2.04.86	Genetic Testing for Duchenne and Becker Muscular Dystrophy		
Original Policy Date:	July 31, 2015	**Effective Date:**	November 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 19

Policy Statement

I. Genetic testing for *DMD* gene variants may be considered **medically necessary** under **any** of the following conditions:
   A. In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
   B. For at-risk female relatives (see Policy Guidelines and Benefit Application sections): for **either** of the following:
      1. To confirm or exclude the need for cardiac surveillance.
      2. For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy.
   C. For at-risk male offspring (see Policy Guidelines and Benefit Application sections):
      1. To confirm or exclude the need for medical and cardiac surveillance.

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

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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 an individual 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.

Coding

See the Codes table for details.

Description

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.

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 individuals 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 an individual 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 individuals 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 an individual 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.

Additional Information

Not applicable

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09
California laws that requires insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
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

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 (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

BMD 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 the 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 the 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

BMD 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 the 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,]

Literature Review

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 Male Individuals 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 individuals 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 Becker muscular dystrophy (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 musde 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 (e.g., receiver operating characteristic, area 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 and 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 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 (RCTs).

No published studies showing the 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 (e.g., glucocorticoids), evaluation by a cardiologist, avoidance of certain agents (e.g., botulinum toxin injections), and prevention of secondary complications (e.g., 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 Female Individuals who are Relatives of an Individual 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 an individual 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 an individual 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 an individual with a *DMD*-associated 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 (e.g., receiver operating characteristic, area 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
See the discussion in the section above on testing males with signs and symptoms of a dystrophinopathy.

Testing Strategy
For carrier testing in at-risk female relatives:

- 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 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.

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 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 at-risk female relatives for *DMD* gene variants includes:

- Testing to identify heterozygous females to confirm or exclude the need for cardiac surveillance.
- Preconception testing of a woman considering offspring who would alter reproductive decision making based on test results.

Section Summary: Testing Female Individuals who are Relatives of an Individual 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

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 (e.g., receiver operating characteristic, area 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

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 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 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 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 an Individual With *DMD*-Associated Dystrophinopathy

Clinical Context and Test Purpose

The purpose of testing a male sibling of an individual 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 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 a lack of medical and cardiac surveillance.

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

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 (e.g., receiver operating characteristic, area 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

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 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 a male sibling of a patient with DMD-associated dystrophinopathy.

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 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 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 an Individual 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.

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.

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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in January 2025 did not identify any ongoing or unpublished trials that would likely influence this review.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Diagnosis and presenting symptoms
  - Past treatment plan and response(s)
  - Familial history as it relates to high-risk female patients
  - Pre-pregnancy considerations
  - Treatment strategy per request

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	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
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/31/2015	BCBSA Medical Policy adoption
06/01/2016	Policy revision without position change
05/01/2017	Policy revision without position change
05/01/2018	Policy revision without position change
06/01/2023	Policy reactivated. Previously archived from 05/01/2020 to 05/31/2023
05/01/2024	Annual review. No change to policy statement. Literature review updated.
11/01/2025	Policy reactivated. Previously archived from 06/01/2024 to 10/31/2025

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Duchenne and Becker Muscular Dystrophy 2.04.86** **Policy Statement:** I. Genetic testing for *DMD* gene variants may be considered **medically necessary** under **any** of the following conditions: A. In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment. B. For at-risk female relatives (see Policy Guidelines and Benefit Application sections): for **either** of the following: 1. To confirm or exclude the need for cardiac surveillance. 2. For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy. C. For at-risk male offspring (see Policy Guidelines and Benefit Application sections): 1. To confirm or exclude the need for medical and cardiac surveillance. II. Genetic testing for *DMD* gene variants is considered **investigational** in all other situations.