2.04.132	Genetic Testing for Limb-Girdle Muscular Dystrophies		
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Policy Statement

I. Genetic testing for genes associated with limb-girdle muscular dystrophy to confirm a diagnosis of limb-girdle muscular dystrophy may be considered **medically necessary** when signs and symptoms of limb-girdle muscular dystrophy are present but a definitive diagnosis cannot be made without genetic testing, and when at least **one** of the following criteria are met:
   A. Results of testing may lead to changes in clinical management that improve outcomes (e.g., confirming or excluding the need for cardiac surveillance)
   B. Genetic testing will allow the affected individual to avoid invasive testing, including muscle biopsy

II. Genetic testing for genes associated with limb-girdle muscular dystrophy in the reproductive setting may be considered **medically necessary** when **both** of the following criteria are met:
   A. There is a diagnosis of limb-girdle muscular dystrophy in one or both of the parents
   B. Results of testing will allow informed reproductive decision making

III. Targeted genetic testing for a known familial variant associated with limb-girdle muscular dystrophy may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **both** of the following criteria are met:
   A. The individual has a close (i.e., first- or second-degree) relative with a known familial variant consistent with limb-girdle muscular dystrophy
   B. Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance)

IV. Genetic testing for genes associated with limb-girdle muscular dystrophy may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **both** of the following criteria are met:
   A. The individual has a close (i.e., first- or second-degree) relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable
   B. Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance)

V. Genetic testing for genes associated with limb-girdle muscular dystrophy is considered **investigational** in all other situations.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 (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; PMID25313375).

Testing Strategy

The 2014 AAN and AANEM joint guidelines have outlined an algorithmic approach to narrowing the differential diagnosis in an individual t 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 individual'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 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

Variant Classification	Definition
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.

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.

Related Policies

- Genetic Testing for Duchenne and Becker Muscular Dystrophy

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

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

Background

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.[1,] 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 patients 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 (e.g., 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.[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 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	

LGMD Type	Involved Gene	Involved Protein	Age at Onset	Rate of Progression	Cardiac Involvement?	Percent AR LGMD Cases
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%
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.
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),[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.
[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.[4,] *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 patients 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.[6,]

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, patients 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.[7,] 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 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 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.[7,] In a study (2012) that evaluated muscle computed tomography in 118 patients 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.[8,]

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.[9,]

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.[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 Moore et al (2006) study (previously described), 9% of all muscle biopsy samples had reduced expression of more than 1 protein tested.[6,] 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.[4,]

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.[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 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 (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 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 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 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 patients with genetically confirmed LGMD2B (dysferlinopathy) showed no benefit and a trend toward worsening strength associated with therapy.[11,] Autologous bone marrow transplant has been investigated for limb-girdle muscular dystrophy but is not in general clinical use.[12,] Adeno-associated virus-mediated gene transfer to the extensor digitorumbrevis 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 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.[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 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.[15,] 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.[16,]
- 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][s] 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*

Literature Review

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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 limb-girdle muscular dystrophy is to establish the diagnosis of limb-girdle muscular dystrophy, 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 limb-girdle muscular dystrophy, potential avoidance of invasive testing, and informing reproductive decision making.

The following PICO was used to select literature to inform this review.

Population

The relevant population of interest is individuals with signs or symptoms of limb-girdle muscular dystrophy.

Intervention

The test being considered is testing of genes associated with limb-girdle muscular dystrophy. Genetic testing is used to confirm a diagnosis of limb-girdle muscular dystrophy. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Comparator

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

Outcomes

General outcomes of interest are overall survival, test accuracy, test validity, changes in reproductive decision making, change in disease status, and morbid events.

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

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.

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.

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort

Review of Evidence

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 limb-girdle muscular dystrophy, clinical validity may refer to the overall yield of testing for any limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy subtype.

Unselected Limb-Girdle Muscular Dystrophy Populations

One potential role for genetic testing in limb-girdle muscular dystrophy is assessing patients with clinically suspected limb-girdle muscular dystrophy but who do not necessarily have results of a muscle biopsy available.

