Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 9/1/24**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Duchenne and Becker Muscular Dystrophy

Description/Background

Dystrophinopathies

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, the disease is classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD); when the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

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,] According to a 2022 systematic review and meta-analysis, the global prevalence of DMD is estimated at 4.8 cases (95% confidence interval [CI], 3.6 to 6.3) per 100,000 people.[2,]. 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 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child's motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. Most 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 (eg, 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 is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. 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-40s.[3] According to a 2022 systematic review and meta-analysis, the global prevalence of BMD is estimated at 1.6 cases (95% CI, 1.1 to 2.4) per 100,000 people.[2,]

Female Carriers

Females heterozygous for a DMD disease-associated variant can manifest symptoms of the disease.[4] An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy.[5] Female carriers are at increased risk for dilated cardiomyopathy. Most heterozygous women 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.[6] In some cases, this compensation can be reversed by a nonrandom or skewed inactivation of the X chromosome, resulting in greater expression of the affected X chromosome and some degree of myopathic features.[7] 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).[4]

Clinical Diagnosis

Duchenne Muscular Dystrophy

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by the observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or detection 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 rising from the floor or tip-toe walking, and pseudohypertrophy 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 5000 IU/L and 150000 IU/L), is nonspecific to DMD but is always present in affected patients.[1] Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests may not be necessary for assessment of DMD.[8] An open skeletal muscle biopsy is needed when a test for deletions or duplications of 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 of a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

Becker Muscular Dystrophy

Becker muscular dystrophy is clinically similar to DMD but is milder 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 of 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 approximately 95% of patients with DMD and BMD.[9]

The dystrophinopathies are X-linked recessive and penetrance is complete in males. 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 5000 reported disease-associated variants, as well as a high spontaneous de novo variant rate.[10]

Treatment

There is no cure for DMD or BMD. Treatment is aimed at controlling symptoms to improve quality of life. However, the natural history of the disease can be changed by strategies such as corticosteroid therapy, proper nutrition, or rehabilitative interventions. Glucocorticoids were shown in a 1991 randomized controlled trial (RCT) to prolong the period of independent ambulation by 3 years.[11] 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 2 to 5 years of age, although there has been no demonstrated benefit of therapy before 5 years of age.[1]

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants.[12] 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, nonshifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials. 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,[13] golodirsen (Vyondys 53),[14] and viltolarsen (Viltepso)[15] for patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping,and casimersen (Amondys 45)[16,] for patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 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.

A gene therapy, delandistrogene moxeparvovec-rokl (Elevidys), was also approved in 2023 to treat ambulatory children 4 to 5 years of age with DMD and a confirmed mutation in the *DMD* gene.[17,]

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.

Medical Policy Statement

Genetic testing for *DMD* gene mutations has been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

- For an individual with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment

- For at-risk female relatives*, for carrier testing

    - To confirm or exclude the need for cardiac surveillance
    - For preconception testing

- For at-risk male offspring**
    - To confirm or exclude the need for medical and cardiac surveillance

*At-risk female relatives are defined as first-and second-degree female relatives of the patient with a *DMD*-associated dystrophinopathy. They include the mother, female siblings, female offspring, maternal grandmother, maternal aunts, and maternal nieces of the patient with a *DMD*-associated dystrophinopathy.

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

Exclusions:
All other indications

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81161 81408

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING MALES WITH SIGNS AND SYMPTOMS OF A DYSTROPHINOPATHY

Clinical Context and Test Purpose

The purpose of genetic testing for Duchenne muscular dystrophy (*DMD)* gene variants to confirm diagnosis without biopsy is to provide a diagnostic option that is an alternative to or an improvement on existing therapies, such as a standard workup without genetic testing, including possible muscle biopsy, in patients who are male and have signs and symptoms of a dystrophinopathy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are male and have signs and symptoms of a dystrophinopathy, such as proximal muscle weakness.

Dystrophinopathy comprises a spectrum of muscle diseases, the mild end including 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 includes progressive muscle disease that leads to morbidity and mortality.

