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.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Individuals:  
- Who are male and have signs and symptoms of a dystrophinopathy | Interventions of interest are:  
- Genetic testing for a DMD mutation to confirm a diagnosis | Comparators of interest are:  
- Standard workup without genetic testing, including possible muscle biopsy | Relevant outcomes include:  
- Test accuracy  
- Test validity  
- Symptoms  
- Change in disease status  
- Morbid events  
- Quality of life  
- Medication use  
- Resource utilization |
| Individuals:  
- Who are female and are a relative of a patient with a DMD-associated dystrophinopathy | Interventions of interest are:  
- Targeted DMD mutation testing for the known pathogenic mutation in the family | Comparators of interest are:  
- Standard workup without genetic testing, including family history and cardiac surveillance | Relevant outcomes include:  
- Test accuracy  
- Test validity  
- Changes in reproductive decision making  
- Symptoms  
- Change in disease status  
- Morbid events  
- Quality of life  
- Medication use  
- Resource utilization |

Description

Mutations 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 and more severe forms, as well as identify female carriers at risk.

Summary of Evidence

The evidence for genetic testing for a DMD gene mutation to confirm a diagnosis in individuals who are male and have signs and symptoms of a dystrophinopathy include case series and database entries describing
screening and results of types of mutations found in patients with clinical signs of DMD/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 point mutations by full gene sequencing, it has been reported to be high (98% to 99%), with false positives being rare. Virtually all males with DMD/BMD have identifiable DMD mutations, indicating a high clinical sensitivity for genetic testing. Clinical utility of DMD gene testing can be established for the index case in confirmation of the diagnosis without a muscle biopsy, to initiate effective treatment, and in distinguishing between DMD and the less severe BMD. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

The evidence for targeted DMD mutation testing for the known pathogenic mutation in a family in individuals who are female and are a relative of a patient with a DMD-associated dystrophinopathy is lacking. Relevant outcomes include 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 mutation 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, but an indirect chain of evidence exists, in that confirmation or exclusion of a pathogenic mutation 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 qualitatively that the technology results in a meaningful improvement in the net health outcome.

Policy

Genetic testing for DMD gene mutations 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.

Genetic testing for DMD gene mutations is considered investigative 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.

Recommendations from consensus best practice guidelines for molecular diagnosis of DMD/BMD indicate that testing of an affected male (the index case) be performed so that carrier testing in female relatives at risk can focus on the mutation found in the affected family member.
**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.

**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 quadriiceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, they are classified as Duchenne or Becker muscular dystrophy and when the heart is primarily affected, 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 new mutations 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 mutation can manifest symptoms of the disease.\(^6\) 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).

Clinical Diagnosis

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 after the discovery 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 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 and 150,000 IU/L), is nonspecific to DMD but is always present in affected patients. Electromyography and nerve conduction were traditional parts of the assessment of neuromuscular disorders, but now 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 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 in which mutations 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 mutational spectrum with over 5000 different reported mutations, as well as a high spontaneous mutation rate.

Treatment

There is no cure for DMD or BMD, 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 two to five years of age although there has been no demonstrated benefit of earlier therapy, before five years of age.
New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted toward specific mutations. Several therapies are currently undergoing clinical trials. Two of the most 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 that is formed without the mutated exon and a normal, nonshifted reading frame. Exon skipping may be able to 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.

**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 Act (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.


