Medical Policy

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 535
BCBSA Reference Number: 2.04.105
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
Genetic Testing for Duchenne and Becker Muscular Dystrophy, #828
Mutation Testing for Limb-Girdle Muscular Dystrophies, #738

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

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.

Facioscapulohumeral muscular dystrophy (FSHD) is typically suspected in an individual with the following: weakness that predominantly involves the facial, scapular stabilizer, and foot dorsiflexor muscles without associated ocular or bulbar muscle weakness, and age of onset usually by 20 years (although mildly affected individuals show signs at a later age and some remain asymptomatic).

Medicare HMO BlueSM and Medicare PPO BlueSM 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.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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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.

CPT Codes
<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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>
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Description
FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY
Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy and involves progressive weakness and wasting of the facial muscles (facio) as well as shoulder and upper arm (scapulohumeral) muscles. The weakness is often most evident in muscles of the face, resulting in difficulty smiling and whistling, and reduced facial expression. The weakness in the shoulder muscles causes the scapula to protrude from the back (“wearing of the scapula”). The muscles are typically affected asymmetrically, and with progression, the lower extremities, both proximal and distal, become involved.¹ The severity of the disease is highly variable, ranging from mildly affected, asymptomatic individuals to severely affected individuals, with approximately 20% of patients eventually requiring a wheelchair. Nonmuscular manifestations include retinal vascular abnormalities that can result in significant loss of vision; however, only about 1% of patients with FSHD experience visual acuity loss.¹ Most people with FSHD eventually develop high-frequency hearing loss, which is usually not noticeable and only detected by audiogram. FSHD usually presents between the ages of 6 and 20 years, and life expectancy is not shortened. It is estimated that 4 to 5 people per 100,000 population have FSHD. FSHD affects males and females equally.

Clinical Diagnosis
FSHD has a characteristic distribution of muscle involvement that often can lead to targeted genetic testing without the need for a muscle biopsy.² However, atypical presentations have been reported, which include scapulohumeral dystrophy with facial sparing.³,⁴ A 2012 retrospective review of an academic center database for the period 1996 to 2011 determined that, of 139 genetically confirmed FSHD cases, 7 had atypical disease, including late age of onset of disease, focal weakness, and dyspnea.⁵

Electromyography (EMG) and muscle biopsy to confirm the clinical diagnosis of FSHD have largely been supplanted by genetic testing. EMG usually shows mild myopathic changes, and muscle biopsy most often shows nonspecific chronic myopathic changes.
**Genetics**

FSHD is likely to be caused by inappropriate expression of the *DUX4* gene in muscle cells. *DUX4* is a double homeobox-containing gene (a homeobox gene being one in a large family of genes that direct the formation of many body structures during early embryonic development). *DUX4* lies in the macrosatellite repeat D4Z4, which is on chromosome 4q35. D4Z4 has a length of 11 to 100 repeat units on normal alleles. The most common form of FSHD (95%) is designated FSHD type 1 (FSHD1), and individuals with FSHD1 have a D4Z4 allele of between 1 and 10 repeat units. There is no absolute linear and inverse correlation between residual repeat size, disease severity, and onset; however, patients with repeat arrays of 1 to 3 units usually have an infantile onset and rapid progression.

The remaining 5% of patients who do not have FSHD1 are designated as FSHD2, which is clinically indistinguishable from FSHD1. Patients with FSHD2 show loss of DNA methylation and heterochromatin markers at the D4Z4 repeat that are similar to patients with D4Z4 contractions (FSHD1), suggesting that a change in D4Z4 chromatin structure unifies FSHD1 and FSHD2. Variants in the *SMCHD1* gene on chromosome 18, which encodes a protein known as structural maintenance of chromosomes flexible hinge domain containing 1, have been associated with FSHD2. Reductions in *SMCHD1* gene product levels have been associated with D4Z4 contraction-independent *DUX4* expression, suggesting that *SMCHD1* acts as an epigenetic modifier of the D4Z4 allele. *SMCHD1* has also been identified as a possible modifier of disease severity in patients with FSHD1.

FSHD is inherited in an autosomal dominant manner. Approximately 70% to 90% of individuals inherit the disease-causing deletion from a parent, and 10% to 30% have FSHD as a result of a de novo deletion. On average, de novo variants are associated with larger contractions of D4Z4 compared with the degree of D4Z4 contraction variants observed segregating in families, and individuals with de novo variants tend to have findings at the more severe end of the phenotypic spectrum.

**Treatment**

There is currently no treatment or prevention of symptoms of FSHD. Clinical management is directed at surveillance to identify possible FSHD-related complications, such as hearing loss, and to improve quality of life (eg, assist devices, physical therapy, orthoses to improve mobility and prevent falls).

**Commercially Available Testing**

The methodology for testing for FSHD1 uses pulsed field gel electrophoresis and Southern blot to detect deletions on chromosome 4q35. Laboratories that offer FSHD1 testing include Athena Diagnostics and the University of Iowa Diagnostic Laboratories.

At least 1 commercial laboratory was identified that offers testing for FSHD2 through sequencing of the *SMCHD1* gene via bidirectional Sanger sequencing (Prevention Genetics, Marshfield, WI). Prevention Genetics also offers testing for FSHD2 through sequencing of the *SMCHD1* gene by next-generation sequencing as part of a panel test for limb-girdle muscular dystrophy.

**Summary**

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disease that typically presents before the age of 20 years with weakness of the facial muscles and the scapular stabilizer muscles. The clinical course is usually of slowly progressive weakness, although the severity is highly variable, and atypical presentations occur. Genetic testing for FSHD can confirm the diagnosis.

For individuals who have clinical signs of FSHD who receive genetic testing for FSHD, the evidence supporting improved outcomes is generally lacking. Relevant outcomes are test accuracy and validity, morbid events, functional outcomes, quality of life, and resource utilization. Test accuracy and validity have been reported to be high. A definitive diagnosis may end the need for additional testing in the etiologic workup, avoid the need for a muscle biopsy, and initiate and direct clinical management changes that can result in improved health outcomes. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.
Policy History

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<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>4/2017</td>
<td>BCBSA National medical policy review. Policy clarified. Policy statements unchanged. 4/1/2017</td>
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<tr>
<td>6/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added.</td>
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<tr>
<td>10/2014</td>
<td>New references added from BCBSA National medical policy.</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