MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY
POLICY NUMBER	MP-2.321

Original Issue Date (Created):	**2/1/2014**
Most Recent Review Date (Revised):	**6/8/2020**
Effective Date:	**9/1/2020**

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 D_4Z_4 on chromosome 4q35 using Southern blot analysis. Depending on the index of suspicion for FSHD, if FSHD1 testing is negative, testing for FSHD2, including D_4Z_4 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 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. .

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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	Diseased-Assoc.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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

American College of Medical Genetics and Genomics; AMP: Association of 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.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital BlueCross and subject to benefit variations as discussed in Section VI. Please see additional information 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: *https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies*

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III. DESCRIPTION/BACKGROUND

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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, 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

The distribution of muscle involvement that is characteristic of facioscapulohumeral muscular dystrophy (FSHD) often can lead to targeted genetic testing without the need for a muscle biopsy.1, However, atypical presentations have been reported, which include scapulohumeral dystrophy with facial sparing.2,,3, 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.4, 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 1 to 3 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 1 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.

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.

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IV. RATIONALE

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SUMMARY OF EVIDENCE

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.

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital BlueCross. Members and providers should consult the member's health benefit plan for information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER

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Capital BlueCross'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. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital BlueCross' Provider Services or Member Services. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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:

CPT Codes®								
81404								

ICD-10-CM Diagnosis Code	Description
G71.02	Facioscapulohumeral muscular dystrophy
G71.09	Other specified muscular dystrophies

IX. REFERENCES

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3. *Pastorello E, Cao M, Trevisan CP. Atypical onset in a series of 122 cases with facioscapulohumeral muscular dystrophy. Clin Neurol Neurosurg. Apr 2012; 114(3):230-234. PMID 22079131*
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14. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.105, Genetic Testing for Facioscapulohumeral Muscular Dystrophy. February 13, 2020*

X. POLICY HISTORY

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MP 2.321	**CAC 9/26/13 New policy adopting BCBSA**. Previously silent. Now medically necessary with criteria. Policy coded.
	CAC 11/25/14 Consensus review. No changes to the policy statements. References and rationale updated**.** FEP variation revised to refer to the FEP medical policy manual. Codes reviewed, added ICD10.
	CAC 11/24/15 Consensus review. No change to policy statements. References and rationale updated. Coding reviewed.
	CAC 11/29/16 Consensus. No change to policy statements. References and rationale reviewed. Variation reformatting**.** Coding reviewed.
	CAC 12/19/17 Consensus. No change to policy statements. References and rationale updated**.** Coding reviewed.
	10/1/18 Admin Update: Removed deleted ICD-10 codes, added new ICD-10 codes effective 10/1/18.
	10/29/18 Consensus review. No change to the policy statements. Background and references updated. Rationale revised.
	07/15/2019 Consensus review. No change to policy statements. References and rationale reviewed.
	6/8/20 Consensus review. No change to policy statement. References, background and policy guidelines updated.

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