Medical Policy

Genetic Testing for Muscular Dystrophies

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Policy Number: 828
BCBSA Reference Number: 2.04.86
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
None

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Duchenne and Becker Muscular Dystrophy

Genetic testing for DMD gene variants may be considered MEDICALLY NECESSARY under the following conditions:
- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives:*
  - To confirm or exclude the need for cardiac surveillance
  - For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy.
- For at-risk male offspring:**
  - To confirm or exclude the need for medical and cardiac surveillance.

*At-risk females are defined as first- and second-degree female relatives and include the proband’s mother, female siblings of the proband, female offspring of the proband, the proband’s maternal grandmother, maternal aunts, and their offspring.

**An at-risk male is defined as an asymptomatic male offspring of a female carrier or an asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy.

Genetic testing for DMD gene variants is considered INVESTIGATIONAL in all other situations.

Emery-Dreifuss Muscular Dystrophy

Genetic testing of LMNA with full sequencing may be considered MEDICALLY NECESSARY in an individual with signs and symptoms suggestive of EDMD.
Genetic testing of EDMD and/or FLHI with full sequencing may be considered MEDICALLY NECESSARY in an individual with signs and symptoms suggestive of EDMD when family history is suggestive of X-linked inheritance (i.e. no male-to-male transmission).

Genetic testing for mutations associated with EDMD may be considered MEDICALLY NECESSARY in an asymptomatic individual to determine future risk of disease when the individual has:

- A close relative (i.e., first- or second-degree relative) with a known mutation consistent with EDMD; AND
- Results of testing will lead to changes in cardiac surveillance, OR
- A close relative (i.e., first- or second-degree relative) diagnosed with EDMD whose genetic status is unavailable. AND
- The individual is at-risk for EDMD, based on family history analysis (i.e. related through maternal line if X-linked EDMD), AND
- Results of testing will lead to changes in cardiac surveillance.

Genetic testing for EDMD is considered INVESTIGATIONAL in all other circumstances.

**Spinal Muscular Atrophy**

Genetic testing for SMA (gene SMN1) with targeted mutation analysis or gene dosage analysis may be considered MEDICALLY NECESSARY in an individual with signs and symptoms suggestive of SMA.

Genetic testing for SMA is considered INVESTIGATIONAL in all other circumstances.

**Congenital Muscular Dystrophy**

Genetic testing for congenital MD may be considered MEDICALLY NECESSARY for diagnosis confirmation when signs and symptoms of congenital MD are present but a definitive diagnosis cannot be made without genetic testing, and when all of the following criteria are met:

- Results of testing may lead to changes in clinical management (e.g. confirm or exclude need for cardiac and/or ophthalmologic screening); OR Genetic testing will allow the affected patient to avoid invasive testing or screening, including muscle biopsy. AND
- Requested testing is directed toward a specific subtype of CMD based on clinical features and/or family history (i.e., LAMA2, dystroglycanopathy, merosinopathy).

Genetic testing for congenital muscular dystrophy is considered INVESTIGATIONAL in all other circumstances.

**Myotonic Dystrophy**

Genetic testing via targeted analysis in DM1 (gene DMPK) may be considered MEDICALLY NECESSARY in an individual with signs and symptoms of myotonic dystrophy type 1.

Genetic testing via targeted analysis in DM2 (gene CNBP) may be considered MEDICALLY NECESSARY in an individual with signs and symptoms of myotonic dystrophy type 2.

Genetic testing for DM1 or DM2 in an asymptomatic individual ≥ age 18 may be considered MEDICALLY NECESSARY when a first or second-degree relative has been diagnosed with DM1 or DM2.

Genetic testing for myotonic dystrophy is considered INVESTIGATIONAL in all other circumstances.

**Facioscapulohumeral Muscular Dystrophy**

Genetic testing for facioscapulohumeral muscular dystrophy may be considered MEDICALLY NECESSARY to confirm a diagnosis in a patient with clinical signs of the disease.

Genetic testing for facioscapulohumeral muscular dystrophy is INVESTIGATIONAL for all other indications.
Collagen VI Disorders

Genetic testing for mutations in COL6A1, COL6A2, COL6A3 associated with collagen VI related disorders may be considered **MEDICALLY NECESSARY** for diagnosis confirmation when signs and symptoms of a collagen VI related disorder 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; OR
- Genetic testing will allow the individual to avoid invasive testing or screening, including muscle biopsy or sedated muscle MRI.

