

(20486)

Medical Benefit		Effective Date: 10/01/17	Next Review Date: 05/18
Preauthorization	Yes	Review Dates: 05/13, 05/14, 05/15, 05/16, 05/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are male and have signs and symptoms of a dystrophinopathy 	Interventions of interest are: <ul style="list-style-type: none"> Genetic testing for DMD gene variants to confirm diagnosis without biopsy 	Comparators of interest are: <ul style="list-style-type: none"> Standard workup without genetic testing, including possible muscle biopsy 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Symptoms Change in disease status Morbid events Quality of life Medication use Resource utilization
Individuals: <ul style="list-style-type: none"> Who are female and are a relative of a patient with a DMD-associated dystrophinopathy 	Interventions of interest are: <ul style="list-style-type: none"> Targeted DMD testing for a known familial variant to determine carrier status 	Comparators of interest are: <ul style="list-style-type: none"> Standard workup without genetic testing, including family history and cardiac surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Changes in reproductive decision making Symptoms Change in disease status Morbid events Quality of life Medication use Resource utilization
Individuals: <ul style="list-style-type: none"> Who are asymptomatic male offspring of a female DMD familial variant carrier 	Interventions of interest are: <ul style="list-style-type: none"> Targeted DMD testing for a known familial variant to determine DMD status 	Comparators of interest are: <ul style="list-style-type: none"> Standard workup without genetic testing, including family history and cardiac surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Symptoms Change in disease status Morbid events Quality of life Medication use Resource utilization

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> Who are an asymptomatic male sibling of a patient with DMD-associated dystrophinopathy 	Interventions of interest are: <ul style="list-style-type: none"> Targeted DMD testing for a known familial variant to determine DMD status 	Comparators of interest are: <ul style="list-style-type: none"> Standard workup without genetic testing, including family history and cardiac surveillance 	Relevant outcomes include: <ul style="list-style-type: none"> Test accuracy Test validity Symptoms Change in disease status Morbid events Quality of life Medication use Resource utilization

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.

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 chromosomal microarray analysis and single-nucleotide variants (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.

Policy

Genetic testing for *DMD* gene variants may be considered **medically necessary** under 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)
 - 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):
 - 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.

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.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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 protocol updates starting in 2017 (see Table PG1). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUMAN Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and 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 in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

For Medicare Advantage genetic testing for DMD gene variants is considered **not medically necessary**.

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 DMD or 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 The incidence of DMD is estimated to be one in 3500 newborn male births,² and 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 two to five. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child's motor status may plateau between three and six years of life with deterioration beginning at six to eight years. Most patients will be wheelchair bound by ages nine to 12 years, but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (e.g., decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death.¹ Few individuals with DMD survive beyond the third decade.

Becker Muscular Dystrophy

BMD is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s.³

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.⁶ 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.⁷ Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome).⁴

Clinical Diagnosis

Duchenne Muscular Dystrophy

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by 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.¹ Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests are no longer believed to be necessary for assessment of DMD.⁸ An open skeletal muscle biopsy is needed when a test for deletions or duplications of the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy, including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis 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 than DMD 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 (five to 100 times the normal level).

Molecular Diagnosis

DMD is the only gene of which variants are known to cause DMD, BMD, and *DMD*-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in 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.¹ A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5000 different disease-associated variants, as well as a high spontaneous de novo variant rate.⁹

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.⁸ The goal of this therapy is to preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways.¹ Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at two to five years of age, although there has been no demonstrated benefit of therapy before five years of age.¹

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants.¹⁰ 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.^{11,12} Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. 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.¹³

Regulatory Status

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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced

procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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