

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Effective: March 1, 2024

Next Review: January 2025

Last Review: January 2024

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Disease-associated variants in the *DMD* gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases. The severe end of the spectrum includes the progressive muscle diseases Duchenne and Becker muscular dystrophy and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less and more severe forms, as well as identify individuals at risk of having affected offspring.

MEDICAL POLICY CRITERIA

Note: This policy does not address reproductive carrier screening for these disorders (see Cross References)

- I. Genetic testing for *DMD* gene variants may be considered **medically necessary** if any of the following are met:
 - A. In patients with signs and symptoms of a dystrophinopathy to confirm the diagnosis and direct treatment; or
 - B. To confirm or exclude the need for cardiac surveillance in at-risk relatives (see Policy Guidelines).

- C. Prenatal (fetal) genetic testing for fetal diagnosis if a parent is known to be a carrier or has a first- or second-degree relative who is affected or known to be a carrier.
- II. Genetic testing for *DMD* gene variants is considered **not medically necessary** if the criteria above are not met.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

Heterozygous individuals are at increased risk for cardiomyopathy and need routine cardiac surveillance and treatment.

At-risk relatives are defined as first- and second-degree relatives with two X chromosomes (e.g., sister, mother, daughter, aunt, etc).

LIST OF INFORMATION NEEDED FOR REVIEW

In order to determine the clinical utility of gene test(s), all of the following information must be submitted for review. If any of these items are not submitted, it could impact our review and decision outcome:

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or disease-associated variant(s) being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test:
 - History and physical exam including any relevant diagnoses related to the genetic testing
 - Date of blood draw for test
 - Conventional testing and outcomes
 - Conservative treatments, if any

CROSS REFERENCES

1. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
2. [Reproductive Carrier Screening for Genetic Diseases](#), Genetic Testing, Policy No. 81

BACKGROUND

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, they are classified as Duchenne or Becker muscular dystrophy and when the heart is primarily affected, as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

DUCHENNE MUSCULAR DYSTROPHY

Duchenne muscular dystrophy (DMD), the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene.^[1] The incidence of DMD is estimated to be one in 3,500 newborn male births,^[2] and approximately one-third of DMD cases arise from de novo variants and have no known family history.^[1] Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool from years two to five. Affected children present with gait problems, calf hypertrophy, positive Gower's sign, and difficulty climbing stairs. The affected child's motor status may plateau between three and six years of life with deterioration beginning at six to eight years. The majority of patients will be wheelchair bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (e.g., decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death.^[1] Few individuals with DMD survive beyond the third decade.

BECKER MUSCULAR DYSTROPHY

Becker muscular dystrophy (BMD) is characterized by later-onset skeletal muscle weakness. Individuals remain ambulatory into their twenties. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-forties.

FEMALE CARRIERS

Females heterozygous for a *DMD* disease-associated variant can manifest symptoms of the disease.^[3] An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from a mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy.^[4] Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous individuals do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated *DMD* gene in the affected X chromosome.^[5] In some cases, this compensation can be reversed by a non-random or skewed inactivation of X chromosome resulting in greater expression of the affected X chromosome and some degree of myopathic features.^[6] Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome).^[3]

CLINICAL DIAGNOSIS

DMD

The suspicion of DMD should be considered irrespective of family history and is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or after the discovery of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting

up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties in rising from the floor or in tip-toe walking, and pseudo hypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and commonly a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5,000 and 150,000 IU/L), is non-specific to DMD but is always present in affected patients.^[1] Electromyography and nerve-conduction were traditional parts of the assessment of neuromuscular disorders, but now these tests are no longer believed to be necessary for the specific assessment of DMD.^[7] An open skeletal muscle biopsy is needed when a negative test for deletions or duplications to the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis on a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

BMD

Becker muscular dystrophy (BMD) has a clinical picture similar to DMD but is milder than DMD and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5 to 100 times the normal level).

