Genetic Testing for Limb-Girdle Muscular Dystrophies

Policy # 00489
Original Effective Date: 01/22/2016
Current Effective Date: 08/14/2023

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

Note: Genetic Testing for 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 may 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.

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Based on review of available data, the Company may consider targeted genetic testing for a known familial variant associated with limb-girdle muscular dystrophy (LGMD) in an asymptomatic individual to determine future risk of disease to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for 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 ALL of 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).

Based on review of available data, the Company may consider genetic testing for genes associated with limb-girdle muscular dystrophy (LGMD) in an asymptomatic individual to determine future risk of disease to be **eligible for coverage.****

Patient Selection Criteria
Coverage eligibility for genetic testing for genes associated with LGMD in an asymptomatic individual to determine future risk of disease may be considered **eligible for coverage**** when ALL of 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), FKRP (81404), CAV3 (81404), and LMNA (81406).

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When Services Are Considered Investigational

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

The use of genetic testing for mutations associated with limb-girdle muscular dystrophy (LGMD) when patient selection criteria are not met is considered to be **investigational.***

Based on review of available data, the Company considers genetic testing for mutations associated with limb-girdle muscular dystrophy (LGMD) in all other situations to be **investigational.***

Policy Guidelines

Limb-Girdle Muscular Dystrophy

Clinical signs and symptoms of limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy recommend that “clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (eg, physical therapy, occupational therapy, respiratory therapy, speech and swallowing therapy, cardiology, pulmonology, orthopedics, and 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; PMID25313375).

Testing Strategy

The 2014 AAN and AANEM joint guidelines have outlined an algorithmic approach to narrowing the differential diagnosis in a patient with suspected limb-girdle muscular dystrophy 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; PMID25313375). 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 limb-girdle muscular dystrophy should begin, if possible, with targeted genetic testing of 1 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 limb-girdle muscular dystrophy (Table 1) may be indicated.

Genetics Nomenclature Update
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It was implemented for genetic testing medical evidence review updates in 2017 (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 and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the 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

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

Genetic Counseling

Experts recommend formal genetic counseling for individuals 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 individuals; 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.

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 and Becker 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, 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 Duchenne muscular dystrophy and Becker muscular dystrophy. Onset can be in childhood or adulthood. The degree of disability depends on the location and degree of weakness. Some limb-girdle muscular dystrophy subtypes are characterized by only mild, slowly progressive weakness, while others are associated with early-onset, severe disease with loss of ambulation. Limb-girdle muscular dystrophies 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 limb-girdle muscular dystrophies. Most individuals have elevated CK levels.

Limb-girdle muscular dystrophies 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 (Duchenne muscular distrophy and Becker muscular dystrophy), facioscapulohumeral muscular dystrophy, and myotonic dystrophy. The prevalence of specific types increases in populations with founder pathogenic variants (eg, Finland, Brazil).

Genetic Basis and Clinical Correlation
As the genetic basis of the limb-girdle muscular dystrophies has been elucidated, it has been recognized there is tremendous heterogeneity in genetic variants that cause the limb-girdle muscular dystrophy phenotype. Limb-girdle muscular dystrophies 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 Limb-Girdle Muscular Dystrophy

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
Autosomal dominant						
1A	*MYOT*	Myotilin	Adulthood	Slow	Yes	
1Ba	*LMNA*	Lamin A/C	Adolescence or variable	Slow	Yes	
1Ca	*CAV3*	Caveolin-3	Variable	Slow	Yes	
1D	*DNAJB6*	DNAJ/Hsp40 homolog	Adulthood	Slow	No	
1E	*DES*	Desmin	Adulthood	Slow	Yes	
1F	*TNPO3*	Transportin3	Variable	Slow	No	
1G	*HNRPDL*	Heterogeneous nuclear ribonucleoprotein D-like protein	Adulthood	Slow	No	
1H			Variable	Slow	No	
Autosomal recessive						
2A	*CAPN3*	Calpain 3	Adolescence to adulthood	Moderate	Rare	~10% to ~40%

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
2B	*DYSF*	Dysferlin	Adolescence to adulthood	Slow	Yes	~5% to ~25%
2C	*SGCG*	g-sarcoglycan	Early childhood	Rapid	Yes	68% with childhood onset; »10% with adult onset
2D	*SGCA*	α-sarcoglycan	Early childhood	Rapid	Yes	
2E	*SGCB*	β-sarcoglycan	Early childhood	Rapid	Yes	
2F	*SGCD*	δ-sarcoglycan	Early childhood	Rapid	Yes	
2G	*TCAP*	Telethonin	Adolescence	Slow	Yes	3%
2H	*TRIM32*	Tripartite motif containing 32	Adulthood	Slow	No	
2I	*FKRP*	Fukutin-related protein	• <10 to >40 y • Late childhood or variable	Moderate	Yes	6%
2J	*TTN*	Titin	Young adulthood	Rapid	No	
2K	*POMT1*	Protein-O-mannosyltransferase 1	Childhood	Slow	No	
2L	*ANO5*	Anoctamin-5	Variable	Slow	No	25% in U.K.