Genetic testing for collagen VI related disorders is **INVESTIGATIONAL** for all other indications.

Limb Girdle Muscular Dystrophy

Genetic testing for mutations 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 and the patient meets at least one criterion in section one AND one criterion in section two:

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

Section Two:
- The individual has a suspected clinical diagnosis of a specific LGMD subtype and the associated single gene testing is being requested, OR
- Clinical features are not consistent with one LGMD subtype but clinical examination and results of conventional testing are suggestive of LGMD and requested testing is directed toward a specific subset of LGMD based on clinical features and/or family history (e.g., sarcoglycanopathy, autosomal dominant LGMD).

Genetic testing for mutations associated with LGMD may be considered **MEDICALLY NECESSARY** in an asymptomatic individual to determine future risk of disease when the individual has:
- A close relative (ie, first- or second-degree relative) with a known mutation consistent with LGMD; OR
- A close relative (ie, first- or second-degree relative) diagnosed with LGMD whose genetic status is unavailable. AND
- Results of testing will lead to changes in clinical management (eg, confirming or excluding the need for cardiac surveillance).

Genetic testing for mutations associated with LGMD is considered **INVESTIGATIONAL** in all other situations.

Panel Testing

Targeted multi-gene panel genetic testing for muscular dystrophies (e.g. Emery-Dreifuss muscular dystrophy, limb girdle muscular dystrophy, and congenital muscular dystrophy) may be considered **MEDICALLY NECESSARY** when signs and symptoms of a specific muscular dystrophy syndrome are present, and when ALL of the following criteria are met:

- Results of testing will lead to changes in clinical management (e.g, confirm or exclude need for cardiac and/or ophthalmologic screening) OR genetic testing will allow the affected patient to avoid invasive testing or screening, including muscle biopsy, AND
- Requested testing is as targeted as possible based on clinical features and/or family history (e.g., dystroglycanopathy, merosinopathy).

Multi-gene panel genetic testing that includes genes for multiple muscular dystrophy syndromes is considered **INVESTIGATIONAL**.
Medicare HMO Blue℠ and Medicare PPO Blue℠ Members

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the link below.

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

| Outpatient | Commercial Managed Care (HMO and POS) | No |
| Commercial PPO and Indemnity | No |
| Medicare HMO Blue℠ | This is not a covered service. |
| Medicare PPO Blue℠ | This is not a covered service. |

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (eg, Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed</td>
</tr>
</tbody>
</table>

The following ICD Diagnosis Codes are considered medically necessary when submitted with the CPT codes above if medical necessity criteria are met:

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>F82</td>
<td>Specific developmental disorder of motor function</td>
</tr>
<tr>
<td>G71.0</td>
<td>Muscular dystrophy</td>
</tr>
<tr>
<td>M62.50</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Site</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>M62.511</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Shoulder</td>
</tr>
<tr>
<td>M62.512</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Shoulder</td>
</tr>
<tr>
<td>M62.519</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Shoulder</td>
</tr>
<tr>
<td>M62.521</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Upper Arm</td>
</tr>
<tr>
<td>M62.522</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Upper Arm</td>
</tr>
<tr>
<td>M62.529</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Upper Arm</td>
</tr>
<tr>
<td>M62.531</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Forearm</td>
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<tr>
<td>M62.532</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Forearm</td>
</tr>
<tr>
<td>M62.539</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Forearm</td>
</tr>
<tr>
<td>M62.541</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Hand</td>
</tr>
<tr>
<td>M62.542</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Hand</td>
</tr>
<tr>
<td>M62.549</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Hand</td>
</tr>
<tr>
<td>M62.551</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Thigh</td>
</tr>
<tr>
<td>M62.552</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Thigh</td>
</tr>
<tr>
<td>M62.559</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Thigh</td>
</tr>
<tr>
<td>M62.561</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Lower Leg</td>
</tr>
<tr>
<td>M62.562</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Lower Leg</td>
</tr>
<tr>
<td>M62.569</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Lower Leg</td>
</tr>
<tr>
<td>M62.571</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Right Ankle And Foot</td>
</tr>
<tr>
<td>M62.572</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Left Ankle And Foot</td>
</tr>
<tr>
<td>M62.579</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Unspecified Ankle And Foot</td>
</tr>
<tr>
<td>M62.58</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Other Site</td>
</tr>
<tr>
<td>M62.59</td>
<td>Muscle Wasting And Atrophy, Not Elsewhere Classified, Multiple Sites</td>
</tr>
<tr>
<td>M62.81</td>
<td>Muscle weakness (generalized)</td>
</tr>
<tr>
<td>R26.0</td>
<td>Ataxic gait</td>
</tr>
<tr>
<td>R26.1</td>
<td>Paralytic gait</td>
</tr>
<tr>
<td>R26.2</td>
<td>Difficulty in walking, not elsewhere classified</td>
</tr>
<tr>
<td>R26.81</td>
<td>Unsteadiness on feet</td>
</tr>
<tr>
<td>R26.89</td>
<td>Other abnormalities of gait and mobility</td>
</tr>
<tr>
<td>R26.9</td>
<td>Unspecified abnormalities of gait and mobility</td>
</tr>
<tr>
<td>R27.9</td>
<td>Unspecified lack of coordination</td>
</tr>
<tr>
<td>R29.6</td>
<td>Repeated falls</td>
</tr>
<tr>
<td>R53.1</td>
<td>Weakness</td>
</tr>
<tr>
<td>R62.0</td>
<td>Delayed milestone in childhood</td>
</tr>
<tr>
<td>Z31.430</td>
<td>Encounter of female for testing for genetic disease carrier status for procreative management</td>
</tr>
<tr>
<td>Z31.438</td>
<td>Encounter for other genetic testing of female for procreative management</td>
</tr>
<tr>
<td>Z31.440</td>
<td>Encounter of male for testing for genetic disease carrier status for procreative management</td>
</tr>
<tr>
<td>Z31.448</td>
<td>Encounter for other genetic testing of male for procreative management</td>
</tr>
<tr>
<td>Z82.0</td>
<td>Family history of epilepsy and other diseases of the nervous system</td>
</tr>
<tr>
<td>Z84.81</td>
<td>Family history of carrier of genetic disease</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
</tr>
<tr>
<td>81401</td>
<td>Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td>81404</td>
<td>Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)</td>
</tr>
<tr>
<td>81405</td>
<td>Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)</td>
</tr>
<tr>
<td>81406</td>
<td>Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)</td>
</tr>
</tbody>
</table>

**Description**

Muscular dystrophies (MDs) are a group of inherited disorders characterized by progressive weakness and degeneration of skeletal muscle, cardiac muscle, or both, which may be association with respiratory muscle involvement or dysphagia and dysarthria. MDs 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 CK levels. MDs have been classified on the basis of clinical presentation and genetic etiology. The most common MDs are the dystrophinopathies, Duchenne (DMD) and Becker (BMD) muscular dystrophies, which are characterized by mutations in the dystrophin gene. Other MDs are characterized by the location of onset of clinical weakness and include the LGMDs, facioscapulohumeral MD, oculopharyngeal MD, distal MD, and humeroperoneal MD (also known as Emery-Dreifuss muscular dystrophy). The congenital MDs are a genetically heterogeneous group of disorders, which historically included infants with hypotonia and weakness at birth and findings of MD 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.

**Duchenne and Becker Muscular Dystrophy**

Duchenne muscular dystrophy (DMD) is an X-linked rapidly progressive dystrophinopathy associated with delayed milestones, proximal weakness, elevated serum creatine kinase (CK) and cardiomyopathy. Most affected individuals are males; however, classic DMD symptoms have been reported with girls as well (Hoogerwaard 1999a). Presentation usually begins in early childhood with few affected individuals surviving beyond the third decade due to respiratory complications and cardiomyopathy. DMD is the only gene associated with DMD and molecular genetic testing can establish the diagnosis avoiding muscle biopsy, with nearly 100% detection rate in males with DMD.

Females who are carriers of DMD are at risk of developing cardiomyopathy. Onset is typically considered to be in adulthood. Carrier females can have cardiac involvement ranging from asymptomatic to having severe heart failure requiring transplantation. Therefore, cardiovascular screening for females who are carriers for DMD is recommended. Specifically, recommendations for cardiac care of carrier females includes referral to a cardiac specialist with familiarity of neuromuscular conditions and/or heart failure, an
initial cardiac evaluation in late adolescence or early adulthood, and a complete cardiac evaluation a minimum of once every 5 years beginning at 25 to 30 years of age (American Academy of Pediatrics 2005). Genetic testing of females plays an important role in reproductive planning.

