Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider genetic testing for Duchenne muscular dystrophy (DMD) gene variants to be eligible for coverage under the following conditions:

Patient Selection Criteria
Coverage eligibility will be considered when any of the following criteria are met:

- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives:
  - 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:
  - To confirm or exclude the need for medical and cardiac surveillance.

Note: 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.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genetic testing for Duchenne muscular dystrophy (DMD) gene variants in all other situations to be investigational.*

Background/Overview
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 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**

Duchenne muscular dystrophy, 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. The incidence of DMD is estimated to be 1 in 3500 newborn male births, and approximately one-third of DMD cases arise from de novo variants and have no known family history. Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool, from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child’s motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. Most patients will be wheelchair bound by ages 9 to 12 years, but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (eg, decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death. Few individuals with DMD survive beyond the third decade.

**Becker Muscular Dystrophy**

Becker muscular dystrophy is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s.

**Female Carriers**

Females heterozygous for a DMD disease-associated variant can manifest symptoms of the disease. 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. 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
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

kinase tested for unrelated indications, or detection of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties rising from the floor or tip-toe walking, and 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
Becker muscular dystrophy is clinically similar to DMD but is milder and has a later onset. Becker muscular dystrophy 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
Duchenne muscular dystrophy 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 different 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 can slow the loss of muscle strength and may be started when a child is diagnosed or when muscle strength begins to decline. 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. 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.

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants. Several therapies are currently in clinical trials. Two of the more promising are antisense oligonucleotide–induced exon-skipping and gene repair and replacement with an adeno-associated viral (AAV) vector. Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. The result is a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping might restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Gene transfer using AAV vector therapy involves the transfer of a functional DMD gene to the patient using this nonpathogenic and low immune response vector.

**FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by 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.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Rationale/Source**
Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes). Following is a summary of the key literature.

**TESTING MALE INDIVIDUALS WITH SIGNS AND SYMPTOMS OF A DYSTROPHINOPATHY**

**Clinical Context and Test Purpose**
The purpose of genetic testing of male individuals who have signs and symptoms of a dystrophinopathy is to establish the diagnosis of a dystrophinopathy without muscle biopsy that may have predictive value in new therapeutic trials where the therapy is targeted at specific pathogenic variants.

The question addressed in this evidence review is: In male individuals who have signs and symptoms of dystrophinopathy, does use of genetic testing eliminate or reduce the need for muscle biopsy to confirm the diagnosis of muscular dystrophy?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest includes male patients who have signs and symptoms of a dystrophinopathy, such as proximal muscle weakness.

**Interventions**
Genetic testing for *DMD* gene variants.

**Comparators**
Standard workup without genetic testing including possible muscle biopsy.

**Outcomes**
The general outcomes of interest include symptoms, change in disease status, quality of life, medication use, test accuracy, and test validity. The main beneficial outcomes of primary interest are to reduce or eliminate the need for muscle biopsy to conform diagnosis.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. 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 time frame for outcomes measures varies from short-term development of symptoms to long-term changes in disease status.

**Setting**
Patients may be referred from primary care 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.

**Analytic Validity**
Analytic validity refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent.

Deletions of 1 or more exons account for 60% to 70% of pathogenic variants in individuals with DMD and BMD. Duplications account for 5% to 10% of pathogenic variants in DMD and BMD.

Multiplex polymerase chain reactions (PCR) may be used to amplify exons known to be most frequently deleted in patients with DMD. Results obtained from testing 2 multiplex PCR sets have suggested a detection rate of 98% with this methodology. Multiplex PCR is the most widely available testing choice, but only detects deletions. In addition, this method does not cover the whole gene, so a deletion might not always be fully characterized. An alternative to multiplex PCR is a quantitative assay (eg, multiplex ligation-
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

dependent probe amplification or chromosomal microarray [CMA] analysis) of all exons. These methods can detect whole exon deletions and duplications.