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
2M	*FKTN*	Fukutin	Early childhood	Slow/moderate	Yes	
2N	*POMT2*	Protein-O-mannosyltransferase 2	Early childhood	Slow/moderate	Rare	
2O	*POMGnT1*	Protein O-linked mannose beta1, 2-Nacetyl-glucosaminyl-transferase	Late childhood	Moderate	No	
2P	*DAG1*	Dystroglycan	Early childhood	Moderate	No	
2Q	*PLEC1*	Plectin	Early childhood	Slow	No	
2R	*DES*	Desmin	Young adulthood		Yesb	
2S	*TRAPPC11*	Transport protein particle complex 11	Young adulthood	Slow	No	
2T	*GMPPB*	GDP-mannose pyrophosphorylase B	Early childhood to young adulthood		Yes	
2U	*ISPD*	Isoprenoid synthase domain containing	Variable	Moderate/rapid	Yes	
2V	*GAA*	Glucosidase, α-1	Variable	Variable	Yes	
2W	*LIMS2*	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.
a Rare recessive cases have been described for IB and IC.
b Atrioventricular conduction block.

The prevalence of different variants and limb-girdle muscular dystrophy subtypes can differ widely by country but the autosomal recessive forms are generally more common. Pathogenic variants in *CAPN3* represent 20% to 40% of limb-girdle muscular dystrophy cases, and LGMD2A is the most frequent limb-girdle muscular dystrophy in most countries. *DYSF* pathogenic variants leading to LGMD2B are the second most common limb-girdle muscular dystrophy in many, but not all, areas (15%-25%). Sarcoglycanopathies constitute about 10% to 15% of all limb-girdle muscular dystrophies but 68% of the severe forms.

In an evaluation of 370 individuals with suspected limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy subtypes based on muscle biopsy results as follows: 12% LGMD2A, 18% LGMD2B, 15% LGMD2C-2F, and 1.5% LGMD1C.

Clinical Variability
Other than presentation with proximal muscle weakness, limb-girdle muscular dystrophy 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 Duchenne muscular dystrophy and Becker muscular dystrophy, with the risk of cardiomyopathy in all forms of the disease.

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

Many genes associated with limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy (LGMD1B), and congenital muscular dystrophy. All forms have been associated with cardiac involvement, including atrial and ventricular arrhythmias and dilated cardiomyopathy.

Clinical Diagnosis
A diagnosis of limb-girdle muscular dystrophy is suspected in individuals 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 limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy subtypes.

Without genetic testing, diagnostic evaluation can typically lead to a general diagnosis of a limb-girdle muscular dystrophy, with limited ability to determine the subcategory. Most cases of limb-girdle muscular dystrophy 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 individuals with limb-girdle muscular dystrophy and 32 controls, there was generally poor overall interobserver agreement (k=0.27), and low sensitivity (40%) and specificity (58%) for limb-girdle muscular dystrophy.

Electromyography has limited value in limb-girdle muscular dystrophy, 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 limb-girdle muscular dystrophy to rule out other, treatable causes of weakness (in some cases), and to attempt to identify a limb-girdle muscular dystrophy subtype. All limb-girdle muscular dystrophy subtypes are characterized on muscle biopsy by dystrophic features, with degeneration and regeneration of muscle fibers, variation in fiber size, fiber splitting, increased numbers of central nuclei, and endomysial fibrosis. Certain subtypes, particularly in dysferlin deficiency (LGMD2B), may show inflammatory infiltrates, which may lead to an inaccurate diagnosis of polymyositis.