The American Academy of Neurology (AAN) and American Association of Neuromuscular & Electrodiagnostic Medicine (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 limb-girdle muscular dystrophy in patients who present with suspected muscular dystrophy.[17,] 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 Limb-Girdle Muscular Dystrophy

LGMD Type	Involved Protein	Evidence Base[a]	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%
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%
LGMD1C	Caveolin-3	3 class III studies	Not described	1.3%-2.6%
LGMD2A	Calpain-3	2 class I studies	1105 patients with genetic muscle disorders; 68 with LGMD	26.5% of all LGMD cases
			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	g-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%

LGMD Type	Involved Protein	Evidence Base[a]	Population	Variant Detection Frequency
	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 FKRP 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 FKRP variant testing	6.5%
LGMD2N	POMT2	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative FKRP variant testing	9.7%
LGMD2O	POMGNT1	1 class III study	92 patients with evidence of dystroglycanopathy on muscle biopsy and negative FKRP variant testing	7.6%

Adapted From Narayanaswami et al (2014).[17,]
CK: creatine kinase; LGMD: limb-girdle muscular dystrophy; MD: muscular dystrophy.
[a] 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).[18,] The population included 1105 cases with various inherited muscle diseases diagnosed and treated 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 limb-girdle muscular dystrophy, of whom 43 (6.15%) had positive genetic testing for a gene associated with limb-girdle muscular dystrophy. Of patients with a clinical diagnosis of limb-girdle muscular dystrophy, 72.1% had positive genetic testing, most commonly for LGMD2A (26.5%; 95% confidence interval [CI], 16.0% to 37.0%).

Variable Gene Expression

For some limb-girdle muscular dystrophy 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).[19,] Of the 78 myopathic patients, 37 (47%) had a limb-girdle muscular dystrophy phenotype (*LGMD1B*), 18 (23%) had a 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 were evaluated at a single European center.[20,] A clinical suspicion of the ANO5 variant (anoctaminopathy) could have been based on clinical examination, muscle assessment, and clinical evaluations including creatine kinase (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 limb-girdle muscular dystrophy 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.[21,] 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.

Limb-Girdle Muscular Dystrophy Patients With Muscle Biopsy Results

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

Fanin et al (2009) evaluated the yield of molecular diagnostics among 550 cases with specific limb-girdle muscular dystrophy related phenotypes, including severe childhood-onset limb-girdle muscular dystrophy, adult-onset limb-girdle muscular dystrophy, distoproximal myopathy, and

asymptomatic hyper-creatine kinase-emia, who had undergone muscle biopsy with multiple protein screening.[22,] 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 α-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 using 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 limb-girdle muscular dystrophy, 186 had adult-onset limb-girdle muscular dystrophy, 38 had distoproximal myopathy, and 204 had asymptomatic hyper-creatine kinase-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-creatine kinase-emia, a molecular diagnosis was made in 205 (59.2%) of 346 cases with a limb-girdle muscular dystrophy phenotype. Patients with childhood-onset limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy and muscle biopsy with dystrophic features.[23,]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 limb-girdle muscular dystrophy subtypes was as follows: LGMD1C (caveolin-3) 1.3%; LGMD2A (calpain-3) 28.4%; LGMD2B (dysferlin) 18.7%; LGMD2C (g-sarcoglycan) 4.5%; LGMD2D (α-sarcoglycan) 8.4%; LGMD2E (β-sarcoglycan) 4.5%; LGMD2F (δ-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 α-sarcoglycan deficiency assessed using immunohistochemistry and immunoblotting of muscle biopsy samples.[24,] 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.[25,] *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.26, In 5 (13.5%) cases, molecular diagnosis could be made directly by identification of compound heterozygous or homozygous variants previously associated with limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy vary by the variants included and the characteristics of the patient populations tested. The true clinical sensitivity and specificity of genetic testing for limb-girdle muscular dystrophy variants, in general, cannot be determined because there is no criterion standard test for diagnosing limb-girdle muscular dystrophy. Studies have reported testing yields ranging from 37% to greater than 70% in patients with clinically suspected limb-girdle muscular dystrophy. The criterion standard for diagnosing a limb-girdle muscular dystrophy subtype is the genetic test. The specificity of a positive limb-girdle

muscular dystrophy genetic test result in predicting the clinical phenotype of limb-girdle muscular dystrophy is not well-defined. However, there is evidence to support a finding that some variants associated with limb-girdle muscular dystrophy 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, more effective therapy, or avoid unnecessary therapy or 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 (RCTs).

