Genetic Testing for Limb-Girdle Muscular Dystrophies

Description

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

OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing improves health outcomes in individuals who have signs and symptoms of a dystrophinopathy. This review does not evaluate individuals who are asymptomatic with a first- or second-degree relative diagnosed with limb-girdle muscular dystrophy, either with a known familial variant or whose genetic status is unknown.

POLICY STATEMENT

Genetic testing for genes associated with limb-girdle muscular dystrophy (LGMD) to confirm a diagnosis of LGMD may be considered medically necessary when signs and symptoms of LGMD are present but a definitive diagnosis cannot be made without genetic testing, and when at least one of the following criteria are met:

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

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POLICY GUIDELINES

Limb-Girdle Muscular Dystrophy

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

Evaluation and diagnosis of LGMD should be carried out by providers with expertise in neuromuscular disorders. The 2014 guidelines from the American Academy of Neurology (AAN) and American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) on treatment of LGMD recommend that "clinicians should refer patients with muscular dystrophy to a clinic that has access to multiple specialties (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).

Testing Strategy

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

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

GENETICS NOMENCLATURE UPDATE

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 is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table 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

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

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

**BENEFIT APPLICATION**

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

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

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Summary of Evidence

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

The American Academy of Neurology and the American Association of Neuromuscular and Electrodiagnostic Medicine (2014) issued evidence-based guidelines for the diagnosis and treatment of limb-girdle and distal dystrophies. The following relevant recommendations were made (see Table 1).

Table 1. Guidelines for LGMDs

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>LOR</th>
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<tr>
<td>Diagnosis of LGMD</td>
<td></td>
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<tr>
<td>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)</td>
<td>B</td>
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<tr>
<td>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</td>
<td>C</td>
</tr>
<tr>
<td>Management of cardiac complications in LGMD</td>
<td></td>
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<tr>
<td>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</td>
<td>B</td>
</tr>
<tr>
<td>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</td>
<td>B</td>
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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**

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).\(^{19}\)

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.
REFERENCES


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**POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tr>
<td>June 2018</td>
<td>New policy</td>
<td>Genetic testing for genes associated with LGMD may be considered medically necessary with conditions.</td>
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<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through February 5, 2019; no references added. Policy statements unchanged.</td>
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