

MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR LIMB GIRDLE MUSCULAR DYSTROPHIES
POLICY NUMBER	MP 2.332

Original Issue Date (Created):	2/1/2016
Most Recent Review Date (Revised):	6/8/2020
Effective Date:	9/1/2020

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I. POLICY

Genetic testing for genes associated with limb-girdle muscular dystrophy (LGMD) to confirm a diagnosis of LGMD may be considered **medically necessary** when signs and symptoms of LGMD are present but a definitive diagnosis cannot be made without genetic testing, and 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;

Genetic testing for genes associated with (LGMD) in the reproductive setting may be considered **medically necessary** when:

- There is a diagnosis of LGMD in one or both of the parents, **AND**
- Results of testing will allow informed reproductive decision making.

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

- The individual has a close relative (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).

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

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

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

Genetic testing for genes associated with LGMD is considered **investigational** in all other situations. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines**LIMB-GIRDLE MUSCULAR DYSTROPHY**

Clinical signs and symptoms of limb-girdle muscular dystrophy (LGMD) include gradually progressive muscle weakness involving predominantly the proximal arms and legs, with normal sensory examination. Distal muscles may be involved, but usually to a lesser extent. Supportive laboratory test results include an elevated creatine kinase (CK) level.

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 (e.g., physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and genetics) designed specifically to care for patients with muscular dystrophy and other neuromuscular disorders in order to provide efficient and effective long-term care” (Narayanaswami et al, 2014).

Testing Strategy

The 2014 AAN and AANEM joint guidelines have outlined an algorithmic approach to narrowing the differential diagnosis in a patient with suspected LGMD to allow focused genetic testing. The guidelines have indicated: “For patients with a suspected muscular dystrophy, clinicians should 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” (Narayanaswami et al, 2014). In general, the guidelines have recommended the use of targeted genetic testing if specific features are present based on clinical findings and muscle biopsy characteristics. If there are no characteristic findings on initial targeted genetic testing or muscle biopsy, then next-generation sequencing panels should be considered.

The evaluation of suspected LGMD should begin, if possible, with targeted genetic testing of one or several single genes based on the patient’s presentation. However, if initial targeted genetic testing results are negative or if clinical features do not suggest a specific genetic subtype, testing with a panel of genes known to be associated with LGMD (see Table 1) may be indicated.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was

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implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Human Genome Variation 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 (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in DNA sequence
	Familial Variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives.

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

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely Pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Cross-reference:

MP-2.257 Genetic Testing for Duchenne and Becker Muscular Dystrophy

MP-2.321 Genetic Testing for Facioscapulohumeral Muscular Dystrophy

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.132 Genetic Testing for Limb-Girdle Muscular Dystrophies. The FEP Medical Policy manual can be found at:

[https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.](https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies)

III. DESCRIPTION/BACKGROUND

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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 on the basis of 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 limb-girdle muscular dystrophies (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.

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.¹ 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 an elevated CK levels.

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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.¹ 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 specific genotype (if known).

Table 1. Summary of Genetic Basis of Limb-Girdle Muscular Dystrophy

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement ?	Percent AR LGMD Cases
<i>Autosomal dominant</i>						
1A	<i>MYOT</i>	Myotilin	Adulthood	Slow	Yes	
1Ba	<i>LMNA</i>	Lamin A/C	Adolescence or variable	Slow	Yes	
1Ca	<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	
<i>Autosomal recessive</i>						
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>	g-sarcoglycan	Early childhood	Rapid	Yes	68% with childhood onset;
2D	<i>SGCA</i>	α-sarcoglycan	Early childhood	Rapid	Yes	»10%

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2E	<i>SCGB</i>	β-sarcoglycan	Early childhood	Rapid	Yes	with adult onset
2F	<i>SCGD</i>	δ-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	
2I	<i>FKRP</i>	Fukutin-related protein	<10 to >40 y Late childhood or variable	Moderate	Yes	6%
2J	<i>TTN</i>	Titin	Young adulthood	Rapid	No	
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	
2O	<i>POMGnT1</i>	Protein O-linked mannose beta1, 2-Nacetylglucosaminyltransferase	Late childhood	Moderate	No	
2P	<i>DAG1</i>	Dystroglycan	Early childhood	Moderate	No	
2Q	<i>PLEC1</i>	Plectin	Early childhood	Slow	No	
2R	<i>DES</i>	Desmin	Young adulthood		Yes	
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	
2U	<i>ISPD</i>	Isoprenoid synthase domain containing	Variable	Moderate/Rapid	Yes	
2V	<i>GAA</i>	Glucosidase, α-1	Variable	Variable	Yes	
2W	<i>LIMS2</i>	Lim and senescent cell antigen-like domains 2	Childhood		Yes	

Adapted from Norwood et al (2007),² Mahmood and Jiang (2014),³ Nigro and Savarese al (2011),⁴ Nigro et al (2014),¹ Pegoraro and Hoffman (2012).⁵
 AR: autosomal recessive; LGMD: limb-girdle muscular dystrophy.

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^a Rare recessive cases have been described for IB and IC.

^b 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.⁴ *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 the distribution of LGMD subtypes based on muscle biopsy results as follows: 12% LGMD2A, 18% LGMD2B, 15% LGMD2C-2F, and 1.5% LGMD1C.⁶

Clinical Variability

Other than presentation with proximal muscle weakness, LGMD subtypes can have considerable clinical variability in terms of 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 risk of cardiomyopathy in all forms of the disease.