Molecular Diagnosis

DMD is the only gene in which variants are known to cause DMD, BMD and DMD-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males. *DMD*, the gene that codes for dystrophin is the largest known human gene^[1] A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5,000 different reported disease-associated variants, as well as a high de novo variant rate.^[8]

Treatment

There is no cure for Duchenne or Becker muscular dystrophy, and treatment is aimed at control of symptoms to improve quality of life. However, the natural history of the disease can be changed by several strategies such as corticosteroid therapy, proper nutrition or rehabilitative interventions. Glucocorticoids can slow the loss of muscle strength and may be started when a child is diagnosed or when muscle strength begins to decline.^[7] The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways.^[1] Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at two to five years of age although there has been no demonstrated benefit of earlier therapy, before five years of age.^[1]

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted toward specific pathogenic variants.^[9] Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, non-shifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Exon-skipping therapies using antisense oligonucleotides approved by the U.S. Food and Drug Administration include: eteplirsen (Exondys 51) for treatment for patients who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping, and golodirsen (Vyondys 53) and viltolarsen (Viltepso) for patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. These approvals were based on improvements in the surrogate outcome of increased dystrophin production in skeletal muscle and benefits in clinical outcomes have not yet been established.

REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature^[10] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. The clinical utility of the test, i.e., 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.

This evidence review focuses on clinical validity and utility.

Clinical Validity

In male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy, the presence of a DMD familial variant is predictive of future developing clinical manifestations of a DMD-associated dystrophinopathy.^[11]

Virtually all males with DMD/BMD have identifiable *DMD* disease-associated variants,

indicating a high clinical sensitivity for genetic testing. In males with DMD and BMD, phenotypes are best correlated with the degree of expression of dystrophin, largely determined by the reading frame of the spliced message obtained from the deleted allele.

A reading frame is the way in which a messenger RNA sequence of nucleotides can be read as a series of base triplets, and affects which protein is made. In DMD, the function of the dystrophin protein is completely lost due to variants that disrupt the reading frame. Therefore, prematurely truncated, unstable dystrophins are generated. In contrast, patients with BMD have low levels of full-length dystrophin or carry in-frame variants that allow for the generation of partially functional proteins. This so-called reading frame rule explains the phenotypic differences between DMD and BMD patients. Since this rule was postulated in 1988,^[12] thousands of variants have been reported for DMD and BMD, of which an estimated 90% fit this rule.^[13]

Manjunath (2015) compared the sensitivity of multiplex ligation-dependant probe amplification (MLPA) and multiplex polymerase chain reaction (mPCR) in detecting deletions in 83 children with suspected DMD.^[14] mPCR detected deletions in 60/83 (72.3%) of children, while MLPA in the same 83 samples detected deletions in 66/83 (79.5%) and duplications in 6/83 (6.5%), indicating that MLPA has the higher detection rate of the two techniques. Muscle biopsy and subsequent immunohistochemistry performed in the 11 MLPA-negative cases showed absent dystrophin staining in 4/83 (36.4%), indicating neither of these techniques are as sensitive as whole gene sequencing by NGS or deletion/duplication detection using a chromosomal microarray.

Clinical Utility

No studies were identified that reported on clinical utility. However, the clinical utility of testing for *DMD* gene variants for the index case includes:

- Establishing the diagnosis and initiating/directing treatment of the disease, such as glucocorticoids, evaluation by a cardiologist, avoidance of certain agents (e.g., botulinum toxin injections), and prevention of secondary complications (immunizations, reducing risk of fractures).
- Distinguishing between DMD and BMD.
- Avoidance of a muscle biopsy in the majority of cases.

The clinical utility of testing for *DMD* gene variants for at-risk relatives includes testing to identify heterozygous individuals to confirm or exclude the need for cardiac surveillance.

