recognized not to have associations with cardiomyopathy or conduction disorders. In these cases, recommendations from AAN and AANEM have indicated that routine cardiac surveillance in asymptomatic individuals is not required.

There is clinical utility for identifying a specific *LGMD* gene variant for patients presenting with signs and symptoms of LGMD to allow discontinuation of cardiac surveillance in patients found to have a variant not associated with cardiac disorders.

On the other hand, there may be clinical utility for testing of asymptomatic family members of a proband with an identified *LGMD* variant to determine cardiovascular risk. Patients with *LMNA* variants, regardless of whether they have an *LGMD1B* phenotype, are at-risk for cardiac arrhythmias. Similarly, *FKTN* variants can be associated with DCM, with or without the presence of myopathy. Murakami et al (2006) reported on a cases series of 6 patients from 4 families with compound heterozygous *FKTN* variants who presented with DCM and no or minimal myopathic symptoms.

### **Section Summary: Clinically Useful**

In patients with clinically suspected LGMD, genetic testing is primarily to confirm a diagnosis, but may also have a prognostic role given the clinical variability across LGMD subtypes. For asymptomatic but at-risk family members, testing may also confirm a diagnosis or allow prediction of symptoms. No direct evidence exists on the impact of testing on outcomes. However, a chain of evidence suggests that the establishment of a specific genetic diagnosis has the potential to change clinical management.

## **TARGETED TESTING OF ASYMPTOMATIC INDIVIDUALS WITH RELATIVES WITH LGMD AND A KNOWN FAMILIAL VARIANT**

### **Clinical Context and Test Purpose**

The purpose of genetic testing of an asymptomatic individual with first- and second-degree relatives with LGMD and a known familial variant is to determine carrier or genetic status to confirm or exclude the need for cardiac surveillance and inform the reproductive planning process.

The question addressed in this evidence review is: In individuals with suspected LGMD, does use of the genetic testing result lead to reductions in unnecessary cardiac surveillance and lead changes in reproductive planning?

The following PICOTS were used to select literature to inform this review.

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### **Patients**

The relevant population of interest is asymptomatic patients with first- and second-degree relatives who have LGMD and a known familial variant.

### **Interventions**

The test being considered is targeted familial variant testing.

### **Comparators**

The following practice is currently being used: standard diagnostic workup without genetic testing.

### **Outcomes**

The potential beneficial outcomes of primary interest would be confirming or excluding the need for cardiac surveillance based on LGMD subtype and changes in reproductive planning.

### **Timing**

The time frame for outcome measures varies from short-term changes in the development of symptoms, disease status, or changes in cardiac function to long-term improvements in outcomes or changes in reproductive decision making.

### **Setting**

In asymptomatic individuals, the evaluation may occur in pediatrics, primary care, or neurology due to the variability in clinical presentation and age of onset. Genetic testing is used to confirm a genetic status of a known familial variant. If the known familial variant is detected, referral to cardiology is important to initiate cardiac surveillance if the specific LGMD subtype is associated with the development of cardiac symptoms. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the discussion of clinical validity in the Testing Individuals With Signs or Symptoms of LGMD section above.

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### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified addressing the clinical utility of managing patients with genetic testing. In the absence of direct evidence of clinical utility, a chain of evidence must be assessed to determine the potential clinical utility of a test.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of asymptomatic individuals with a first- or second-degree relation with LGMD may have clinical utility in:

- Confirming or excluding the need for cardiac surveillance based on the presence or absence of a known familial variant.
- Informing the reproductive decision making process for preimplantation testing and/or prenatal (in utero) testing when a known familial variant is present in a parent.

### **Section Summary: Targeted Testing of Asymptomatic Individuals With Relatives With LGMD and a Known Familial Variant**

For individuals who are asymptomatic with a first- or second-degree relative with LGMD and a known familial variant who are tested for targeted familial variants, the evidence is limited. Data on the clinical validity for testing for a known familial variant are lacking but validity 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.