No RCTs 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 limb-girdle muscular dystrophy for an index case (a patient with clinically suspected limb-girdle muscular dystrophy) includes:

- Confirming the diagnosis of limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy, 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 limb-girdle muscular dystrophy 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 Duchenne and Becker muscular dystrophies, patients with limb-girdle muscular dystrophy are at higher risk of cardiac abnormalities, including dilated cardiomyopathy and various arrhythmias.[27,] Specific limb-girdle muscular dystrophy 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 muscular dystrophy. These guidelines have recommended considering implantation of a permanent pacemaker for patients with limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy subtypes are more strongly associated with cardiac disorders than others. Limb-girdle muscular dystrophy types 2C through 2F and 2I are associated with a primary dilated cardiomyopathy, with conduction disorders occurring as a secondary phenomenon.[28,] Other limb-girdle muscular dystrophy 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.[17,]

There is clinical utility for identifying a specific limb-girdle muscular dystrophy gene variant for patients presenting with signs and symptoms of limb-girdle muscular dystrophy 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.[27,] Similarly, *FKTN* variants can be associated with dilated cardiomyopathy, with or without the presence of myopathy. Murakami et al (2006) reported on a case series of 6 patients from 4 families with compound heterozygous *FKTN* variants who presented with dilated cardiomyopathy and no or minimal myopathic symptoms.[29,]

Section Summary: Clinically Useful

In patients with clinically suspected limb-girdle muscular dystrophy, genetic testing is used primarily to confirm a diagnosis but may also have a prognostic role given the clinical variability across limb-girdle muscular dystrophy 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 Who Have Relatives With Limb-Girdle Muscular Dystrophy 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 limb-girdle muscular dystrophy 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 following PICO was used to select literature to inform this review.

Population

The relevant population of interest is asymptomatic individuals with first- and second-degree relatives who have limb-girdle muscular dystrophy and a known familial variant.

Intervention

The test being considered is targeted familial variant testing.

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 limb-girdle muscular dystrophy 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.

Comparator
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 limb-girdle muscular dystrophy subtype and changes in reproductive planning.

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.

Study Selection Criteria
For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort

Review of Evidence
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 Limb-Girdle Muscular Dystrophy* 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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

No RCTs 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 relative with limb-girdle muscular dystrophy 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 Who Have Relatives With Limb-Girdle Muscular Dystrophy and a Known Familial Variant

For individuals who are asymptomatic with a first- or second-degree relative with limb-girdle muscular dystrophy 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 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.

Testing of Asymptomatic Individuals Who Have Relatives With Limb-Girdle Muscular Dystrophy and Unknown Genetic Status

Clinical Context and Test Purpose

The purpose of genetic testing of asymptomatic individuals with first- and second-degree relatives who have limb-girdle muscular dystrophy 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.

The following PICO was used to select literature to inform this review.

Population

The relevant population of interest is asymptomatic individuals with first- and second-degree relatives who have limb-girdle muscular dystrophy whose genetic status is unknown.

Intervention

The test being considered is genetic testing for genes associated with limb-girdle muscular dystrophy.

Genetic testing is used to confirm the genetic status of a pathogenic variant in an limb-girdle muscular dystrophy associated gene. If the pathogenic variant in an limb-girdle muscular dystrophy associated gene is detected, referral to cardiology is important to initiate cardiac surveillance if the specific limb-girdle muscular dystrophy 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.

Comparator

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 limb-girdle muscular dystrophy subtype and changes in reproductive planning.

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.

Study Selection Criteria

For the evaluation of clinical validity of the tests, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from the development cohort

Review of Evidence

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 Limb-Girdle Muscular Dystrophy* 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, more effective therapy, or avoid unnecessary therapy or 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 RCTs.

No RCTs 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 relatives with limb-girdle muscular dystrophy 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 limb-girdle muscular dystrophy associated gene.
- Informing the reproductive decision making process for preimplantation testing and/or prenatal (in utero) testing when a pathogenic variant in a limb-girdle muscular dystrophy associated gene is present in a parent.

