Policy Statement

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

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

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

Policy Guidelines

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

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

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

Index Case Testing

Consensus recommendations from best practice guidelines for molecular diagnosis of Duchenne and Becker muscular dystrophy have indicated that testing of an affected male (the index case) be performed so that carrier testing in female relatives at risk can focus on the known familial variant. Testing of at-risk asymptomatic males can focus on the known familial variant to diagnose a DMD-associated dystrophinopathy prior to disease manifestation. However, coverage for testing of the affected index case depends on contract benefit language.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.
Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td></td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
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</tbody>
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Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling
Experts recommend formal genetic counseling for patients 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 patients; 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
The following CPT codes are applicable to this testing:
- **81161**: DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed
- **81408**: (Molecular Pathology Procedure Level 9) Includes DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy), full gene sequence

Description
Variants in the DMD gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases, including the progressive diseases Duchenne (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.

Related Policies
- N/A

Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these
instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**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. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments 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 (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 2014 systematic review, the incidence of DMD ranges from 1 in 3600 to 1 in 9300 male births.\(^2\) 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.\(^3\) 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.\(^3\)

**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 a 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. In some cases, this compensation can be reversed by a nonrandom or skewed inactivation of X chromosome, resulting in greater expression of the affected X chromosome and some degree of myopathic features. 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).

### Clinical Diagnosis

#### Duchenne Muscular Dystrophy

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by an observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or detection of increased serum transaminases (aspartate aminotransferase and alanine aminotransferase). 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 pseudo-hypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and, commonly, a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5000 IU/L and 150,000 IU/L), is nonspecific to DMD but is always present in affected patients. Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests are may not be necessary for assessment of DMD. 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 on 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 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 (5-100 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 most patients with DMD and BMD. The dystrophinopathies are X-linked recessive and penetrance is complete in males. The gene that codes for dystrophin is the largest known human gene. 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.

### 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 to prolong the period of independent ambulation by 3 years. 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.
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.\(^1\) Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, non-shifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials and an exon-skipping therapy using antisense oligonucleotides (eteplirsen [Exondys 51]) has been approved for treatment for patients who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping.\(^1\)

**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 a 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 Therapy Purpose**

The purpose of genetic testing for 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 question addressed in this evidence review is: does genetic testing improve the net health outcome in symptomatic males with dystrophinopathy?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are 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. Treatment for individuals diagnosed with dystrophinopathy include a corticosteroid regimen.

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.

Timing
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. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients who are male and have signs and symptoms of a dystrophinopathy are actively managed by genetic disease specialists and primary care providers in a genetic testing facility and outpatient clinical settings.

Patients may be referred from a primary care clinician to a medical geneticist for investigation and management of a dystrophinopathy. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

a. The study population represents the population of interest. Eligibility and selection are described.

b. The test is compared with a credible reference standard.

c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.

d. 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., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.

e. Studies should also report reclassification of diagnostic or risk category.

Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
- Technically reliable
- Clinically valid
- Clinically useful

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a
condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection, because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition, and can be either a beneficial response or an adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**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).

Virtually all male individuals with Duchenne (DMD) or Becker muscular dystrophy (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. Thousands of pathogenic variants have been reported for DMD and BMD, of which an estimated 90% fit this rule.

**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, vs 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 immuno histochemistry studies of dystrophin.

**Section Summary: Clinically Valid**
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.
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.

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: Clinically Useful
Direct evidence for the clinical usefulness of genetic testing 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 a Patient with a DMD-Associated Dystrophinopathy
Clinical Context and Therapy 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 patients who are female and are a relative of a patient with a DMD-associated dystrophinopathy.

The question addressed in this evidence review is: does genetic testing improves the net health outcome in symptomatic males with dystrophinopathy, females with a relative with DMD-associated dystrophinopathy, or asymptomatic male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are 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. Treatment for individuals diagnosed with dystrophinopathy include a corticosteroid regimen.