**Limb-Girdle Muscular Dystrophy**

Limb girdle muscular dystrophy (LGMD) is a heterogeneous group of disorders characterized by progressive muscle weakness with dystrophic muscle pathology caused by autosomal dominant or recessive gene mutations [Mitsuhashi and Kahn, 2012]. The muscle weakness is typically progressive and primarily limited to proximal muscle weakness, with relative sparing of heart and bulbar muscles, except for some subtypes [Rosales et al 2012; Bushby et al 2009]. Onset, progression, and distribution of the weakness and wasting may vary considerably among individuals and genetic subtypes and etiologies [Pegoraro and Hoffman 2012]. Although there are few pathognomonic features, many LGMD disorders have distinguishing clinical features [Narayanaswami et al 2014].

The major forms of LGMD result from mutations in genes encoding constituents of the sarcolemmal dystrophin complex, e.g., laminin (LGMD1B), sarcoglycan (LGMD2C-F), and dysferlin (LGMD2B) [Bogershausen et al 2013]. Other forms, however, result from mutations in genes affecting muscle function via different pathomechanisms involving membrane trafficking, muscle remodeling, and posttranslational modification of sarcolemmal proteins [Minetti et al 1998; Richard et al 1995; Mercuri et al 2012]. The term LGMD1 (including, e.g., LGMD1A, LGMD1B) refers to genetic types showing dominant inheritance, whereas LGMD2 refers to types with autosomal recessive inheritance [Pegoraro and Hoffman 2012].

To establish a clinical diagnosis of LGMD, a comprehensive approach is typically needed, which may include a thorough evaluation by an experienced clinician, serum creatine kinase measurements, genetic testing, and muscle biopsy [Mitsuhashi and Kahm, 2012]. Mutations at over 50 loci with either autosomal-dominant (LGMD1) or autosomal-recessive inheritance (LGMD2) have been described [Pegoraro and Hoffman 2012]. Recent guidelines from the American Academy of Neurology propose that clinicians 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) [Narayanaswami et al 2014]. From this clinical evaluation, a directed plan for genetic testing can be identified. This guideline recommends that if initial directed genetic testing is negative, clinicians may obtain genetic consultation or perform further testing by next-generation sequencing technologies to identify the genetic abnormality [Narayanaswami et al 2014].

LGMD2I, caused by mutations in the FKRP gene, presently accounts for about 6% of LGMD autosomal recessive diagnoses [Pegoraro and Hoffman 2012]. The LGMD2I (FKRP) phenotype ranges from severe (similar to Duchenne muscular dystrophy) to mild with no clinically apparent skeletal muscle involvement [Muller et al 2005; Boito et al 2005]. Most importantly, cardiac involvement occurs in 10%-55% of affected individuals [Pegoraro and Hoffman 2012].

LGMD1B is caused by mutations in the LMNA gene, although LMNA mutations result in at least 11 allelic conditions, including well-described hereditary cardiac conditions. In LGMD1B, muscle weakness and cardiac involvement are present by the third decade. Mutations in this gene can lead to severe cardiac events and sudden death [Pegoraro and Hoffman 2012]. Left ventricular hypertrophy and atrioventricular conduction defect are common and can progress to second-degree heart block requiring a pacemaker; rarely, dilated cardiomyopathy is present. In individuals identified with a LMNA mutation requiring pacemaker placement (i.e. history of arrhythmia or known risk of arrhythmia), the use of a pacing ICD rather than a pacemaker has been recommended due to the risk of ventricular arrhythmias and sudden death [Meune et al 2006; Hershberger et al 2009].

**Emery-Dreifuss Muscular Dystrophy**

Emery-Dreifuss muscular dystrophy (EDMD) is a slowly progressive muscular dystrophy associated with joint contractures, proximal muscle weakness, and cardiac disease. The age of onset and severity is variable both between and within families. Typically, contractures are present in childhood or adolescence...
and may precede the muscle weakness. EDMD is associated with progressive cardiac involvement, including both cardiomyopathy and cardiac conduction defects. Serum creatine kinase levels may be normal or moderately elevated (2-20 fold increase).

