

MEDICAL POLICY

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

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

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I. POLICY

Genetic testing for facioscapulohumeral muscular dystrophy (FSHD) may be considered **medically necessary** to confirm a diagnosis in an individual 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 general 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 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 FSHD 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.

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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 (ACMG) and 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	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

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

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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 Product Variations.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy Manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>.

III. DESCRIPTION/BACKGROUND

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Facioscapulohumeral muscular dystrophy 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.

Diagnosis

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 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 microsatellite 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 1 to 3 units usually have an infantile onset and rapid progression.

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The remaining 5% of patients who do not have FSHD1 are designated as FSHD type 2 (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.

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.

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 Quest/Athena Diagnostics, Bionano Laboratories, PerkinElmer Genomics, 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 (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. 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 facioscapulohumeral muscular dystrophy (FSHD) who receive genetic testing for FSHD, the evidence includes several observational studies. 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 an improvement in the net health outcome.

V. DEFINITIONS

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N/A

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 are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies 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 Blue Cross' Provider Services or Member Services. Capital Blue Cross 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:

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Procedure 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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X. POLICY HISTORY

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MP 2.321	06/08/2020 Consensus Review. No change to policy statement. References, background, and policy guidelines updated.
	04/14/2021 Consensus Review. No changes to policy statement. Background and guidelines updated. References and coding reviewed.
	04/12/2022 Consensus Review. No changes to policy statement. Background and references updated. Coding reviewed.
	03/05/2024 Consensus Review. No change to policy statement. Policy Guidelines, Background and Rationale updated. References updated.
	02/17/2025 Consensus Review. No change to policy statement.
	03/09/2026 Retirement Review. EviCore Delegation.

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