BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.105 Genetic Testing for Facioscapulohumeral Muscular Dystrophy

Effective Policy Date: July 1, 2022

Original Policy Date: December 2013

Related Policies:

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

Genetic Testing for Facioscapulohumeral Muscular Dystrophy

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.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing for facioscapulohumeral muscular dystrophy improves the net health outcome in persons with clinical signs of the disease.

POLICY STATEMENT

Genetic testing for facioscapulohumeral muscular dystrophy 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.

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.

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"<97>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

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA 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.

RATIONALE

Summary of Evidence

For individuals who have clinical signs of Facioscapulohumeral muscular dystrophy (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 an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information" if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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 guideline on facioscapulohumeral muscular dystrophy (FSHD) for patients and their families stated the following[15,]:

"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."

This guideline was reaffirmed on September 18, 2021.[16,]

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.

REFERENCES

1. Menezes MP, North KN. Inherited neuromuscular disorders: pathway to diagnosis. J Paediatr Child Health. Jun 2012; 48(6): 458-65. PMID 22050238
2. Lemmers RJLF, Miller DG, van der Maarel SM. Facioscapulohumeral Muscular Dystrophy. GeneReviews. 1993 (updated 2014). PMID 20301616
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): 230-4. PMID 22079131
4. Hassan A, Jones LK, Milone M, et al. Focal and other unusual presentations of facioscapulohumeral muscular dystrophy. Muscle Nerve. Sep 2012; 46(3): 421-5. PMID 22907234
5. van der Maarel SM, Tawil R, Tapscott SJ. Facioscapulohumeral muscular dystrophy and DUX4: breaking the silence. Trends Mol Med. May 2011; 17(5): 252-8. PMID 21288772
6. Lemmers RJ, Tawil R, Petek LM, et al. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. Nat Genet. Dec 2012; 44(12): 1370-4. PMID 23143600
7. Sacconi S, Lemmers RJ, Balog J, et al. The FSHD2 gene SMCHD1 is a modifier of disease severity in families affected by FSHD1. Am J Hum Genet. Oct 03 2013; 93(4): 744-51. PMID 24075187
8. Lemmers RJLF, Miller DG, van der Maarel SM. Facioscapulohumeral Muscular Dystrophy. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.
9. Rieken A, Bossler AD, Mathews KD, et al. CLIA Laboratory Testing for Facioscapulohumeral Dystrophy: A Retrospective Analysis. Neurology. Feb 16 2021; 96(7): e1054-e1062. PMID 33443126
10. Ricci G, Scionti I, Sera F, et al. Large scale genotype-phenotype analyses indicate that novel prognostic tools are required for families with facioscapulohumeral muscular dystrophy. Brain. Nov 2013; 136(Pt 11): 3408-17. PMID 24030947
11. Lutz KL, Holte L, Kliethermes SA, et al. Clinical and genetic features of hearing loss in facioscapulohumeral muscular dystrophy. Neurology. Oct 15 2013; 81(16): 1374-7. PMID 24042093
12. Statland JM, Tawil R. Risk of functional impairment in Facioscapulohumeral muscular dystrophy. Muscle Nerve. Apr 2014; 49(4): 520-7. PMID 23873337
13. Katz NK, Hogan J, Delbango R, et al. Predictors of functional outcomes in patients with facioscapulohumeral muscular dystrophy. Brain. Dec 16 2021; 144(11): 3451-3460. PMID 34542603
14. Tawil R, van der Maarel S, Padberg GW, et al. 171st ENMC international workshop: Standards of care and management of facioscapulohumeral muscular dystrophy. Neuromuscul Disord. Jul 2010; 20(7): 471-5. PMID 20554202
15. American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine. Summary of evidence-based guideline for patients and their families: facioscapulohumeral muscular dystrophy. American Academy of Neurology. 2015. https://www.aan.com/Guidelines/home/GetGuidelineContent/702. Accessed December 9, 2021.
16. American Academy of Neurology and American Association of Neuromuscular & Electrodiagnostic Medicine. EVIDENCE-BASED GUIDELINE SUMMARY: EVALUATION, DIAGNOSIS, AND MANAGEMENT OF FACIOSCAPULOHUMERAL MUSCULAR DYSTROPHY. American Academy of Neurology. 2015. https://www.aan.com/Guidelines/home/GuidelineDetail/701. Accessed December 10, 2021.

POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2013	New Policy	Genetic testing for facioscapulohumeral muscular dystrophy may be considered medically necessary to confirm a diagnosis in a patient with clinical signs of the disease, but is considered investigational for all other indications.
December 2014	Replace policy	Genetic testing for facioscapulohumeral muscular dystrophy may be considered medically necessary to confirm a diagnosis in a patient with clinical signs of the disease, but is considered investigational for all other indications.
March 2017	Replace policy	Policy updated with literature review through January 20, 2017; no references added. The policy is revised with updated genetics nomenclature. Policy statements unchanged.
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; reference 8 added. Policy statements unchanged.
June 2019	Replace policy	Policy updated with literature review through December 6, 2018; no references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through November 17, 2020; no references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through December 9, 2021; references added. Policy statements unchanged.