Treatment of EDMD involves monitoring respiratory and cardiac function. Cardiac screening includes annual ECG, holter monitoring, and echocardiography. Cardiac MRI may be recommended, when available and clinically indicated. Implantation of a cardiac defibrillator is recommended for many affected individuals, due to the risk for sudden cardiac death. In addition, complications related to anesthesia should be considered prior to surgical procedures, including a theoretical association with malignant hyperthermia. Neuromuscular symptoms require symptomatic management. EDMD carriers are at risk for cardiac involvement, which can present as sudden cardiac death.

EDMD can have multiple inheritance patterns, including X-linked, autosomal dominant and recessive. The most common form is X-linked recessive.

Genetic testing is available for three genes known to be associated with EDMD. EMD and FHL1 are located on the X-chromosome and LMNA is located on chromosome 1. Mutations in these genes account for greater than 50% of all genetically confirmed EDMD. EMD and FHL1-related EDMD are inherited in an X-linked recessive pattern. LMNA-related EDMD is inherited in an autosomal dominant pattern. A majority (76%) of the LMNA mutations are de novo.

Genetic testing is recommended for all at-risk family members due to the associated risk for cardiac involvement, including sudden cardiac death. Knowledge of genetic status can be used to appropriately manage potential cardiac complications and guide cardiac screening in gene positive individuals, as well as discontinue costly screening in those who are gene negative. Cardiac monitoring is recommended for all at-risk family members if a pathogenic variant has not been identified in the family.

Genetic testing involves evaluating EMD, FHL1, and LMNA both by sequencing and deletion/duplication analysis. Clinical symptoms and inheritance pattern can help prioritize which test(s) to perform.

**Congenital Muscular Dystrophy**

Congenital muscular dystrophy (CMD) describes a broad group of conditions with heterogeneous clinical presentations and genetic etiologies. Muscle weakness is usually present at birth or in infancy, and progresses over time. Developmental delay (motor and/or cognitive) may be present. Certain subtypes can feature cardiac involvement, eye abnormalities, and/or risk for seizures. There can be overlap between congenital muscular dystrophies and congenital myopathies, as well as late-onset muscular dystrophies like Limb-Girdle muscular dystrophy. Three main subtypes of CMD have been described: collagen VI-related myopathies, merosinopathies, and dystroglycanopathies; however, other rare CMDs exist, which do not fit into the above listed three categories.

Brain MRI, creatine kinase, muscle biopsy, immunohistochemical staining, EMG/NCV, and genetic testing can all be used to aid in the diagnosis of a specific congenital muscular dystrophy. Brain MRI and muscle biopsy are typically first steps in the work-up of a child with congenital muscular dystrophy. Unfortunately, there are few pathognomonic findings on MRI or muscle biopsy to fully distinguish amongst these overlapping conditions, and normal results do not rule out CMD. Molecular genetic testing may be useful for establishing a diagnosis, prediction of prognosis, reproductive planning, and to guide frequency of surveillance by other medical specialists (eg, cardiology, ophthalmology, sleep studies). In some instances, molecular genetic testing may replace the need for more invasive skin or muscle biopsy in an affected individual with highly suggestive clinical features. However, when multiple genes are on the differential, results from immunohistochemistry analysis of a muscle biopsy sample may narrow the list to allow for more targeted genetic testing. Importantly, the use of muscle biopsy is recommended for experienced centers with the technical and knowledge expertise to allow for accurate interpretation of results.

Given the large number of genes associated with overlapping clinical presentations, panel genetic testing may be an appropriate consideration in cases where results will clearly impact medical management. The
International Standard of Care Committee for Congenital Muscular Dystrophies Consensus Guidelines recommend panel testing for alpha-dystroglycanopathy genes in cases with absent alpha-dystroglycan staining on muscle biopsy or those with normal staining where clinical suspicion remains high (Bonnemann et al, 2014). However, the detection rate of these panels is not known, and is likely that more genes will be identified in the future. When possible, targeted gene testing is preferred.

Chae et al. (2015) conducted a study of 43 patients presenting with early onset neuromuscular disorders from unknown genetic origin who were tested by NGS for 579 nuclear genes associated with myopathy and identified the definite genetic cause in 21 individuals (48%). The study therefore concludes a targeted NGS panel can offer cost effective, safe and fairly rapid turnaround time.

