Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/11/2018

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 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 the use of genetic testing for *DMD* gene variants when patient selection criteria are not met to be **investigational.***
Based on review of available data, the Company considers genetic testing for *DMD* gene variants in all other situations to be **investigational.***

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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 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. According to a 2014 systematic review, the incidence of DMD ranges from 1 in 3600 to 1 in 9300 male births. 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 (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. 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.

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 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

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. 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. Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials 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.

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 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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
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.

Rationale/Source

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

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess

the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

TESTING MALE INDIVIDUALS WITH SIGNS AND SYMPTOMS OF A DYSTROPHINOPATHY
Clinical Context and Test Purpose
The purpose of genetic testing 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 to target therapy 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
The test being considered is genetic testing for *DMD* gene variants.

Comparators
The following practice is currently being used to make decisions about diagnosing dystrophinopathy: standard workup including possible muscle biopsy but without genetic testing.

Outcomes
The main beneficial outcomes of primary interest are to reduce or eliminate the need for muscle biopsy to confirm 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 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.

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 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 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 (mRNA) 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 immunohistochemistry 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 FEMALES 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 female individuals who are relatives of a patient with *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 carrier status: standard workup care including family history and cardiac surveillance, without genetic testing.

Outcomes
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 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.

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 OR MALE SIBLING OF A PATIENT WITH A *DMD*-ASSOCIATED DYSTROPHINOPATHY
Clinical Context and Test Purpose
The purpose of testing male offspring of a female *DMD* familial variant carrier or 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.

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Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/11/2018

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 offspring or 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 offspring of a female *DMD* familial variant carrier or 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.

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 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 or 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 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.

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

SUMMARY OF EVIDENCE
For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for *DMD* gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD 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.

For individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier or an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine *DMD* status, the evidence includes case series and database entries. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for clinical validity of testing for a known familial variant are lacking, but is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in asymptomatic male offspring of a female *DMD* familial variant carrier or male sibling of a patient with a *DMD*-associated dystrophinopathy is lacking. However, the chain of evidence is strong, because detection of the *DMD* familial variant necessitates or eliminates the need for increased medical surveillance or cardiac surveillance in an asymptomatic male 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.

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Policy History

Original Effective Date: 07/15/2015
Current Effective Date: 07/11/2018

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

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Policy # 00471
Original Effective Date: 07/15/2015
Current Effective Date: 07/11/2018

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.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 07/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81161, 81408
HCPCS	No codes
ICD-10 Diagnosis	G71.0, R62.59, R63.8, Z31.430

*****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:
    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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