2.04.105	Genetic Testing for Facioscapulohumeral Muscular Dystrophy		
Original Policy Date:	October 31, 2014	**Effective Date:**	April 1, 2019
Section:	2.0 Medicine	**Page:**	Page 1 of 10

Policy Statement

Genetic testing for facioscapulohumeral muscular dystrophy (FSHD) may be considered **medically necessary** to confirm a diagnosis in a patient with clinical signs of the disease (see the Policy Guidelines section).

Genetic testing for facioscapulohumeral muscular dystrophy is considered **investigational** for **all** other indications.

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.

Genetics Nomenclature Update

The 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). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization (HUGO), and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) 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 Classification	Definition
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.

Coding

CPT code **81404** (Molecular Pathology Procedure Level 5) includes the following testing for FSHD:

- *FSHMD1A (facioscapulohumeral muscular dystrophy 1A)* (e.g., facioscapulohumeral muscular dystrophy), evaluation to detect abnormal (e.g., deleted) alleles
- *FSHMD1A (facioscapulohumeral muscular dystrophy 1A)* (e.g., facioscapulohumeral muscular dystrophy), characterization of haplotype(s) (i.e., chromosome 4A and 4B haplotypes)

Description

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.

Related Policies

- Genetic Testing for Duchenne and Becker Muscular Dystrophy
- Genetic Testing for Limb-Girdle Muscular Dystrophies

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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. Genetic testing for FSHD is available 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.

Rationale

Background

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, whistling, and reduced facial expression. The weakness in the shoulder muscles 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.[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 for mobility. 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 an 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 100000 population have FSHD. FSHD affects males and females equally.

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 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 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.[3,] There is no absolute linear and inverse correlation between residual repeat size, disease severity, and onset; however, patients with repeat arrays of one to three units usually have an infantile onset and rapid progression.[1,]

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.[6] *SMCHD1* has also been identified as a possible modifier of disease severity in patients with FSHD1.[7]

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.[3]

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 (e.g., 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 (Prevention Genetics, Marshfield, WI) 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.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Facioscapulohumeral Muscular Dystrophy
Clinical Context and Test Purpose
The purpose of testing patients who have clinical signs of FSHD is to inform a decision on clinical surveillance to identify and manage FSHD-related complications (e.g., hearing loss, function) and to differentiate FSHD from other similar diagnoses.

The question addressed in this evidence review is: Does genetic testing of persons with clinical signs of FSHD improve the net health outcome?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are individuals with clinical signs of FSHD.

Interventions
The test being considered is genetic testing for FSHD.

Comparators
Currently, standard clinical management without genetic testing is being used to make clinical management decisions about FSHD, which may include anti-inflammatory agents and orthotics and possibly surgery.

Outcomes
The general outcomes of interest include a change in management when test results are positive (i.e., avoidance of muscle biopsy, increased ophthalmologic surveillance, evaluation for physical therapy).

Timing
The time frame for the outcome varies from months to years, with management implications lasting over the course of the disease.

Setting
Clinicians in a specialty practice managing patients with FSHD.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops, or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predict response to therapy.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse). Another aspect of clinical validity for FSHD is the degree to which test results correlate with severity or prognosis of the disease.

Identification of a characteristic 4q35 deletion is about 95% specific for the disease.[8,] 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.[9,]

Several studies have reported on correlations 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.[3,]

Lutz et al (2013) retrospectively analyzed 59 patients with FSHD seen at a single institution to evaluate the relationship between the D4Z4 repeat size and progression of hearing loss.[10,] 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 enzyme or EcoRI/BlnI fragment, with an EcoRI fragment of less than 38 kilobases (kb) or an EcoRI/BlnI fragment of less than 35 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 FSHD type 1 enrolled in the National Registry of FSHD Patients and Family Members, Statland et al (2014) evaluated the association between patient characteristics, including the D4Z4 allele size, and FSHD-related outcomes.[11,] 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).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about 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 have 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 clinically similar to FSHD, especially the limb-girdle muscular dystrophies and scapuloperoneal 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 or 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[3,,12,]:
- "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."
- "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. Ricci et al (2013) evaluated the D4Z4 site in 367 relatives of 163 FSHD index cases which carried D4Z4 "alleles of reduced size" of 8 or less repeating units.[9,] Among relatives, D4Z4 "alleles of reduced size" with 1 to 3 repeating units and 4 to 6 repeating units were 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: Clinically Useful
No studies were identified describing how a molecular diagnosis of FSHD would change patient management, so there is no direct evidence supporting the clinical use of genetic testing for suspected FSHD. However, a chain of evidence can be constructed because 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. The relevant outcomes are test validity, morbid events, functional outcomes, quality of life, and resource utilization. Test 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.

Supplemental Information

Practice Guidelines and Position Statements

In a report from the 171st European Neuromuscular Centre international workshop standards of care and management of facioscapulohumeral muscular dystrophy held in 2010, it was stated that when a physician suspects facioscapulohumeral muscular dystrophy based on clinical findings, the odds favor a diagnosis of facioscapulohumeral muscular dystrophy, and genetic testing is the preferred diagnostic choice.[13]

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			
NCT01970735	Clinical, Genetic and Epigenetic Characterization of Patients With FSHD Type 1 and FSHD Type 2	100	Oct 2016 (unknown)
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)

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

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Documentation for Clinical Review

Please provide the following documentation (if/when requested):

- History and physical and/or consultation notes including:
  - Presumptive diagnosis of FSHD has been made based on clinical signs
  - Previous treatment plan and results
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

Type	Code	Description
CPT®	81404	Molecular Pathology Procedure Level 5
HCPCS	None	
ICD-10 Procedure	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action	Reason
10/31/2014	BCBSA Medical Policy adoption	Medical Policy Committee
01/01/2017	Policy revision without position change	Medical Policy Committee
04/01/2017	Policy revision without position change	Medical Policy Committee

Effective Date	Action	Reason
04/01/2018	Policy revision without position change	Medical Policy Committee
04/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.