Myotonic Dystrophy
Myotonic dystrophy is a progressive multisystem genetic disorder affecting about 1 in 8000 people worldwide. The unstable repeat expansions of (CTG)n or (CCTG)n in the DMPK and CNBP (ZNF9) genes cause the two known subtypes of myotonic dystrophy: myotonic dystrophy type 1 (DM1) and myotonic dystrophy type 2 (DM2), respectively.

DM1 is characterized by three somewhat overlapping phenotypes: mild, classic, and congenital. Mild DM1 is characterized by cataract and mild myotonia (sustained muscle contraction); lifespan is normal. Classic DM1 is characterized by muscle weakness and wasting, myotonia, cataract, and often cardiac conduction abnormalities; adults may become physically disabled and may have a shortened life span. Congenital DM1 is characterized by hypotonia and severe generalized weakness at birth, often with respiratory insufficiency and early death; intellectual disability is common.

Diagnostic testing for DM1 often includes muscle biopsy. Muscle pathology includes atrophic fibers, scattered severely atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central nuclei, all of which occur in both DM1 and DM2 and thus cannot be used to distinguish between the two conditions. Type 1 fiber atrophy is a common feature in individuals with congenital DM1, distinguishing it from DM2.

DMPK is the only gene in which mutations are known to cause DM1. Essentially 100% of individuals with DM1 have an increased number (i.e., an expansion) of the CTG trinucleotide repeat in DMPK. Molecular genetic testing is considered the basis of diagnosis of DM1 and testing may have clinical utility to clarify the diagnosis and/or when management will be directly impacted. Genetic testing, via targeted mutation analysis for the CTG repeat known to cause DM1, detects pathogenic variants in nearly 100% of patients with DM1.

Although there is no cure for DM1, appropriate management may reduce morbidity and mortality. No specific treatment exists for the progressive weakness in individuals with DM1 however the use of ankle-foot orthoses, wheelchairs, or other mobility and assistive devices may aid in coping with symptoms. Other screening and surveillance includes: annual ECG or 24-hour Holter monitoring; annual measurement of fasting serum glucose concentration and glycosylated hemoglobin concentration; assessment of thyroid function; eye examination every two years; and attention to nutritional status. Avoidance of cholesterol-lowering medications (i.e., statins), which can cause muscle pain and weakness and the anesthetic agent vecuronium may be recommended.

DM2 is characterized by myotonia (in greater than 90% of affected individuals) and muscle dysfunction, weakness, pain, and stiffness (in greater than 82% of affected individuals). Affected individuals less commonly have cardiac conduction defects, iridescent posterior subcapsular cataracts, insulin-insensitive type 2 diabetes mellitus, and testicular failure. The onset of DM2 is typically in the third decade of life. Symptoms most commonly occur with fluctuating or episodic muscle pain that can be debilitating and weakness of the neck flexors and finger flexors. Subsequently, weakness occurs in the elbow extensors and the hip flexors and extensors.

Diagnostic testing for DM2 often includes muscle biopsy. Muscle pathology includes atrophic fibers, scattered severely atrophic fibers with pyknotic myonuclei, and marked proliferation of fibers with central
nuclei, all of which occur in both DM1 and DM2 and thus cannot be used to distinguish between the two conditions. Type 1 fiber atrophy is a common feature in individuals with congenital DM1, distinguishing it from DM2. Preferential type 2 fiber atrophy has been observed in individuals with DM2.

CNBP (ZNF9) is the only gene known to cause DM2 and testing shows an increased number (i.e., an expansion) of the CCTG trinucleotide repeat in CNBP. Molecular genetic testing is considered the basis of diagnosis of DM2 and testing may have clinical utility to clarify the diagnosis and/or when management will be directly impacted. Genetic testing, via targeted mutation analysis for the CCTG repeat known to cause DM2, detects pathogenic variants in 99% of patients with DM2.

Although there is no cure, appropriate management of DM2 may reduce the morbidity and mortality in this condition and prevent costly complications of the disease. No specific treatment exists for the progressive weakness in individuals with DM2 however the use of ankle-foot orthoses, wheelchairs, or other mobility and assistive devices may aid weakness. Other management considerations include: a defibrillator placement for those with arrhythmias; removal of cataracts that impair vision; and testosterone replacement therapy for hypogonadism in males. Myotonia rarely requires treatment. Routine physical activity appears to help maintain muscle strength and endurance and to control musculoskeletal pain. Medications used with some success in pain management include mexilitene, gabapentin, nonsteroidal anti-inflammatory drugs (NSAIDS), low-dose thyroid replacement, low-dose steroids (e.g., 5 mg prednisone on alternate days), and tricyclic antidepressants. Avoidance of certain cholesterol-lowering medications may be recommended when associated with increased weakness.