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.

Timing
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. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients who are female and are a relative of a patient with a DMD-associated dystrophinopathy are actively managed by genetic disease specialists and primary care providers in a genetic testing facility and outpatient clinical settings.

Patients may be referred from a primary care clinician to an obstetrician or medical geneticist for investigation and dystrophinopathy carrier status management. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.

a. The study population represents the population of interest. Eligibility and selection are described.
b. The test is compared with a credible reference standard.
c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
d. 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., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
e. Studies should also report reclassification of diagnostic or risk category.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.
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).

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 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.

Section Summary: Clinically Valid
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 known familial variant.

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.

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: Clinically Useful
Direct evidence of the clinical usefulness of genetic testing 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 Therapy 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 patients who are asymptomatic male offspring of a female DMD familial variant carrier.

The question addressed in this evidence review is: does genetic testing improves the net health outcome in symptomatic males with dystrophinopathy, females with a relative with DMD-associated dystrophinopathy, or asymptomatic male offspring of a female DMD familial variant carrier or male sibling of a patient with a DMD-associated dystrophinopathy?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are 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. Treatment for individuals diagnosed with dystrophinopathy include a corticosteroid regimen.

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 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.

Timing
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. While studies described below all reported at least one outcome of interest, longer follow-up was necessary to fully observe outcomes.

Setting
Patients who are asymptomatic male offspring of a female DMD familial variant carrier are actively managed by genetic disease specialists and primary care providers in a genetic testing facility and outpatient clinical settings.
Patients may be referred from a primary care clinician to a pediatrician or medical geneticist for investigation and dystrophinopathy disease management. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

Study Selection Criteria
Below are selection criteria for studies to assess whether a test is clinically valid.
   a. The study population represents the population of interest. Eligibility and selection are described.
   b. The test is compared with a credible reference standard.
   c. If the test is intended to replace or be an adjunct to an existing test; it should also be compared with that test.
   d. 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., ROC, AUROC, c-statistic, likelihood ratios) may be included but are less informative.
   e. Studies should also report reclassification of diagnostic or risk category.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

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).

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.

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.

Section Summary: Clinically Valid
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.

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.
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 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: Clinically Useful
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 Therapy Purpose
The purpose of testing male offspring of 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 question addressed in this evidence review is: Does targeted genetic testing of male offspring of a female DMD familial variant carrier or male sibling of a patient to identify a known DMD familial variant rule in or rule out the at-risk male for medical and cardiac surveillance?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes male offspring of female DMD familial variant carriers or male siblings of a patient 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.

**Timing**
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.

**Setting**
Patients may be referred from a primary care clinician to a pediatrician or medical geneticist for investigation and dystrophinopathy disease management. Referral for genetic counseling is important for explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.

**Technically Reliable**
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist.

**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).

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.15

**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.

**Section Summary: Clinically Valid**
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 familiar variant testing confirms or excludes diagnosis of a DMD-associated dystrophinopathy prior to manifestation of disease.

**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.

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 a 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 male to confirm or exclude the need for medical and cardiac surveillance prior to manifestation of a DMD-associated dystrophinopathy.

Section Summary: Clinically Useful
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 an 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 or 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 a meaningful 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 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 a meaningful improvement in the net health outcome.
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 a meaningful 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 a symptomatic 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 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 a meaningful improvement in the net health outcome.

Supplemental Information
Practice Guidelines and Position Statements
A meeting of 29 senior scientists from the United States, Europe, India, and Australia established consensus best practice guidelines in 2010 for the molecular diagnosis of Duchenne and Becker muscular dystrophy. 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.

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 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

References


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**
- 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**
- Results/reports of tests performed
- Procedure report(s)

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or
Genetic Testing for Duchenne and Becker Muscular Dystrophy

when the code describes application of a product in the position statement that is investigational.

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Policy History

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

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Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.