Section Summary: Testing of Asymptomatic Individuals Who Have Relatives With Limb-Girdle Muscular Dystrophy and Unknown Genetic Status

For individuals who are asymptomatic and have a first- or second-degree relative with limb-girdle muscular dystrophy whose genetic status is unknown who are given genetic testing for limb-girdle muscular dystrophy 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 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.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.[17,].The guideline was reaffirmed in October 2017. The following relevant recommendations were made (Table 4).

Table 4. Guidelines for LGMDs

Recommendations	LOR
Diagnosis of LGMD	
For patients 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 (e.g., early contractures, cardiac, or respiratory involvement)	B
In patients 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 patients with (1) LGMD1A, LGMD1B, LGMD1D, LGMD1E, LGMD2C-K, LGMD2M-P or (2) muscular dystrophy without a specific genetic diagnosis for cardiology evaluation, including ECG and structural evaluation (echocardiography or cardiac MRI), even if they are asymptomatic from a cardiac standpoint, to guide appropriate management.	B
If ECG or structural cardiac evaluation (e.g., echocardiography) has abnormal results, or if the patient has episodes of syncope, near-syncope, or palpitations, clinicians should order rhythm evaluation (e.g., Holter monitor or event monitor) to guide appropriate management	B
Clinicians should refer muscular dystrophy patients 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 patients 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 patients at the time of diagnosis, or if they develop pulmonary symptoms later in their course.	B
In patients with a known high risk of respiratory failure (e.g., those with LGMD2I), clinicians should obtain periodic pulmonary function testing (spirometry and maximal inspiratory/expiratory force in the upright position and, if normal, in the supine position) or evaluation by a pulmonologist to identify and treat respiratory insufficiency.	B
It is not obligatory for clinicians to refer patients with LGMD2B and LGMD2L for pulmonary evaluation unless they are symptomatic.	C

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

Adapted from Narayanaswami et al (2014).[17,]
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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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:

  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	81400	Molecular pathology procedure, Level 1
	81404	Molecular pathology procedure, Level 5
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81408	Molecular pathology procedure Level 9
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/01/2016	BCBSA Medical Policy Adoption
07/01/2017	Policy title change from Mutation Testing for Limb-Girdle Muscular Dystrophies Policy revision without position change
06/01/2018	Policy revision without position change
06/01/2019	Policy revision without position change
07/01/2023	Policy reactivated. Previously archived from 06/01/2020 to 06/30/2023.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
Reactivated policy **Policy Statement:** **N/A**	**Genetic Testing for Limb-Girdle Muscular Dystrophies 2.04.132** **Policy Statement:** I. Genetic testing for genes associated with limb-girdle muscular dystrophy to confirm a diagnosis of limb-girdle muscular dystrophy may be considered **medically necessary** when signs and symptoms of limb-girdle muscular dystrophy are present but a definitive diagnosis cannot be made without genetic testing, and when at least **one** of the following criteria are met: A. Results of testing may lead to changes in clinical management that improve outcomes (e.g., confirming or excluding the need for cardiac surveillance) B. Genetic testing will allow the affected individual to avoid invasive testing, including muscle biopsy II. Genetic testing for genes associated with limb-girdle muscular dystrophy in the reproductive setting may be considered **medically necessary** when **both** of the following criteria are met: A. There is a diagnosis of limb-girdle muscular dystrophy in one or both of the parents B. Results of testing will allow informed reproductive decision making III. Targeted genetic testing for a known familial variant associated with limb-girdle muscular dystrophy may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **both** of the following criteria are met: A. The individual has a close (i.e., first- or second-degree) relative with a known familial variant consistent with limb-girdle muscular dystrophy B. Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance)

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
	IV. Genetic testing for genes associated with limb-girdle muscular dystrophy may be considered **medically necessary** in an asymptomatic individual to determine future risk of disease when **both** of the following criteria are met: A. The individual has a close (i.e., first- or second-degree) relative diagnosed with limb-girdle muscular dystrophy whose genetic status is unavailable B. Results of testing will lead to changes in clinical management (e.g., confirming or excluding the need for cardiac surveillance) V. Genetic testing for genes associated with limb-girdle muscular dystrophy is considered **investigational** in all other situations.