I. POLICY

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 Policy Guidelines)

Genetic testing for facioscapulohumeral muscular dystrophy is considered investigational for all other indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

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 of age (although mildly affected individuals show signs at a later age and some remain asymptomatic).

Testing Strategy

Because 95% of cases of FSHD are FSHD1, genetic testing for FSHD should begin with testing for contraction mutation 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.

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.

_Cross-reference:_
NA

II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless
otherwise indicated below.

FEP PPO*

*Refer to FEP Medical Policy Manual MP-2.04.105, Genetic Testing for Facioscapulohumeral
Muscular Dystrophy. The FEP Medical Policy Manual can be found at: [www.fepblue.org](http://www.fepblue.org)

III. DESCRIPTION/BACKGROUND

Facioscapulohumeral muscular dystrophy (FSHD) is an autosomal dominant disease that
typically presents before the age of 20 with weakness of the facial muscles and the scapular
stabilizer muscles, however, atypical presentations occur. The clinical course is usually of slowly
progressive weakness, although the severity is highly variable. Approximately 95% of
individuals with FSHD have contraction mutation of the D4Z4 locus.

_Description of the disease_

Facioscapulohumeral muscular dystrophy (FSHD) 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 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, with approximately
20% of patients eventually requiring a wheelchair. Non-muscular manifestations include retinal
vascular abnormalities which can result in significant loss of vision, however, only about 1% of
patients with FSHD experience visual acuity loss. (1) 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 4-5 people per 100,000 population have FSHD. FSHD affects males and females equally.

**Clinical diagnosis of FSHD**

FSHD 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 of FSHD**

FSHD 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 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 FSHD1, and these individuals have a D4Z4 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 D4Z4 repeat that are similar to patients with D4Z4 contractions (FSHD1), suggesting that a change in D4Z4 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 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.

**Treatment of FSHD**

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 (e.g., assist devices, physical therapy, orthoses to improve mobility and prevent falls).

**Commercially Available Testing for FSHD**
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.

**Regulatory Status**

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. Food and Drug Administration has chosen not to require any regulatory review of these tests.

**IV. RATIONALE**

**Analytic Validity**
Analytic validity is the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent.

According to 1 laboratory, Southern blotting diagnostic methods enable the identification of FSHD1 in about 95% of cases.\(^8\)

No studies that assessed the analytic validity of SMCHD1 gene testing were identified.

**Clinical Validity**
Clinical validity is the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease.

According to a large reference laboratory, the identification of a characteristic 4q35 deletion is more than 90% specific for the disease.\(^9\) However, several studies have identified patients with no clinical signs of FSHD who have characteristic D\(_4\)Z\(_4\) contractures, which has prompted the
hypothesis that FSHD occurs only when the D4Z4 contracture occurs in a characteristic “permissive” background.\(^\text{10}\)

There are reports of a correlation between the degree of the mutation 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 describe 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 been able to confirm a correlation between disease severity and degree of D4Z4 contraction mutations.\(^\text{3}\)

On average, de novo mutations are associated with larger contractions of D4Z4 compared with the degree of D4Z4 contraction mutations observed segregating in families, and individuals with de novo mutations tend to have findings at the more severe end of the phenotypic spectrum.\(^\text{3}\)

No studies that assessed clinical validity of \textit{SMCHD1} gene testing were identified.

\textbf{Clinical Utility}

How the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

\textbf{Testing in 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.

Several studies suggest that the size of the D4Z4 repeat contraction is associated with differences in patients’ outcomes. Lutz et al conducted a retrospective analysis of 59 patients with FSHD seen at a single institution to evaluate the relationship between the D4Z4 repeat size and progression of hearing loss.\(^\text{11}\) Eleven of the 59 patients evaluated had hearing loss that was 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 kB or an EcoRI/BlnI fragment of less than 35 kg 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 evaluated the association between patient characteristics, including size of the D4Z4 contraction, and FSHD-related outcomes.\(^\text{12}\) Three hundred thirteen clinically affected participants with D4Z4 contractions of 38 kB or less were included. Those with D4Z4 contractions of 18 kg 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).

There is no direct evidence for the clinical utility of genetic testing in these patients, as no studies were identified that described how a molecular diagnosis of FSHD changed patient management.
However, for patients who are diagnosed with FSHD by identifying a \(D_4Z_4\) contraction mutation, 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 scapuloperoneal muscular dystrophy syndromes.
- Avoidance of a muscle biopsy in most cases.

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 applies\(^3\,\,13\):

- Regular assessment of pain
- Routine screening for hypoventilation in those with moderate to severe disease, and yearly forced vital capacity measurements 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 performed as part of school-based testing. In severe infantile onset forms of FSHD, hearing screens are important as hearing loss can result in delayed language acquisition. Adults should have a formal hearing evaluation based on symptoms.
- Annual dilated opthalmoscopy in childhood is indicated. In adults, a dilated retinal exam should be performed at the time of diagnosis, and if vascular disease is absent, follow-up exams are only necessary if visual symptoms develop.

**Testing of Family Members With Individuals With FSHD**

Most individuals diagnosed with FSHD have a parent with clinical findings of FSHD and one \(D_4Z_4\) allele with a contraction mutation (70-90% of individuals with FSHD), although 10% to 30% of probands with FSHD have the disorder as a result of a \(D_4Z_4\) de novo contraction mutation.\(^3\) 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 \(D_4Z_4\) site in 367 relatives of 163 FSHD index cases who carried \(D_4Z_4\) “alleles of reduced size” of 8 or less repeating units.\(^10\) Among relatives, a \(D_4Z_4\) 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.
However, for this population, no evidence was identified that compared outcomes in family members tested for genetic mutations with family members not tested for genetic mutations, and conclusions cannot be made on whether genetic testing of asymptomatic family members of a patient with known FSHD improves outcomes. In contrast to patients with diagnosed FSHD, there are no established treatment guidelines or follow-up guidelines for at-risk relatives.

**Section Summary: Clinical Utility**

D4Z4 contractions are associated with FSHD, and the size of the contracture is associated with more severe symptoms. Although there is no direct evidence for the clinical utility of genetic testing for patients with suspected FSHD, as no studies were identified that described how a molecular diagnosis of FSHD changed patient management, a chain of evidence supports the use of D4Z4 contraction mutation testing for suspected FSHD to establish a diagnosis and initiate therapies consistent with appropriate guidelines and avoid a muscle biopsy in most cases.

**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

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<th>Trial Name</th>
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NCT: national clinical trial.

**Summary of Evidence**

The evidence for genetic testing in patients who have clinical signs of FSHD syndrome is generally lacking. Relevant outcomes are test accuracy, test 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. Therefore, the evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

**Practice Guidelines and Position Statements**

In a report from the 171st European Neuromuscular Centre International Workshop Standards of Care and Management of FSHD held in January 2010, it is stated that when a physician concludes facioscapulohumeral syndrome based on clinical findings, the odds are in favor of FSHD, and genetic testing is the preferred diagnostic choice.\(^{14}\)

**U.S. Preventive Services Task Force Recommendations**

Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

V. DEFINITIONS
NA

VI. BENEFIT VARIATIONS
The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. DISCLAIMER
Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION
Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

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IX. REFERENCES


Other:

X. POLICY HISTORY

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