



Louisiana

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

Policy # 00392

Original Effective Date: 12/18/2013

Current Effective Date: 12/20/2017

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

When Services Are Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member's contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for facioscapulohumeral muscular dystrophy (FSHD) to confirm a diagnosis in a patient with clinical signs of the disease to be **eligible for coverage**.

When Services Are Considered Investigational

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

Based on review of available data, the Company considers genetic testing for facioscapulohumeral muscular dystrophy (FSHD) for all other indications to be **investigational**.*

Policy Guidelines

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).

TESTING STRATEGY

Because 95% of cases of FSHD are FSHD type 1 (FSHD1), genetic testing for FSHD should begin with testing for contraction in the macrosatellite repeat D4Z4 on chromosome 4q35 using Southern blot analysis. Depending on the index of suspicion for FSHD, if FSHD1 testing is negative, testing for FSHD2, including D4Z4 methylation analysis and testing of the *SMCHD1* gene, could be considered.

GENETICS NOMENCLATURE UPDATE

Human Genome Variation Society (HGVS) 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). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

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The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

GENETIC COUNSELING

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Facioscapulohumeral muscular dystrophy is the third most common muscular dystrophy and involves progressive weakness and wasting of the facial muscles (facio), and shoulder and upper arm (scapulohumeral) muscles. The weakness is often most evident in the muscles of the face, resulting in difficulty smiling and whistling, and reduced facial expression. The weakness in the shoulder muscles

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causes the scapula to protrude from the back (“winging of the scapula”). The muscles are typically affected asymmetrically, and with progression, the lower extremities, both proximal and distal, become involved. 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. Most people with FSHD will 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 populations have FSHD. FSHD affects males and females equally.

Clinical Diagnosis

Facioscapulohumeral muscular dystrophy has a characteristic distribution of muscle involvement that often can lead to targeted genetic testing without the need for a muscle biopsy. However, atypical presentations have been reported, which include scapulohumeral dystrophy with facial sparing. A retrospective review of an academic center database of 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.

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

Genetics

Facioscapulohumeral muscular dystrophy is likely to be caused by inappropriate expression of the gene *DUX4* 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 D_4Z_4 , which is on chromosome 4q35. D_4Z_4 has a length of 11 to 100 repeat units on normal alleles. The most common form of FSHD (95%) is designated FSHD1, and these individuals have a D_4Z_4 allele of between 1 and 10 repeat units. There is no absolute linear and inverse correlation between residual repeat size and 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 D_4Z_4 repeat that are similar to patients with D_4Z_4 contractions (FSHD1), suggesting that a change in D_4Z_4 chromatin structure unifies FSHD1 and FSHD2. Mutations 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 D_4Z_4 contraction-independent *DUX4* expression, suggesting that *SMCHD1* acts as an epigenetic modifier of the D_4Z_4 allele. *SMCHD1* has also been identified as a possible modifier of disease severity in patients with FSHD1.

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Facioscapulohumeral muscular dystrophy 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, and 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 one 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general standards of the Clinical Improvement Act (CLIA). Genetic testing for FSHD is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of these tests.

Centers for Medicare and Medicaid Services (CMS)

No coverage determination is identified.

Rationale/Source

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes

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in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.

FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY

Analytic Validity

Analytic validity is the technical accuracy of a test in detecting a variant that is present or in excluding a variant that is absent. According to 1 laboratory, Southern blotting diagnostic methods enable the identification of FSHD1 in about 95% of cases.

No studies that assessed the analytic validity of *SMCHD1* gene testing were identified, but standard techniques used to detect the copy variation are expected to have good analytic validity.

Clinical Validity

Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease. Another aspect of clinical validity for this condition is the degree to which test results correlate with severity or prognosis of the disease.

According to a large reference laboratory, the identification of a characteristic 4q35 deletion is more than 90% specific for the disease. However, although the penetrance of FSHD is considered to be high, several studies have identified patients with no clinical signs of FSHD who have characteristic D4Z4 allele sizes, which has prompted the hypothesis that FSHD occurs only when the D4Z4 allele size occurs in a characteristic "permissive" background.

Several studies have reported correlation between the degree of the variant of the D4Z4 locus and the age at onset of symptoms, age at loss of ambulation, and muscle strength, as measured by quantitative isometric myometry. Some reports in the literature have described individuals with a large contraction of the D4Z4 locus having earlier onset disease and more rapid progression than those with smaller contractions of the D4Z4 locus, although other reports have not confirmed a correlation between disease severity and degree of D4Z4 contraction variants.