Single-nucleotide variants (SNVs) (single-base changes, splicing variants) and small deletions or insertions account for 25% to 35% of variants in males with DMD and 10% to 20% of males with BMD. If deletion/duplication detection is negative, then dystrophin gene sequencing should be done to look for SNVs or small deletions/insertions.

Sequencing of the entire DMD gene to detect SNVs can be performed by traditional PCR and Sanger sequencing, or by more automated methods such as universal long PCR combined with massive pyrosequencing. Wang et al (2014) used next-generation sequencing (NGS) of the entire DMD gene to detect SNVs in 10 males with DMD, 5 of whom were negative and 5 of whom were positive for deletions and duplications. In the 5 deletion/duplication-negative patients, all identified variants were considered pathogenic and validated by Sanger sequencing, including 4 novel variants. In the 5 deletion/duplication-positive patients, NGS detected deletions and duplications by breakpoint analysis. Because NGS breakpoint analysis requires development of precise primers to identify and verify breakpoints, clinical use of NGS for this purpose is limited.

Certain types of assays may cause false-positive results if the method identifies an apparent single-exon deletion or duplication based on the absence or increased amplification, respectively, of a single PCR amplification or hybridization; when this occurs, the result must be confirmed using an alternative assay. This different assay will verify whether the initial result could have been caused by a sequence variant preventing hybridization of, eg, a primer, probe, or for duplications, if the result was an anomaly. Therefore, false positives are expected to be infrequent.

There is a lack of peer-review literature evaluating analytic validity. According to information from the website of a large reference laboratory, deletion/duplication analysis by CMA analysis and SNVs by full gene sequencing detects 98% to 99% of variants in both males and females.

Clinical Validity
Clinical validity refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values).

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 ribonucleic acid (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/duplication analysis first.
- If a copy number variant (CNV) is not identified, perform sequence analysis for an 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.

**Section Summary: Clinical Validity**

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.

**Clinical Utility**

Clinical utility refers to how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

No published studies showing the clinical utility of testing for *DMD* gene variants were identified. As outlined next, clinical utility is established based on a chain of evidence indicating the benefits of testing for symptomatic individuals to establish diagnosis.

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

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

**Section Summary: Clinical Utility**

Direct evidence for the clinical utility 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 utility.
TESTING FEMALE INDIVIDUALS WHO ARE RELATIVES OF A PATIENT WITH A DMD-ASSOCIATED DYSTROPHINOPATHY

Clinical Context and Test Purpose

The purpose of genetic testing of female relatives of affected males is to identify heterozygous carriers for the familial disease-associated variant. Female carriers are at risk for dilated cardiomyopathy and may be manifesting carriers who develop myopathic symptoms. Thus female carriers undergo surveillance for cardiac and myopathic manifestations. Noncarriers can avoid surveillance that would be indicated by knowledge of family history alone. Knowledge of carrier status also informs reproductive decisions.

The question addressed in this evidence review is: Does targeted genetic testing of female relatives of affected patients rule in or rule out carrier status, so that noncarrier individuals appropriately avoid surveillance for disease manifestations?

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

**Patients**
The relevant population of interest is comprised of female individuals who are relatives of a patient with DMD-associated dystrophinopathy.

**Interventions**
Genetic testing for a known DMD familial variant.

**Comparators**
Standard workup care without genetic testing including family history and cardiac surveillance.

**Outcomes**
The general outcomes of interest include changes in reproductive decision making, symptoms, change in disease status, test accuracy, and test validity. The main beneficial outcome of interest is initiation of cardiac surveillance in DMD familial variant carriers.

Potential harmful outcomes are those resulting from a false-positive or false-negative test results. 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 time frame for outcomes measures varies from short-term development of symptoms to long-term changes in disease status and changes reproductive decision making.

**Setting**
Patients may be referred from primary care 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.
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

Analytic Validity
Same as the Analytic Validity: Testing Male Individuals With Signs and Symptoms of a Dystrophinopathy section.

Clinical Validity
Same as the Clinical Validity: Testing Male Individuals with Signs and Symptoms of a Dystrophinopathy section.

