Genetic Testing for Duchenne and Becker Muscular Dystrophy

Description of Procedure or Service

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 (BMD) muscular dystrophy and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less and more severe forms, as well as identify female carriers at risk.

Background

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 (BMD) muscular dystrophy and when the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and congestive heart failure).

Duchenne Muscular Dystrophy

Duchenne Muscular Dystrophy (DMD), the most common muscular dystrophy, is a severe childhood X-linked recessive disorder which 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 3,600 to 1 in 9,300 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. The majority of 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

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.
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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 non-random 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 of Duchenne Muscular Dystrophy

The suspicion of DMD should be considered irrespective of family history, and 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 in rising from the floor or in 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 (CK), at least 10-20 times normal levels (between 5000 and 150,000 IU/L), is non-specific 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 no longer believed to be necessary for the specific assessment of DMD. An open skeletal muscle biopsy is needed when a test for deletions or duplications to 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.

Clinical Diagnosis of Becker Muscular Dystrophy

BMD has a clinical picture 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 (5-100 times the normal level).

Molecular Diagnosis

DMD is the only gene in 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.
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Treatment of Duchenne Muscular Dystrophy

There is no cure for Duchenne or Becker muscular dystrophy and treatment is aimed at control of symptoms to improve quality of life. However, the natural history of the disease can be changed by several 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 earlier therapy before 5 years of age.

New therapeautic trials require accurate diagnoses of these disorders, especially when the therapy is targeted towards 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. The result is a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping may restore DMD protein function so that the treated patient’s phenotypic expression more closely resembles BMD. Several of these therapies are currently undergoing clinical trials. An exon-skipping therapy using antisense oligonucleotides has been introduced as a possible treatment for patients who have confirmed variant of the dystrophin gene amenable to exon 51 skipping. However, the clinical benefit of treatment has not been demonstrated. Further clinical trials to establish clinical benefit are necessary.

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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

BCBSNC will provide coverage for Genetic Testing for Duchenne and Becker Muscular Dystrophy when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Duchenne and Becker Muscular Dystrophy is covered

Genetic testing for DMD gene variants may be considered medically necessary under the following conditions:
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1. In an individual with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.

2. For at-risk relatives:
   a. To confirm or exclude the need for cardiac surveillance
   b. For preconception testing to determine the likelihood of an affected offspring in an individual considering a pregnancy.

3. For at-risk male offspring:
   a. To confirm or exclude the need for medical and cardiac surveillance.

When Genetic Testing for Duchenne and Becker Muscular Dystrophy is not covered

Genetic testing for Duchene and Becker Muscular Dystrophy is considered investigational in all other indications not listed above.

Policy Guidelines

The evidence for genetic testing for a DMD gene variant to confirm a diagnosis without biopsy in individuals who are male and have signs and symptoms of a dystrophinopathy, includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of Duchenne (DMD) and Becker muscular dystrophy (BMD). Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Virtually all males with DMD or BMD have identifiable DMD disease-associated variants, indicating a high clinical sensitivity for genetic testing. 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.

The evidence for targeted DMD testing for a known familial variant to determine carrier status in individuals who are female, and are a relative of a patient with a DMD-associated dystrophinopathy, 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, and 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.

The evidence for targeted DMD testing 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, for a known familial variant to determine DMD status, 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
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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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81161, 81408

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


Medical Director review 4/2013.


Specialty Matched Consultant Advisory Panel review 8/2014

Medical Director review 8/2014


Specialty Matched Consultant Advisory Panel review 8/2015

Medical Director review 8/2015

Genetic Testing for Duchenne and Becker Muscular Dystrophy

Medical Director review 7/2016
Medical Director review 3/2017
Specialty Matched Consultant Advisory Panel review 7/2017
Medical Director review 7/2017
Medical Director review 3/2018
Specialty Matched Consultant Advisory Panel review 7/2018
Medical Director review 7/2018

Policy Implementation/Update Information

5/14/13 New Evidence Based Guideline developed. Genetic testing for DMD gene mutations is recommended under the following conditions: 1. In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment. 2. For at-risk female relatives: a. To confirm or exclude the need for cardiac surveillance, b. For preconception testing to determine the likelihood of an affected offspring in a woman considering a pregnancy. Medical Director review 4/2013. (mco)

4/29/14 References updated. No changes to Guideline Statements. (mco)


3/20/16 Policy Guidelines updated. No changes to covered indications in the policy statement. (jd)


12/30/16 Minor revisions to When Covered section. No change to policy statement/intent. (jd)

4/28/17 When Covered section updated to include item number 3: “For at-risk male offspring: To confirm or exclude the need for medical and cardiac surveillance”. No change to policy intent. Policy guidelines and references updated. Medical Director review 3/2017. (jd)


2/9/18 Language updated from “not medically necessary” to “investigational” under the When not Covered section. No change to policy intent. (jd)
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4/13/18  Description section, policy guidelines and references updated. No change to policy intent. Medical Director review 3/2018. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.