Following standard histologic analysis, immunohistochemistry and immunoblotting are typically used to evaluate myocyte protein components, which may include sarcolemma-related proteins (eg, α-dystroglycan, sarcoglycans, dysferlin, caveolin-3), cytoplasmic proteins (eg, calpain-3, desmin), or nuclear proteins (eg, lamin A/C). Characteristic findings on muscle biopsy immunostaining or immunoblotting can be seen for calpainopathy (LGMD2A), sarcoglycanopathies (LGMD2C-2F), dysferlinopathy (LGMD2B), and *O*-linked glycosylation defects (dystroglycanopathies; LGMD2I, LGMD2K, LGMD2M, LGMD2O, LGMD2N). However, muscle biopsy is imperfect: secondary deficiencies in protein expression can be seen in some LGMD. In the Moore et al (2006) 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 individuals may retain normal amounts of nonfunctional protein.

A blood-based dysferlin protein assay, which evaluates dysferlin levels in peripheral blood CD14 (cluster of differentiation 14)-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 limb-girdle muscular dystrophies. Treatment is focused on supportive care to improve muscle strength, slow decline in strength, preserve ambulation, and treat and prevent musculoskeletal complications that may result from skeletal muscle weakness (eg, contractures, scoliosis). Clinical management guidelines are available from the American Academy of Neurology and Association of

Neuromuscular & Electrodiagnostic Medicine (see Practice Guidelines and Position Statements section).

Monitoring for Complications
Different genetic variants associated with clinical limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy subtypes associated with respiratory or cardiac involvement because individuals are often asymptomatic until they have significant organ involvement. When respiratory depression is present, individuals 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.

Individuals 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 limb-girdle muscular dystrophy. 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 individuals with genetically confirmed LGMD2B (dysferlinopathy) showed no benefit and a trend toward worsening strength associated with therapy. Autologous bone marrow transplant has been investigated for limb-girdle muscular dystrophy but is not in general clinical use. Adeno-associated virus-mediated gene transfer to the extensor digitorumbrevis 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 limb-girdle muscular dystrophy are single nucleotide variants, the primary method of variant detection is gene sequencing using Sanger sequencing or next-generation sequencing methods. In cases in which a limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy that rely on Sanger sequencing or next-generation sequencing. The following list is not exhaustive.

- GeneDx offers the Limb-Girdle Muscular Dystrophy Panel. 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 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 limb-girdle muscular dystrophy tests. They include an autosomal dominant limb-girdle muscular dystrophy Sanger sequencing panel, which includes MYOT, LMNA, DNAJB6, and CAV3 sequencing either individually or as a panel, followed by array comparative genomic hybridization for deletions and duplications. The company also offers an autosomal recessive limb-girdle muscular dystrophy 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 array comparative genomic hybridization for deletions/duplications. Also, Prevention Genetics offers 2 next-generation sequencing panels for limb-girdle muscular dystrophy, which involve next-generation sequencing followed by array comparative genomic hybridization if the variant analysis is negative. Additional Sanger sequencing is performed for any regions not captured or with an insufficient number of sequence reads. All pathogenic, undocumented and questionable variant calls are confirmed by Sanger sequencing.
- Counsyl offers a Foresight™‡ Carrier Screen, which includes testing for multiple diseases that may require early intervention or cause shortened life or intellectual disability and is designed as a carrier test for reproductive planning. Testing for LGMD2D and LGMD2E may be added to the panel. Testing is conducted by next-generation sequencing, without evaluation for large duplications or deletions.
- Centogene (Rostock) offers a 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.
- Athena Diagnostics offers next-generation sequencing testing for FKRP, LMNA, DYSF, CAV3, and CAPN3 (next-generation sequencing followed by dosage analysis), along with a next-generation sequencing panel, with deletion and 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***		
MYOT	X	X		X	X
LMNA	X	X		X	X
CAV3	X	X		X	X
DNAJB6	X	X		X	X
DES	X	X	X	X	X
TNPO3	X	X		X	
HNRPDL				X	
CAPN3	X		X	X	X
DYSF	X		X	X	X
SGCG	X		X	X	X
SGCA	X		X	X	X

SGCB	X		X	X	X
SGCD	X		X	X	X
TCAP	X		X	X	X
TRIM32	X		X	X	X
FKRP	X		X	X	X
TTN	X		X	X	X
POMT1	X			X	X
ANO5	X		X	X	X
FKTN	X			X	X
POMT2	X			X	X
POMGnT1	X			X	X
DAG1				X	X
PLEC1				X	X
TRAPPC11			X	X	X
GMPPB	X		X	X	
ISPD			X		
GAA				X	
LIMS2			X	X	

[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*

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Tests from laboratories such as GeneDx, Prevention Genetics, Centogene, Counsyl, and Athena Diagnostics are offered under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Rationale/Source