Lutz et al (2013) retrospectively analyzed 59 patients with FSHD seen at a single institution to evaluate the relation between the D4Z4 repeat size and progression of hearing loss. Eleven of the 59 patients evaluated had hearing loss not attributable to another cause. Truncated D4Z4 (1-10 D4Z4 repeats) was evaluated by the size of EcoRI or EcoRI/BlnI fragment, with an EcoRI fragment of less than 38 kilobases (kb) or an EcoRI/BlnI fragment of less than 35 kilobases (kb) corresponding to 1 to 10 D4Z4 repeats. There was a statistically significant negative association between hearing loss and fragment size in a simple logistic regression model ($p=0.021$). Six of the 11 patients with hearing loss had a history of hearing loss progression.

In a retrospective analysis of a cohort of patients with FSHD1 enrolled in the National Registry of FSHD Patients and Family Members, Statland et al (2014) evaluated the association between patient

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characteristics, including the D4Z4 allele size, and FSHD-related outcomes. Three hundred thirteen clinically affected participants with D4Z4 contractions of 38 kb or less were included. Those with D4Z4 contractions of 18 kb or less started using wheelchairs earlier than those with contractions from 19 to 28 kb (24.1 years vs 48.1 years, $p < 0.001$) or those with contractions of greater than 38 kb (58.6 years, $p < 0.001$).

Clinical Utility

Testing Individuals With Suspected FSHD

The clinical utility for patients with suspected FSHD depends on the ability of genetic testing to make a definitive diagnosis and for that diagnosis to lead to management changes that improve outcomes.

There is no direct evidence for the clinical utility of genetic testing in these patients. No studies were identified that described how a molecular diagnosis of FSHD changed patient management. It is unclear to what extent the prognostic value of knowing the degree of D4Z4 is clinically useful. However, for patients who are diagnosed with FSHD by identifying a D4Z4 contraction variant, the clinical utility of molecular genetic testing for FSHD includes:

- Establishing the diagnosis and initiating/directing treatment, such as evaluation for physical therapy and the need for assistive devices, assessment for hearing loss, ophthalmologic examination for the presence of retinal telangiectasias and continued ophthalmologic surveillance, and possible orthopedic intervention.
- Distinguishing from other disorders that are similar clinically to FSHD, especially the limb-girdle muscular dystrophies and scapulooperoneal muscular dystrophy syndromes.
- Potential avoidance of a muscle biopsy.

Treatment after a confirmed diagnosis of FSHD includes physical therapy and rehabilitation, exercise, pain management, ventilator support for those with hypoventilation, therapy for hearing loss, orthopedic intervention (ankle/foot orthoses; surgical fixation of the scapula to the chest wall to improve range of motion) and ophthalmologic management including lubricants or taping the eyes shut at night for exposure keratitis.

For those with a confirmed diagnosis of FSHD, the following surveillance guidelines apply:

- Regular assessment of pain
- "Affected individuals with moderate to severe FSHD ... should be routinely screened for hypoventilation.
- "Yearly forced vital capacity ... measurements should be monitored for all affected individuals who are wheelchair bound, have pelvic girdle weakness and superimposed pulmonary disease, and/or have moderate to severe kyphoscoliosis, lumbar hyperlordosis, or chest wall deformities."
- Hearing loss assessment in children as "routinely by periodic assessment as part of school-based testing.
- "Hearing screens are particularly important in severe infantile onset forms of FSHD, as hearing loss can result in delayed language acquisition."

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- “Adults should have a formal hearing evaluation based on symptoms.”
- “Annual dilated ophthalmoscopy in childhood is indicated.”
- “In adults, a dilated retinal exam should be performed at the time of diagnosis; if vascular disease is absent, follow-up exams are only necessary if visual symptoms develop.”

Testing Family Members With Individuals With FSHD

Evaluation of at-risk relatives may determine that they may be affected but escaped previous diagnosis because of a milder phenotypic presentation. In 2013, Ricci et al evaluated the D4Z4 site in 367 relatives of 163 FSHD index cases who carried D4Z4 “alleles of reduced size” of 8 or less repeating units. Among relatives, a D4Z4 “alleles of reduced size” with 1 to 3 repeating units and 4 to 6 repeating units was identified in 42 and 133 subjects, respectively. Of those relatives with 1 to 3 repeating units, about 40% demonstrated severe muscle symptoms by age 30, while none of those with 4 or more repeating units had severe symptoms in that age range. Identification of previously unknown mild cases of FSHD results in knowledge of risk status and potential for transmission to offspring.

Section Summary: Clinical Utility

Although there is no direct evidence for the clinical utility of genetic testing patients with suspected FSHD, because no studies were identified describing how a molecular diagnosis of FSHD would change patient management, D4Z4 contraction variant testing for suspected FSHD establishes a diagnosis, avoids further workup including muscle biopsy, and suggests initiating therapies consistent with appropriate guidelines.

SUMMARY OF EVIDENCE

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.

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12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. New policy.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. No change to coverage.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:	12/2018

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Code Type	Code
CPT	81404
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

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

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- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

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

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