Facioscapulohumeral Muscular Dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is characterized by muscle weakness in the face, shoulders, upper arms, and lower legs. The weakness may be more pronounced on one side than the other and generally begins in the third decade of life. There is a great deal of variability in presenting symptoms and age of onset both between individuals and within families. Cases of atypical age of onset have been reported; albeit these cases are rare. Pastorello (2012) evaluated 122 symptomatic individuals from 76 unrelated families with genetically confirmed FSHD showing a mean age of onset as 23 years. 18 cases of atypical onset were noted, including facial-sparing cases, with a mean onset at 39 years of age and lower limbs proximal weakness cases with a mean age of onset at 36 years of age.

FSHD is inherited in an autosomal dominant pattern. It is estimated that up to 10-30% of affected individuals have a de novo mutation, while 70-90% of individuals with FSHD inherit the causative mutation from a parent. FSHD is most often caused by a contraction mutation on chromosome 4. This change disrupts a regulatory region, called D4Z4. The D4Z4 region contains a number of repeat units that tell the cell when to make or stop making certain proteins. In individuals affected with FSHD type 1 (FSHD1), the number of D4Z4 repeat units on the A allele is reduced. FSHD1 accounts for 95% of cases of FSHD. FSHD type 2 (FSHD2) is a genetically distinct, but clinically identical form of FSHD. FSHD2 is due to a more lax chromatin structure of the D4Z4 region caused by mutations in the SMCHD1 gene, and accounts for approximately 5% of all FSHD. Deletion testing to look for the contracted region detects nearly 100% of individuals affected with FSHD1, equaling nearly 95% of all affected persons.

The standard analysis for FSHD includes testing for the presence or absence of a chromosome 4q-like D4Z4 repeat array of between one and ten units by a Southern blot based analysis (Lemmers, 2014). Southern blot analysis is considered the standard of care at this time. However, alternative molecular techniques for FSHD analysis are emerging, including molecular combing and long-range PCR analysis. Molecular combing, which was developed for FSHD1 analysis, is based on florescence in situ hybridization (FISH) of stretched DNA molecules. Although this methodology is not currently considered standard of care, it may become a useful diagnostic method for FSHD in the future if it proves to be an accurate and time-effective method of D4Z4 analysis (Lemmers, 2014).

Practice recommendations from the American Academy of Neurology and the American Association of Neuromuscular & Electrodiagnostic Medicine recommend that clinicians obtain genetic confirmation of FSHD1 in patients for whom FSHD is suspected and there are no first-degree relatives with genetic confirmation of disease (Tawil, 2015). According to these panelists, when the clinical presentation of
FSHD is typical and the inheritance pattern is consistent with autosomal dominant inheritance, the clinical diagnosis of FSHD is considered straightforward. In addition, if the diagnosis is genetically confirmed in a first-degree relative, then genetic testing is not considered necessary for each affected individual in the family (Tawil, 2015).

Summary
There are over 30 different muscular dystrophy syndromes, with varied severity, age of onset, inheritance pattern, and genetic etiology. Clinical, family history, and screening data can all be used to assist in accurate diagnosis. However, there is growing literature to support overlap within this group of conditions and clinical presentation alone sometimes does not differentiate syndromes. Genetic testing can help facilitate diagnosis confirmation and, under certain circumstances, directly inform medical decision-making as it relates to the need for cardiac and/or ophthalmologic screening. In other instances, genetic testing with high detection rate and syndrome specificity can avoid the need for invasive and sometimes risky screening procedures, such as muscle biopsy or sedated MRI. Genetic testing is most valuable when targeted to a particular muscular dystrophy syndrome to allow for more accurate test result interpretation and medical management recommendations.

Policy History

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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>8/2017</td>
<td>BCBSA National medical policy review. The policy statement was updated to add a third indication for male offspring of female carriers and male sibling of affected male. “Mutations” was changed to “variants.” Effective 8/1/2017.</td>
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Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

References


BCBSA


Endnotes

1 Based on BCBSA MPRM 2.04.86
2 Based on expert opinion