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

Description

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

Summary of Evidence

For individuals who have signs or symptoms of a limb-girdle muscular dystrophy who receive genetic testing for limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy, in general, cannot be determined. While the genetic testing yield in individuals with clinically suspected limb-girdle muscular dystrophy varies by population characteristics (ie, individuals with only clinical symptoms versus individuals with biopsy findings suggestive of limb-girdle muscular dystrophy), the available body of evidence suggests that testing yield is reasonably high. Genetic testing is generally

considered the criterion standard for diagnosis of specific limb-girdle muscular dystrophy subtypes. For individuals with clinically suspected limb-girdle muscular dystrophy, there is clinical utility in genetic testing to confirm a diagnosis,to 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 limb-girdle muscular dystrophy, potentially to avoid invasive testing, and to allow reproductive planning. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic with a first- or second-degree relative with a limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy associated familial variant testing in asymptomatic relatives is lacking. However, the chain of evidence is strong, because determination of carrier status for a limb-girdle muscular dystrophy 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 an improvement in the net health outcome.

For individuals who are asymptomatic with a first- or second-degree relative with a limb-girdle muscular dystrophy whose genetic status is unknown who receive genetic testing for limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy associated genes in asymptomatic relatives is lacking. However, the chain of evidence is strong, because determination of carrier status for a limb-girdle muscular dystrophy 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 an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

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

American Academy of Neurology

In 2014, the American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine issued evidenced-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. The guideline was reaffirmed in October 2017. The following relevant recommendations were made (Table 3).

Table 3. Guidelines for LGMDs

Recommendations	LOR
Diagnosis of LGMD	
For individuals with 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 (eg, early contractures, cardiac, or respiratory involvement)	B
In individuals with suspected muscular dystrophy in whom initial clinically directed genetic testing does not provide a diagnosis, clinicians may obtain genetic consultation or perform parallel sequencing of targeted exomes, whole-exome sequencing, whole genome screening, or next-generation sequencing to identify the genetic abnormality	C
Management of cardiac complications in LGMD	
Clinicians should refer newly diagnosed individuals with (1) LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C-K, LGMD2M-P or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including ECG and structural	B

Recommendations	LOR
evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management.	
If ECG or structural cardiac evaluation (eg, echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (eg, Holter monitor or event monitor) to guide appropriate management	B
Clinicians should refer muscular dystrophy individuals with palpitations, symptomatic or asymptomatic tachycardia or arrhythmias, or signs and symptoms of cardiac failure for cardiology evaluation	B
It is not obligatory for clinicians to refer individuals with LGMD2A, LGMD2B, and LGMD2L for cardiac evaluation unless they develop overt cardiac signs or symptoms	B
Management of respiratory complications in LGMD	
Clinicians should order pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright and, if normal, supine positions) or refer for pulmonary evaluation (to identify and treat respiratory insufficiency) in muscular dystrophy individuals at the time of diagnosis, or if they develop pulmonary symptoms later in their course.	B
In individuals with a known high risk of respiratory failure (eg, those with LGMD2I), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency.	B
It is not obligatory for clinicians to refer individuals with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.	C
Clinicians should refer muscular dystrophy individuals with excessive daytime somnolence, nonrestorative sleep (eg, frequent nocturnal arousals, morning headaches, excessive daytime fatigue), or respiratory insufficiency based on	B

Recommendations	LOR
pulmonary function tests for pulmonary or sleep medicine consultation for consideration of noninvasive ventilation to improve quality of life.	

Adapted from Narayanaswami et al (2014).
ECG: electrocardiogram; LGMD: limb-girdle muscular dystrophies; LOR: level of recommendation; MRI: magnetic resonance imaging.

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

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

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in February 2023 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

Original Effective Date: 01/22/2016
Current Effective Date: 08/14/2023

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.
01/01/2019	Coding update
07/03/2019	Medical Policy Committee review
07/18/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/11/2020	Coding update
07/02/2020	Medical Policy Committee review
07/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/16/2020	Coding update
07/01/2021	Medical Policy Committee review
07/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/07/2022	Medical Policy Committee review
07/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Genetic Testing for Limb-Girdle Muscular Dystrophies

Policy # 00489
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07/06/2023 Medical Policy Committee review
07/12/2023 Medical Policy Implementation Committee approval. Replaced "patients" with individuals" in the coverage section. Coverage eligibility unchanged.
Next Scheduled Review Date: 07/2024

Coding

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Genetic Testing for Limb-Girdle Muscular Dystrophies

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

Code Type	Code
CPT	81173, 81174, 81204, 81400, 81404, 81405, 81406, 81408, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related Diagnoses

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

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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