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/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: Clinical Validity
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.

Clinical Utility
Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

No published studies showing the clinical utility of testing for DMD gene variants were identified. As outlined next, clinical utility is established based on the benefits of testing female relatives of affected individuals to assess risk.

The clinical utility 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: Clinical Utility
Direct evidence of the clinical utility 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.
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy #  00471
Original Effective Date:  07/15/2015
Current Effective Date:  07/19/2017

TESTING MALE OFFSPRING OF A FEMALE CARRIER OR MALE SIBLING OF A PATIENT WITH A DMD-ASSOCIATED DYSTROPHINOPATHY

Clinical Context and Test Purpose
The purpose of genetic testing of male offspring of a female DMD familial variant carrier or 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
Genetic testing for a known DMD familial variant.

Comparators
Standard workup care without genetic testing including family history and cardiac surveillance.

Outcomes
The general outcomes of interest include changes in symptoms, change in disease status, test accuracy and test validity. 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 primary care 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.
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

Analytic Validity
Same as the Analytic Validity: Testing Male Individuals With Signs and Symptoms of a Dystrophinopathy section.

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

Testing Strategy
For DMD familial variant testing in at-risk male offspring or sibling:
- 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/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 or a male sibling of a patient with DMD-associated dystrophinopathy.

Section Summary: Clinical Validity
Evidence from studies have 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 or 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.

Clinical Utility
Clinical utility is how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

No published studies showing the clinical utility of testing for DMD gene variants were identified. As outlined next, clinical utility is established based on the benefits of testing for asymptomatic male offspring of a female DMD familial variant carrier or an asymptomatic male sibling of a patient with a DMD-associated dystrophinopathy is to confirm or exclude diagnosis of a DMD-associated dystrophinopathy prior to manifestation of disease.

The clinical utility of testing at-risk male offspring or male siblings for DMD gene variants includes:
- Testing to identify 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: Clinical Utility
Direct evidence of the clinical utility of genetic testing in individuals who are asymptomatic male offspring of a female DMD familial variant carrier or asymptomatic male siblings of a patient with DMD-associated dystrophinopathy prior to manifestation of disease is provided by the aforementioned studies.
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

dystrophinopathy is lacking. A chain of evidence exists in that confirmation or exclusion of a DMD familial variant predicts clinical manifestations in asymptomatic at-risk males and necessitates or eliminates the need for medical and cardiac surveillance.

SUMMARY OF EVIDENCE
For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for DMD gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD and BMD. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published studies of analytic validity are lacking, however, for deletion/duplication analysis by CMA analysis and SNVs by full gene sequencing, analytic validity has been reported to be high (98%-99%), with false positives being rare. Virtually all males with DMD or BMD have identifiable DMD disease-associated variants, indicating a high clinical sensitivity for genetic testing. 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 analytic and clinical validity for testing for a known familial variant are lacking, but the 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 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, 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 the analytic and clinical validity of testing for a known familial variant are lacking, but the 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 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.
Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
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References


Policy History

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Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/19/2017

06/25/2015 Medical Policy Committee review
07/15/2015 Medical Policy Implementation Committee approval. New Policy.
06/30/2016 Medical Policy Committee review
07/20/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017 Coding update: Removing ICD-9 Diagnosis codes
07/06/2017 Medical Policy Committee review
07/19/2017 Medical Policy Implementation Committee approval. The coverage statement was updated to add a third indication for male offspring of female carriers and male sibling of affected male. "Mutations" was changed to "variants" in the policy statements in keeping with updated genetics nomenclature. A new definition for "at-risk males" Note was added in the coverage section.

Next Scheduled Review Date: 7/2018

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<td>G71.0, R62.59, R63.8, Z31.430</td>
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</tbody>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
Genetic Testing for Duchenne and Becker Muscular Dystrophy

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Current Effective Date: 07/19/2017

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:
   A. In accordance with nationally accepted standards of medical practice;
   B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
   C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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 that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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Page 15 of 15