Virtually all males with DMD or BMD have identifiable *DMD* disease-associated variants, indicating a high clinical sensitivity for genetic testing.

Interventions

The test being considered is genetic testing for *DMD* gene variants to confirm diagnosis without biopsy.

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.

Comparators
Comparators of interest include a standard workup without genetic testing, including possible muscle biopsy.

Outcomes
The general outcomes of interest are primarily eliminating the need for muscle biopsy, in addition to test accuracy, test validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to inappropriate initiation of treatments. False-negative test results can lead to invasive muscle biopsy or exclusion from potentially efficacious treatments.

The existing literature evaluating genetic testing for *DMD* gene variants to confirm diagnosis without biopsy as a diagnosis for males with signs and symptoms of a dystrophinopathy has varying lengths of follow up.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.
1. The study population represents the population of interest. Eligibility and selection are described.
2. The test is compared with a credible reference standard.
3. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
4. Studies should report sensitivity, specificity, and predictive values. Studies that completely report true- and false-positive results are ideal. Studies reporting other measures (eg, receiver operating characteristic, areas under receiver operating characteristic, c-statistic, likelihood ratios) may be included but are less informative.
5. Studies should also report reclassification of diagnostic or risk category.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE
Virtually all male individuals with DMD or BMD have identifiable *DMD* pathogenic 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 lost due to pathogenic 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.[18] Thousands of pathogenic variants have been reported for DMD and BMD, of which an estimated 90% fit this rule.[19]

Testing Strategy
To establish the diagnosis of a male proband with DMD or BMD with clinical findings suggesting 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 single nucleotide variant (SNV).
- If a disease-causing *DMD* variant is identified, the diagnosis of a dystrophinopathy is established.
- Where a distinction between DMD and BMD is difficult, the reading frame rule states that the type of deletion or 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% to 92% accuracy.
- If no disease-causing *DMD* variant is identified, skeletal muscle biopsy is warranted for Western blot and immunohistochemistry studies of dystrophin.

Clinically Useful
A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No published studies showing clinical utility of testing for *DMD* gene variants were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical utility of testing the index case for *DMD* gene variants includes:

- Establishing the diagnosis and initiating or directing treatment of the disease (eg, glucocorticoids), evaluation by a cardiologist, avoidance of certain agents (eg, botulinum toxin injections), and prevention of secondary complications (eg, immunizations, fracture risk reduction).
- Distinguishing between DMD and BMD.
- Avoidance of a muscle biopsy in most cases.

Section Summary: Testing Male Individuals With Signs and Symptoms of a Dystrophinopathy

The clinical sensitivity of genetic testing is high given that DMD is the only gene for which variants are known to cause DMD, BMD, and *DMD*-associated cardiomyopathy. Identification of a pathogenic variant in DMD establishes a diagnosis of a dystrophinopathy without muscle biopsies in most patients with DMD and BMD. Direct evidence for the clinical usefulness of

genetic testing in male individuals who have signs and symptoms of a dystrophinopathy is lacking. A chain of evidence for the clinical validity of *DMD* genetic variants in establishing diagnosis of a dystrophinopathy and initiating or directing treatment of the disease and cardiac surveillance provides a chain of evidence on clinical usefulness of this testing.

TESTING FEMALES INDIVIDUALS WHO ARE RELATIVES OF A PATIENT WITH A *DMD*-ASSOCIATED DYSTROPHINOPATHY

Clinical Context and Test Purpose

The purpose of targeted *DMD* testing for a known familial variant to determine carrier status is to provide a diagnostic option that is an alternative to or an improvement on existing therapies, such as a standard workup without genetic testing, including family history and cardiac surveillance, in individuals who are female and are a relative of a patient with a *DMD*-associated dystrophinopathy.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals who are female and are a relative of a patient with a *DMD*-associated dystrophinopathy.

Dystrophinopathy comprises a spectrum of muscle diseases, the mild end including 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 includes progressive muscle disease that leads to morbidity and mortality.