PRACTICE GUIDELINE SUMMARY

DUCHENNE MUSCULAR DYSTROPHY CARE CONSIDERATIONS WORKING GROUP

In 2010, an international working group comprised of 84 clinicians and scientists from government agencies, including the U.S. Centers for Disease Control and Prevention, and advocacy organizations provided recommendations for providing coordinated multidisciplinary care in the diagnosis and treatment of DMD.^[7] 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.^[15] 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 EUROAGENTEST

An international consortium of scientists conferred and developed the consensus-based, “Best Practice Guidelines on Molecular Diagnosis in DMD/BMD Muscular Dystrophies.” The guidelines recommend genetic testing when there is a clinical suspicion of a dystrophinopathy. In addition, the guidelines recommend to first screen for deletions and duplications. If no deletion or duplication is detected, but the clinical diagnosis is verified, the guidelines recommend screening for single nucleotide variants (SNVs).^[9] In 2020, these guidelines were updated to summarize current recommended technologies and methodologies in DMD gene analysis.^[16] The guideline's recommendations for testing are similar to the 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. 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.

THE AMERICAN ACADEMY OF NEUROLOGY AND AMERICAN ASSOCIATION OF NEUROMUSCULAR AND ELECTRODIAGNOSTIC MEDICINE

The American Academy of Neurology and American Association of Neuromuscular and Electrodiagnostic Medicine guidelines (2015, reaffirmed in 2021) on evaluation, diagnosis and management of congenital muscular dystrophy (CMD) include the recommendation that, “when available and feasibly, physicians might order targeted genetic testing for specific CMD subtypes that have well-characterized molecular causes.”^[17] This is a level C recommendation, the lowest allowable recommendation level.

SUMMARY

There is enough research to show that genetic testing, including prenatal fetal testing, can improve health outcomes when dystrophinopathy is suspected and for at-risk relatives. Clinical guidelines based on research recommend testing of the *DMD* gene in patients that have signs and symptoms of Duchenne and/or Becker muscular dystrophy. Therefore, genetic testing for *DMD* gene disease-associated variants may be considered medically necessary to establish a diagnosis in an individual with clinical signs and symptoms suggestive of a dystrophinopathy and in at-risk relatives. Similarly, prenatal fetal testing may be considered medically necessary when policy criteria are met.

Screening for *DMD* variants is not recommended for people without symptoms or who are not at-risk relatives. Therefore, genetic testing for *DMD* gene disease-associated variants is considered not medically necessary when the policy criteria are not met.

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CODES

| Codes | Number | Description |
|-------|--------|--|
| CPT | 0218U | Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants |
| | 81161 | DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis and duplication analysis, if performed |
| | 81408 | Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis) --includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy), full gene sequence |
| HCPCS | None | |

Table 1. Testing Strategy

To establish the diagnosis of a proband with DMD or BMD in a male with clinical findings that suggest a dystrophinopathy:

- Perform DMD genetic testing for deletion/duplication analysis first.
- If a copy number variant (CNV) is not identified, perform sequence analysis for a SNV.
- If a disease-causing DMD variant is identified, the diagnosis of a dystrophinopathy is established.
- In cases where a distinction between DMD and BMD is difficult, the reading frame “rule” states that the type of deletion/duplication (those that alter the reading frame [out-of-frame], which correlates with the more severe phenotype of DMD versus those that do not alter the reading frame [in-frame] which correlate with the milder BMD phenotype) can distinguish the DMD and BMD phenotypes with 91-92% accuracy.
- If no disease-causing DMD variant is identified, skeletal muscle biopsy is warranted for western blot and immunohistochemistry studies of dystrophin.

For carrier testing in at-risk female relatives:

- When the proband’s DMD disease-associated variant is known, test for that deletion/duplication or SNV using appropriate testing method.
- When an affected male is not available for testing, perform testing by deletion/duplication first and if no variant is identified, by sequence analysis.

The evaluation of relatives at risk includes females who are the sisters or maternal female relatives of an affected male and females who are a first-degree relative of a known or possible carrier female.

Date of Origin: January 2014