Genetic Testing for Facioscapulohumeral Muscular Dystrophy

Policy # 00392
Original Effective Date: 12/18/2013
Current Effective Date: 01/11/2021

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.

Note: Genetic Testing for Limb-Girdle Muscular Dystrophies is addressed separately in medical policy 00489.

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

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).

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.

Targeted testing of the parents of a proband with facioscapulohumeral muscular dystrophy and a confirmed genetic variant to identify mode of transmission (germline vs. *de novo*) may be considered appropriate and guide clinical management of previously undiagnosed mild presentations. It is appropriate in those families with a confirmed germline variant to consider targeted genetic testing of other first degree relatives to the proband.

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 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

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

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.

Background/Overview

Diagnosis

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The distribution of muscle involvement that is characteristic of FSHD 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 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.

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

Genetics
FSHD is likely 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 1to 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.

FSHDis 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 preventive therapy to control 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, assistive 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 (Prevention Genetics, Marshfield, Wisconsin) was identified that offers testing for FSHD2 through sequencing of the *SMCHD1* gene via bidirectional Sanger sequencing. Prevention Genetics also offers testing for FSHD2 through next-generation sequencing of the *SMCHD1* gene 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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for FSHD is available 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. FDA has chosen not to require any regulatory review of this test.

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Rationale/Source

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

For individuals who have clinical signs of FSHD who receive genetic testing for FSHD, the relevant outcomes are test validity, morbid events, functional outcomes, quality of life, and resource utilization. Although evidence supporting improved outcomes is generally lacking, studies have reported high test validity, and 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.

Supplemental Information

Practice Guidelines and Position Statements

In 2010, a report from the 171st European Neuromuscular Centre international workshop on standards of care and management of FSHD muscular dystrophy stated that when a physician suspects FSHD based on clinical findings, the odds favor a diagnosis of FSHD, and genetic testing is the preferred diagnostic choice.

American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine

In 2015, the American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine guidelines on FSHD for patients and their families stated the following:

"Genetic testing can confirm the diagnosis in many patients with FSHD type 1….If the patient tests negative for the D4Z4 contraction, the doctor will test for FSHD type 2 or other myopathies. Although these cases are rare, they are important to diagnose. Research on FSHD type 2 is increasing….If a family member's diagnosis was confirmed by genetic testing, the patient [with the family member] may not need to be tested."

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U.S. Preventive Services Task Force Recommendations
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
Some currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT01437345[a]	A Multicenter Collaborative Study on the Clinical Features, Expression Profiling, and Quality of Life of Infantile Onset Facioscapulohumeral Muscular Dystrophy	53	Aug 2017 (completed; updated 10/11/17)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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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.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. No change to coverage.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. No change to coverage.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 12/2021

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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. Food and Drug Administration (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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**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.