Interventions

The test being considered is targeted *DMD* testing for a known familial variant to determine carrier status.

Comparators

Comparators of interest include a standard workup without genetic testing, including family history and cardiac surveillance.

Outcomes

The general outcomes of interest are test accuracy, test validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. 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.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary cardiac surveillance or an irreversible reproductive decision. False-negative test results can lead to lack of cardiac surveillance.

The existing literature evaluating targeted *DMD* testing for a known familial variant to determine carrier status as a diagnosis for individuals who are female and are a relative of a patient with a *DMD*-associated dystrophinopathy has varying lengths of follow-up.

Study Selection Criteria
Study selection criteria is outlined under the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

In a male offspring of a female *DMD* familial variant carrier, the presence of a *DMD* familial variant is predictive of developing clinical manifestations of a *DMD*-associated dystrophinopathy.[20,]

Testing Strategy
For *DMD* familial variant testing in at-risk male offspring:

- When the proband's *DMD* pathogenic variant is known, test for that deletion or duplication or SNV using an appropriate testing method.
- When an affected male is not available for testing, test by deletion and duplication analysis first and, if no CNV is identified, by sequence analysis.

The evaluation of relatives at risk includes male offspring of a female *DMD* familial variant carrier.

Clinically Useful
A test is clinically useful if use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No published studies showing the clinical usefulness of testing for *DMD* gene variants were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical usefulness of testing is established based on the benefits for asymptomatic male offspring of a female *DMD* familial variant carrier to confirm or exclude a diagnosis of a *DMD*-associated dystrophinopathy prior to manifestation of disease. The clinical usefulness of testing at-risk male offspring or male siblings for *DMD* gene variants includes:

- Testing to identify a *DMD* familial variant in at-risk males to confirm or exclude the need for medical and cardiac surveillance prior to manifestation of a *DMD*-associated dystrophinopathy.

Section Summary: Testing Female Individuals who are Relatives of a Patient with a DMD-Associated Dystrophinopathy
The clinical sensitivity of genetic testing is high given that DMD is the only gene for which variants are known to cause DMD, BMD, and DMD-associated cardiomyopathy. For female relatives of an individual with a *DMD*-associated dystrophinopathy, targeted DMD familial variant testing confirms or excludes carrier status for a known familial variant. Direct evidence of the clinical usefulness of genetic testing in female relatives of a patient with a *DMD*-associated dystrophinopathy is lacking. A chain of evidence exists in that confirmation or exclusion of a *DMD* familial variant necessitates or eliminates the need for cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children.

TESTING MALE OFFSPRING OF A FEMALE CARRIER OF A *DMD*-ASSOCIATED DYSTROPHINOPATHY

Clinical Context and Test Purpose
The purpose of targeted *DMD* testing for a known familial variant to determine carrier status is to provide a diagnostic option that is an alternative to or an improvement on existing therapies, such as a standard workup without genetic testing, including family history and cardiac surveillance, in individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier.

Dystrophinopathy comprises a spectrum of muscle diseases, the mild end including 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 includes progressive muscle disease that leads to morbidity and mortality.

Interventions
The test being considered is targeted *DMD* testing for a known familial variant to determine carrier status.

Comparators
Comparators of interest include a standard workup without genetic testing, including family history and cardiac surveillance.

Outcomes
The general outcomes of interest are test accuracy, test validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. 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 with a *DMD*-associated dystrophinopathy.

Potential harmful outcomes are those resulting from a false-positive or false-negative test result. False-positive test results can lead to unnecessary cardiac surveillance or an irreversible reproductive decision. False-negative test results can lead to lack of cardiac surveillance.

The existing literature evaluating targeted *DMD* testing for a known familial variant to determine carrier status as a diagnosis for individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier has varying lengths of follow-up.

