BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.86 Genetic Testing for Duchenne and Becker Muscular Dystrophy

Annual Effective Policy Date: July 1, 2024

Original Policy Date: September 2013

Related Policies:

None

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Description

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Variants in the Duchenne muscular dystrophy (*DMD)* gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases, including the progressive diseases Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less from more severe forms, as well as identify female carriers at risk.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing improves the net health outcome in symptomatic males with dystrophinopathy, females with a relative with Duchenne muscular dystrophy (*DMD)*-associated dystrophinopathy, asymptomatic male offspring of a female *DMD* familial variant carrier, or male sibling of a patient with a *DMD*-associated dystrophinopathy.

POLICY STATEMENT

Genetic testing for *DMD* gene variants may be considered **medically necessary** under the following conditions:

- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives (see Policy Guidelines and Benefit Application sections):
    - To confirm or exclude the need for cardiac surveillance.
    - For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy.
- For at-risk male offspring (see Policy Guidelines and Benefit Application sections):
    - To confirm or exclude the need for medical and cardiac surveillance.

Genetic testing for *DMD* gene variants is considered **investigational** in all other situations.

POLICY GUIDELINES

DMD gene testing

Females heterozygous for a Duchenne muscular dystrophy (*DMD)* disease-associated variant are at increased risk for cardiomyopathy and need routine cardiac surveillance and treatment.

At-risk females are defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts, and their offspring.

An at-risk male is defined as an asymptomatic male offspring of a female carrier or an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy.

Genetic Counseling

Experts recommend formal genetic counseling for individuals 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 individuals ; 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.

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). 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 are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for Duchenne muscular dystrophy (*DMD)* gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or Becker muscular dystrophy (BMD). Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Virtually all males with DMD or BMD have identifiable *DMD* disease-associated variants, indicating a high clinical sensitivity for genetic testing. The clinical utility of *DMD* gene testing can be established for the index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between DMD and the less severe BMD. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are female and are a relative of a patient with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine carrier status, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or BMD. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for the clinical validity for testing for a known familial variant are lacking but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in at-risk female relatives is lacking. However, the chain of evidence is strong, because determination of carrier status in a female for a *DMD* familial variant necessitates or eliminates the need for routine cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier or an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine *DMD* status, the evidence includes case series and database entries. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for clinical validity of testing for a known familial variant are lacking, but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in asymptomatic male offspring of a female *DMD* familial variant carrier or male sibling of a patient with a *DMD*-associated dystrophinopathy is also lacking. However, the chain of evidence is strong, because detection of the *DMD* familial variant necessitates or eliminates the need for increased medical surveillance or cardiac surveillance in an asymptomatic male offspring of a female carrier or the asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy. 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.

Duchenne muscular dystrophy Care Considerations Working Group

In 2010, an international working group comprised of 84 clinicians and scientists from government agencies, including the US Centers for Disease Control and Prevention, and advocacy organizations provided recommendations for providing coordinated multidisciplinary care in the diagnosis and treatment of Duchenne muscular dystrophy (DMD).[8,] Per the working group, genetic testing should first be used to screen for deletions and duplications. If no deletion or duplication is detected, screening for single nucleotide variants should be performed. For patients diagnosed by genetic testing, muscle biopsy is optional to distinguish DMD from milder phenotypes.

In 2018, the DMD Care Considerations Working Group updated its Care Considerations recommendations.[21,] Their recommendations for genetic testing utilization in DMD diagnosis remained similar to their 2010 recommendations, with a recommendation to first screen for deletions and duplications, followed by genetic sequencing if no deletion or duplication is detected. A muscle biopsy is only recommended if genetic testing does not confirm a clinical diagnosis and DMD is still considered likely. The working group also recommended genetic counseling to family members of an individual with DMD to establish who is at risk of being a carrier. Carrier testing is recommended for female relatives of a male who has been genetically confirmed to have DMD.

The European Molecular Genetics Quality Network and EuroGenTest

In 2010, a meeting of 29 senior scientists from the United States, Europe, India, and Australia established consensus best practice guidelines for the molecular diagnosis of Duchenne and Becker muscular dystrophy.[12,] Recommendations for testing were: if there is a clinical suspicion of a dystrophinopathy, first screen for deletions and duplications. If no deletion or duplication is detected, but the clinical diagnosis is verified, screen for single nucleotide variants.

In 2020, the best practice guidelines were updated to summarize current recommended technologies and methodologies in DMD gene analysis.[22,] The guideline's recommendations for testing are similar to 2010 recommendations. In terms of an initial screen, a diagnostic test that detects whole-exon deletions or duplications should be offered to detect copy number variations. The use of RNA-based analysis is recommended in patients with a clinical diagnosis of dystrophinopathy but no copy number variations or small variants that were identified.

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.

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

Date	Action	Description
September 2013	New policy	
June 2014	Replace policy	Policy updated with literature review. No change to policy statement. References 11, 14, 17, and 18 added.
June 2015	Replace policy	Policy updated with literature review, references 19-21 added; reference deleted. Policy statements unchanged.
June 2018	Replace policy	Policy updated with literature review through January 8, 2018;references 2, 10, and 12 were added; references 8 and 13-22 were deleted. Policy statement for at-risk female relatives removed. Objective section added stating: This policy does NOT evaluate individuals who are females with a relative of a patient with a DMD-associated dystrophinopathy, or individuals who are asymptomatic male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy (see Policy Guidelines and Benefit Applications).
June 2019	Replace policy	Policy updated with literature review through January 6, 2019. no references added. Policy statements unchanged.
June 2020	Replace policy	Policy updated with literature review through January 13, 2020; no references added. Policy statements unchanged.
June 2021	Replace policy	Policy updated with literature review through January 13, 2021; references added. Policy statements unchanged.
June 2022	Replace policy	Policy updated with literature review through January 19, 2022; references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through January 30, 2023; references added. Minor editorial refinements to policy statements; intent unchanged
June 2024	Replace policy	Policy updated with literature review through January 15, 2024; references added. Policy statements unchanged.