Duchenne and Becker Muscular Dystrophy Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What are Duchenne and Becker Muscular Dystrophy

Definition

Duchenne muscular dystrophy (DMD) is an X-linked inherited neuromuscular disorder. The prevalence of DMD has been reported as 15.9 cases per 100,000 live male births in the USA and 19.5 cases per 100,000 live male births in the UK. It is caused by pathogenic variants in the DMD gene. It is typically diagnosed by age 5.

- The main clinical findings of DMD include:
  - rapidly progressive skeletal muscle weakness and wasting that is more proximal than distal
  - a delay in motor milestones (such as walking at 18 months)
  - calf pseudohypertrophy
  - wheelchair dependency by 13 years
  - dilated cardiomyopathy
  - reduced life expectancy
  - greatly elevated serum creatine kinase (CK) concentration

- Genetic testing confirms a clinical diagnosis in affected males. Muscle biopsy may be used for diagnosis when molecular testing does not find a mutation.
- Although this is an X-linked disorder, some carrier females may exhibit symptoms, sometimes later in life, including muscle weakness and cardiomyopathy.
• Physiotherapy and treatment with glucocorticoids remain the mainstays of DMD treatment and should continue after loss of ambulation. The benefits of long-term glucocorticoid therapy have been shown to include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery. The FDA has also granted full approval for deflazacort, making this the first glucocorticoid with a labeled indication specifically for DMD.²

• “In September, 2016, the US Food and Drug Administration (FDA) approved use of eteplirsen, which targets the approximately 13% of boys with a mutation in the dystrophin gene that is amenable to exon 51 skipping, via an accelerated approval pathway. Ataluren and eteplirsen are the first of a series of mutation-specific therapies to gain regulatory approval.”² However, the manufacturer is required to conduct a trial to determine whether eteplirsen improves motor function of individuals with DMD with an amenable dystrophin gene pathogenic variant. Ataluren is not approved for treating DMD in the US. Other therapies are under investigation.¹

• Becker muscular dystrophy (BMD) is a similar disorder, caused by mutations in the same gene, which has a later age of onset and is less common than DMD. It is typically diagnosed by age 10, and people with BMD are often still able to walk into their 20s. The typical features include:¹
  o progressive skeletal muscle weakness, proximal more than distal
  o wheelchair dependence after age 16 years if at all
  o flexion contractures of the elbows
  o preservation of neck flexor muscle strength (differentiates BMD from DMD)
  o dilated cardiomyopathy
  o greatly elevated serum CK concentration

Test information
• DMD deletion/duplication testing is the best first test, which detects genetic changes in about 65-80% of males with DMD and up to 95% of males with BMD.¹ DMD deletion/duplication testing can also be used to identify a mutation in a known or suspected carrier female if an affected male is not available for molecular analysis.¹

• DMD sequence analysis will identify about 20-35% of DMD genetic changes.¹ DMD sequencing analysis can also be used to identify a mutation in a known or suspected carrier female, if an affected male is not available for molecular analysis.¹

• Once the familial mutation is identified, at-risk family members can have reliable and accurate testing for just that mutation.¹
• “If genetic testing does not confirm a clinical diagnosis of DMD, then a muscle biopsy sample should be tested for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract. Skeletal muscle biopsy continues to be used only rarely in the diagnosis of dystrophinopathies.”

Guidelines and evidence

• The Centers for Disease Control and Prevention (CDC) selected the Care Considerations Working Group (2018) to create guidelines for diagnosis and management of DMD:
  o “If deletion/duplication testing is negative, then dystrophin gene sequencing should be done to look for the remaining types of mutations that are attributed to DMD [e.g., point mutations or small deletions/insertions]”

  o “Carriers of DMD or BMD should be made aware of the risk of developing cardiomyopathy and educated about the signs and symptoms of heart failure.”
  o “Carriers of DMD or BMD should be referred for evaluation by a cardiac specialist with experience in the treatment of heart failure and/or neuromuscular disorders. Patients should undergo initial complete cardiac evaluation in late adolescence or early adulthood or at the onset of cardiac signs and symptoms, if these signs or symptoms appear earlier.”
  o “Carriers should be screened with a complete cardiac evaluation at a minimum of every 5 years starting at 25 to 30 years of age.”
  o “Treatment of cardiac disease is similar to that outlined for boys with DMD or BMD.”

Criteria

DMD Known Familial Mutation Analysis

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o No previous genetic testing of DMD by a method that would detect the familial variant, AND

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• Diagnostic Testing for Symptomatic Individuals:
  o DMD mutation identified in 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} degree biologic relative(s), OR
• Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At-Risk Individuals:
  o DMD mutation identified in 1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} degree biologic relative(s), OR
• Prenatal Testing for At-Risk Pregnancies:
  o DMD mutation identified in mother or sibling

**DMD Deletion/Duplication Analysis**

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
• Previous Testing:
  o No previous deletion/duplication analysis of DMD, and
  o If sequence analysis of DMD was performed, no mutations detected, AND
• Diagnostic Testing for Symptomatic Individuals:
  o Progressive symmetric muscle weakness (proximal greater than distal)—e.g., leg, pelvic and shoulder girdle muscles, and calf hypertrophy, and positive Gower maneuver, or
  o Elevated serum CK concentration, and
  o Progressive symmetric muscle weakness (proximal greater than distal)—e.g., leg, pelvic and shoulder girdle muscles, or
  o Calf hypertrophy, or
  o Positive Gower maneuver, or
  o Male gender, or
  o Onset of symptoms by early adulthood (usually by adolescence), or
  o Delayed motor milestones, or
  o Gait problems; waddling gait or
  o Learning difficulties, or
  o Quadriceps weakness; activity-induced cramping, or
  o Family history consistent with X-linked inheritance, OR
• Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic at Risk Individuals:
  o DMD or BMD diagnosed in 1st or 2nd degree family member and no known mutation at time of testing, AND
  o Family history consistent with X-linked inheritance

DMD Sequencing

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous testing:
  o No mutations detected by deletion/duplication analysis in DMD, and
  o No previous full sequencing analysis of DMD

References