Study Selection Criteria
Study selection criteria is outlined under the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE
In a male offspring of a female *DMD* familial variant carrier, the presence of a *DMD* familial variant is predictive of developing clinical manifestations of a *DMD*-associated dystrophinopathy.[20]

Testing Strategy
For *DMD* familial variant testing in at-risk male offspring:

- When the proband's *DMD* pathogenic variant is known, test for that deletion or duplication or SNV using appropriate testing method.
- When an affected male is not available for testing, test by deletion and duplication analysis first and, if no CNV is identified, by sequence analysis.

The evaluation of relatives at risk includes male offspring of a female *DMD* familial variant carrier.

Clinically Useful
A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No published studies showing the clinical usefulness of testing for *DMD* gene variants were identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

The clinical usefulness of testing is established based on the benefits for asymptomatic male offspring of a female DMD familial variant carrier is to confirm or exclude diagnosis of a DMD-associated dystrophinopathy prior to manifestation of disease. The clinical usefulness of testing at-risk male offspring or male siblings for DMD gene variants includes:

- Testing to identify a DMD familial variant in at-risk males to confirm or exclude the need for medical and cardiac surveillance prior to manifestation of a DMD-associated dystrophinopathy.

Section Summary: Testing Male Offspring of a Female Carrier of a DMD-Associated Dystrophinopathy

Evidence from studies has indicated that the clinical sensitivity of genetic testing is high given that DMD is the only gene for which variants are known to cause DMD, BMD, and DMD-associated cardiomyopathy. For male offspring of female carriers, targeted DMD familial variant testing confirms or excludes diagnosis of a *DMD*-associated dystrophinopathy prior to manifestation of disease. Direct evidence of the clinical usefulness of genetic testing in individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier is lacking. A chain of evidence exists in that confirmation or exclusion of a *DMD* familial variant predicts clinical manifestations in asymptomatic at-risk males and necessitates or eliminates the need for medical and cardiac surveillance.

TESTING MALE SIBLING OF A PATIENT WITH *DMD*-ASSOCIATED DYSTROPHINOPATHY

Clinical Context and Test Purpose

The purpose of testing a male sibling of a patient with a DMD-associated dystrophinopathy is to diagnose at-risk males prior to manifestation of disease and initiate medical and cardiac surveillance. At-risk males with an identified DMD familial variant will undergo surveillance for cardiac and myopathic manifestations. Males who do not have the DMD familial variant can avoid surveillance that would be indicated by knowledge of family history alone.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is male siblings of an individual with a *DMD*-associated dystrophinopathy.

Interventions

The test being considered is genetic testing for a known DMD familial variant.

Comparators

The following practice is currently being used to make decisions about ruling in or out male siblings of those with a known DMD familial variant: standard workup care including family history and cardiac surveillance, without genetic testing.

Outcomes
The main beneficial outcomes of interest include initiation of medical and cardiac surveillance in *DMD* familial variant carriers and exclusion from surveillance when a *DMD* familial variant is not found.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. False-positive test results can lead to unnecessary medical and cardiac surveillance. False-negative test results can lead to lack of medical and cardiac surveillance.

The time frame for outcomes measures varies from short-term development of symptoms and early initiation of treatment to long-term changes in disease status.

Study Selection Criteria
Study selection criteria is outlined under the first indication.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE
In a male sibling of a patient with a *DMD*-associated dystrophinopathy, the presence of a *DMD* familial variant is predictive of developing clinical manifestations of a DMD-associated dystrophinopathy.[20]

Testing Strategy
For *DMD* familial variant testing in at-risk male siblings:

- When the proband's *DMD* pathogenic variant is known, test for that deletion or duplication or SNV using appropriate testing method.
- When an affected male is not available for testing, test by deletion and duplication analysis first and, if no CNV is identified, by sequence analysis.

The evaluation of relatives at risk includes a male sibling of a patient with *DMD*-associated dystrophinopathy.

Clinically Useful
A test is clinically useful if use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No published studies showing the clinical usefulness of testing for DMD gene variants were identified.