Of particular clinical importance is that fact that 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 of the 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.⁷ 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.² Certain LGMD subtypes may be suspected on the basis of family history, patterns of weakness, CK levels, and associated clinical findings. However, there is considerable clinical heterogeneity and overlap across the LGMD subtypes.

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Without genetic testing, diagnostic evaluation can typically lead to a general diagnosis of a 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 (CT) or magnetic resonance imaging (MRI) may be obtained to assess areas of involvement and guide muscle biopsy. MRI or CT may be used to evaluate patterns of muscle involvement. At least for calpainopathy (LGMD2A) and dysferlinopathy (LGMD2B), MRI may show patterns distinct from other neuromuscular disorders, including hyaline body myopathy and myotonic dystrophy. 7, In 1 study (2012) that evaluated muscle CT 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. 8

Electromyography (EMG) has limited value in LGMD, although it may have clinical utility if there is clinical concern for type III spinal muscular atrophy. EMG typically shows myopathic changes with small polyphasic potentials. .9

Muscle biopsy may be used in suspected LGMD to rule out other, treatable causes of weakness (in some cases), and to attempt to identify a 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.^{2,9} 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., α -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).⁵ 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.⁶ In some types of 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.⁴

A blood-based dysferlin protein assay, which evaluates dysferlin levels in peripheral blood CD14⁺ monocytes, has been evaluated in a sample of 77 individuals with suspected dysferlinopathy .10 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

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result from skeletal muscle weakness (e.g., 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, 1 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. 11 Autologous bone marrow transplant has been investigated for LGMD, but is not in general clinical use. 12 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. 13 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 NGS methods. In cases in which a LGMD is suspected but gene sequencing is normal, deletion/duplication analysis through targeted comparative genomic hybridization or multiplex ligation–dependent probe amplification (MLPA) 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.14, This panel uses next-generation sequencing and reports only on panel genes, with concurrent targeted array comparative genomic hybridization 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

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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. 15 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/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 variant analysis is negative. Additional Sanger sequencing is performed for any regions not captured or with 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 testing 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 next-generation sequencing panel for Muscular Dystrophy, not specific to limb-girdle muscular dystrophy, which includes sequencing of the included variants and deletion and duplication testing by multiplex ligation-dependent probe amplification, with whole genome sequencing if no variants are identified.¹⁶
- Athena Diagnostics offers NGS testing for *FKRP*, *LMNA*, *DYSF*, *CAV3*, and *CAPN3* (NGS followed by dosage analysis), along with a NGS panel, with deletion/duplication testing for *SGCA*, *SGCG*, and *CAPN3*.

Variants included in some of the currently available next-generation sequencing testing panels are summarized in Table 2.

Table 2. Limb-Girdle Muscular Dystrophy Variants Included in Commercial Next-Generation Sequencing Test Panels

Gene	GeneDx	Prevention Genetics		Centogene	Athena Diagnostics ^b
		Autosomal Dominant ^a	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	X
<i>TNPO3</i>	X	X		X	
<i>HNRPDL</i>				X	
<i>CAPN3</i>	X		X	X	X

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<i>DYSF</i>	X		X	X	X
<i>SGCG</i>	X		X	X	X
<i>SGCA</i>	X		X	X	X
<i>SGCA</i>	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	X
<i>GMPPB</i>	X		X	X	
<i>ISPD</i>			X		
<i>GAA</i>				X	
<i>LIMS2</i>			X	X	

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*

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). Tests from laboratories such as GeneDx, Prevention Genetics, Centogene, Counsyl, and Athena Diagnostics are offered under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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Summary of Evidence

For individuals who have signs or symptoms of limb-girdle muscular dystrophy (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 yield of genetic testing. Relevant outcomes are overall survival, test accuracy and validity, changes in reproductive decision making, change in disease status, and morbid events. The analytic validity of genetic testing for LGMD-associated genes 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 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

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testing is generally considered the criterion standard for diagnosis of a 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 LGMD with 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 analytic and clinical validity for testing for a known familial variant are lacking, but the validity is expected to be high. Direct evidence on the clinical utility of LGMD-associated familial variant testing in asymptomatic relatives is lacking. However, the chain of evidence is strong, because determination of carrier status for a 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 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 for the analytic and clinical validity of testing for a known familial variant are lacking, but the 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 a 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.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are

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excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member’s health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member’s plan of benefits, please contact Capital BlueCross’ Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

CPT Codes®							
81404	81405	81406	81408	81479			

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ICD-10-CM Diagnosis Code	Description
G71.09	Other specified muscular dystrophies

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.332	CAC 9/29/15 New policy adopting BCBSA. Testing for LGMD is medically necessary when criteria are met. Coding added.
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	Admin Update 11/11/16: Variation reformatting.
	CAC 1/31/17 Consensus. No change to policy statements. References updated. Rationale reviewed. Coding reviewed.
	12/5/17 Minor revision. Policy title changed to “Genetic Testing for Limb Girdle Muscular Dystrophies. Policy statement updated to separate “targeted familial variant testing” and “genetic testing of LGMD-associated genes in asymptomatic individuals”. In addition, the policy was revised throughout with updated genetics nomenclature. Background and rationale revised. References reviewed. Appendix added. Coding reviewed.
	10/1/18 Admin Update: Removed deleted ICD-10 code, added new ICD-10 code effective 10/1/18.
	10/18/18 Consensus. No change to policy statements. References updated. Rationale condensed.
	7/17/19 Consensus review. Literature reviewed, tables reformatted.
	6/8/20 Consensus review. No change to policy statement. References, background (tables added) and policy guidelines (genetic counseling) updated.

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