### **TESTING OF ASYMPTOMATIC INDIVIDUALS WITH RELATIVES WITH LGMD AND UNKNOWN GENETIC STATUS**

#### **Clinical Context and Test Purpose**

The purpose of genetic testing of asymptomatic individuals with first- and second-degree who have LGMD and an unknown genetic status is to determine carrier or genetic status to confirm or exclude the need for cardiac surveillance and inform the reproductive planning process.

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The question addressed in this evidence review is: In individuals with suspected LGMD, does use of the genetic testing result lead to reductions in unnecessary cardiac surveillance and changes in reproductive planning?

The following PICOTS were used to select literature to inform this review.

### **Patients**

The relevant population of interest is asymptomatic patients with first- and second-degree relatives who have LGMD whose genetic status is unknown.

### **Interventions**

The test being considered is genetic testing for genes associated with LGMD.

### **Comparators**

The following practice is currently being used: standard diagnostic workup without genetic testing.

### **Outcomes**

The potential beneficial outcomes of primary interest would be confirming or excluding the need for cardiac surveillance based on LGMD subtype and changes in reproductive planning.

### **Timing**

The time frame for outcome measures varies from short-term changes in the development of symptoms, disease status, or changes in cardiac function to long-term improvements in outcomes or changes in reproductive decision making.

### **Setting**

In asymptomatic individuals, the evaluation may occur in pediatric, primary care, or neurology departments due to the variability in clinical presentation and age of onset. Genetic testing is used to confirm the genetic status of a pathogenic variant in an LGMD-associated gene. If the pathogenic variant in an LGMD-associated gene is detected, referral to cardiology is important to initiate cardiac surveillance if the specific LGMD subtype is associated with the development of cardiac symptoms. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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### **Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

See the discussion of clinical validity in the Testing Individuals With Signs or Symptoms of LGMD section above.

### **Clinically Useful**

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

### **Direct Evidence**

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No randomized controlled trials were identified addressing the clinical utility of managing patients with genetic testing. In the absence of direct evidence of clinical utility, a chain of evidence must be assessed to determine the potential clinical utility of a test.

### **Chain of Evidence**

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Genetic testing of asymptomatic individuals with first- and second-degree relations with LGMD whose genetic status is unknown may have clinical utility in:

- Confirming or excluding the need for cardiac surveillance based on the presence or absence of a pathogenic variant in an LGMD-associated gene.
- Informing the reproductive decision making process for preimplantation testing and/or prenatal (in utero) testing when a pathogenic variant in an LGMD-associated gene is present in a parent.

### **Section Summary: Testing of Asymptomatic Individuals With Relatives With LGMD and unknown Genetic Status**

For individuals who are asymptomatic and have a first- or second-degree relative with LGMD whose genetic status is unknown who are given genetic testing for LGMD-associated genes, the evidence is limited. Data for the clinical validity of testing for a known familial variant are lacking but validity 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.

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# Louisiana

## Genetic Testing for Limb-Girdle Muscular Dystrophies

Policy # 00489

Original Effective Date: 01/22/2016

Current Effective Date: 07/11/2018

### **SUMMARY OF EVIDENCE**

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 (i.e., 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.

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### Policy History

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01/07/2016 Medical Policy Committee review

01/22/2016 Medical Policy Implementation Committee approval. New Policy.

01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

07/06/2017 Medical Policy Committee review

07/19/2017 Medical Policy Implementation Committee approval. The policy is revised with updated genetics nomenclature. "Mutations" changed to "variants" in policy statements. Removed coverage statement with criteria for genetic testing in the reproductive setting. Coverage statements updated to separate "targeted familial variant testing" and "genetic testing of LGMD-associated genes" in asymptomatic individuals. Added a "Note" in two places to the coverage to include the most common genes associated with LGMD. Policy title changed to "Genetic Testing for Limb-Girdle Muscular Dystrophies", so that "Genetic" replaces "Mutation".

07/05/2018 Medical Policy Committee review

07/11/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2019

### Coding

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ICD-10 Diagnosis	G71.0

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- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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