Chain of Evidence

- Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. The clinical usefulness of testing is established based on the benefits to an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy, to confirm or exclude diagnosis of a *DMD*-associated dystrophinopathy prior to manifestation of disease. The clinical usefulness of testing at-risk male offspring or male siblings for *DMD* gene variants includes: Testing to identify a DMD familial variant in at-risk males to confirm or exclude the need for medical and cardiac surveillance prior to manifestation of a *DMD*-associated dystrophinopathy.

Section Summary: Testing Male Sibling of a Patient With DMD-Associated Dystrophinopathy

Evidence from studies has indicated that the clinical sensitivity of genetic testing is high given that DMD is the only gene for which variants are known to cause DMD, BMD, and *DMD*-associated cardiomyopathy. For male siblings of an affected male with a DMD-associated dystrophinopathy, targeted DMD familial variant testing confirms or excludes diagnosis of a DMD-associated dystrophinopathy prior to manifestation of disease. Direct evidence of the clinical usefulness of genetic testing in individuals who are asymptomatic male siblings of a patient with *DMD*-associated dystrophinopathy is lacking. A chain of evidence exists in that confirmation or exclusion of a *DMD* familial variant predicts clinical manifestations in asymptomatic at-risk males and necessitates or eliminates the need for medical and cardiac surveillance.

SUMMARY OF EVIDENCE

For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for *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 and 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 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 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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
No NCD on this topic.

Local:
Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD) MolDX: Molecular Diagnostic Tests (MDT) (L36807)
Original Effective Date: For services performed on or after 02/16/2017
Revision Effective Date: For services performed on or after 04/27/2023

Coverage Indications, Limitations, and/or Medical Necessity
Tests evaluated through the application process and/or technical assessment will be reviewed to answer the following questions:

Is the test performed in the absence of clinical signs and symptoms of disease?
Will the test results provide the clinician with information that will improve patient outcomes and/or change physician care and treatment of the patient?
Will the test results confirm a diagnosis or known information?
Is the test performed to determine risk for developing a disease or condition?
Will risk assessment change management of the patient?
Is there a diagnosis specific indication to perform the test?
Is the test performed to measure the quality of a process or for Quality Control/Quality Assurance (QC/QA), i.e., a test to ensure a tissue specimen matches the patient?

[As of the review date of this policy, there is no LCD that specifically addresses DMD or BMD testing.]

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding MolDX: Molecular Diagnostic Tests (MDT) (A57772)
Original Effective Date: 11/01/2019
Revision Effective Date: 01/01/2024

Code 81161 is found in the Group 1 Codes list.

Article Guidance
Article Text

The information in this article contains billing, coding, or other guidelines that complement the Local Coverage Determination (LCD) for MolDX: Molecular Diagnostic Tests (MDT) L36807. To report a Molecular Diagnostic Test service, please submit the following claim information:

- Select appropriate CPT code
- Enter 1 unit of service (UOS)
- Enter the appropriate DEX Z-Code™ identifier adjacent to the CPT® code in the comment/narrative field for the following Part B claim field/types:
  - Loop 2400 or SV101-7 for the 5010A1 837P
  - Box 19 for paper claim
- Enter the appropriate DEX Z-Code™ identifier adjacent to the CPT® code in the comment/narrative field for the following Part A claim field/types:
  - Line SV202-7 for 837I electronic claim
  - Block 80 for the UB04 claim form

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling
Genetic Testing for Myotonic Muscular Dystrophy

References

1. Verma S, Anziska Y, Cracco J. Review of Duchenne muscular dystrophy (DMD) for the pediatricians in the community. Clin Pediatr (Phila) 2010; 49(11):1011-7. PMID 20724320
2. Salari N, Fatahi B, Valipour E, et al. Global prevalence of Duchenne and Becker muscular dystrophy: a systematic review and meta-analysis. J Orthop Surg Res. Feb 15 2022; 17(1): 96. PMID 35168641

3. Darras BT, Miller DT, Urion DK. Dystrophinopathies. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2014.
4. Yoon J, Kim SH, Ki CS, et al. Carrier woman of Duchenne muscular dystrophy mimicking inflammatory myositis. J Korean Med Sci. Apr 2011;26(4):587-591. PMID 21468271
5. Soltanzadeh P, Friez MJ, Dunn D, et al. Clinical and genetic characterization of manifesting carriers of DMD mutations. Neuromuscul Disord. Aug 2010;20(8):499-504. PMID 20630757
6. Bonilla E, Schmidt B, Samitt CE, et al. Normal and dystrophin-deficient muscle fibers in carriers of the gene for Duchenne muscular dystrophy. Am J Pathol. Dec 1988;133(3):440-445. PMID 3059802
7. Yoshioka M, Yorifuji T, Mituyoshi I. Skewed X inactivation in manifesting carriers of Duchenne muscular dystrophy. Clin Genet. Feb 1998;53(2):102-107. PMID 9611069
8. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010; 9(1):77-93.
9. Andrews JG, Galindo MK, Thomas S, et al. DMD Gene and Dystrophinopathy Phenotypes Associated With Mutations: A Systematic Review for Clinicians. J Clin Neuromuscul Dis. Jun 01 2023; 24(4): 171-187. PMID 37219861
10. Mah JK, Selby K, Campbell C, et al. A population-based study of dystrophin mutations in Canada. Can J Neurol Sci. May 2011; 38(3): 465-74. PMID 21515508
11. Griggs RC, Moxley RT, 3rd, Mendell JR, et al. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol. Apr 1991;48(4):383-388. PMID 2012511
12. Abbs S, Tuffery-Giraud S, Bakker E, et al. Best practice guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies. Neuromuscul Disord 2010; 20(6):422-7. PMID 20466545
13. Food and Drug Administration (FDA). FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. 2016; https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm Accessed 5/3/24.
14. Food and Drug Administration. VYONDYS 53 (golodirsen) Prescribing Information. 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf Accessed 5/3/24.
15. Food and Drug Administration. VILTEPSO (viltolarsen) Prescribing Information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212154Orig1s000lbl.pdf Accessed 5/3/24.
16. Food and Drug Administration (FDA). FDA News Release: FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation. 2021; accessed 4/2/24 https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0.
17. Food and Drug Administration (FDA). FDA News Release: FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy. 2023; https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy. Assessed 4/2/24
18. Monaco AP, Bertelson CJ, Liechti-Gallati S, et al. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. Genomics 1988; 2(1):90-5. PMID 3384440
19. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, et al. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical

cases that confirm the reading-frame rule. Muscle Nerve 2006; 34(2):135-44. PMID 16770791
20. Ross LF, Saal HM, David KL, et al. Technical report: Ethical and policy issues in genetic testing and screening of children. Genet Med. Mar 2013;15(3):234-245. PMID 23429433
21. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. Mar 2018; 17(3): 251-267. PMID 29395989
22. Fratter C, Dalgleish R, Allen SK, et al. EMQN best practice guidelines for genetic testing in dystrophinopathies. Eur J Hum Genet. Sep 2020; 28(9): 1141-1159. PMID 32424326

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 5/3/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	9/11/13	9/10/13	Joint policy established
11/1/15	8/24/15	9/14/15	Routine maintenance
11/1/16	8/16/16	8/16/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance Inclusion added for male offspring of female carriers and male sibling of affected male. Added “or female” to first bullet under Inclusions and to testing strategy if suspected of dystrophinopathy. “Mutations” was changed to “variants” throughout policy. Rationale revised. Local Medicare information updated. Procedure codes 81161 and 81408 for DMD are listed on the excluded test list. WPS GHA has determined that testing for these genes/gene components does not meet the Medicare criteria for a covered service.
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance; ref 13,14 added
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (jf) Vendor Managed: NA
9/1/24	6/11/24		Routine maintenance (jf) Vendor Managed: NA Ref Added: 2,9,16,17 and 22

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR DUCHENNE AND BECKER MUSCULAR DYSTROPHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.