Test Specific Guidelines

Duchenne and Becker Muscular Dystrophy Genetic Testing

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Introduction

Duchenne and Becker muscular dystrophy testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
DMD Deletion/Duplication Analysis	81161
DMD Known Familial Mutation Analysis	81403
DMD Sequencing	81408
Genomic Unity DMD Analysis	0218U

What Are Duchenne and Becker Muscular Dystrophy?

Definition

Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are inherited neuromuscular disorders.[1,2]

Prevalence

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.[2] In northern England, BMD was diagnosed in 1 in 18,450 live male births.[1]

Symptoms

DMD is typically diagnosed by 5 years of age. The main clinical findings of DMD include:[1]

rapidly progressive skeletal muscle weakness and wasting that is more proximal than distala 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

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 years, and people with BMD are often still able to walk into their 20s. The typical features include:[1]

progressive skeletal muscle weakness, proximal more than distal

wheelchair dependence after age 16 years, if at all

flexion contractures of the elbows

preservation of neck flexor muscle strength (differentiates BMD from DMD)

dilated cardiomyopathy greatly elevated serum CK concentration

Cause

DMD and BMD are caused by pathogenic mutations in the DMD gene.

Inheritance

DMD and BMD are inherited in an X-linked manner. Although this is an X-linked disorder, some carrier females may exhibit symptoms, sometimes later in life, including muscle weakness and cardiomyopathy.[1]

X-Linked Inheritance

In X-linked inheritance, the mutation is carried on the X chromosome. Females have two X chromosomes, and males have one. Males typically have more severe symptoms than females. A female with a mutation has a 50% chance to pass that mutation to her children. A male with a mutation cannot pass the mutation to any sons, but will pass it to all daughters. A process called X-inactivation in females results in random inactivation of expression of one X-chromosome in each cell of the body. For females with one mutation, the percentage and distribution of cells with expression of the X chromosome carrying the mutation can influence the degree of severity.

Diagnosis

Genetic testing confirms a clinical diagnosis in affected males. Muscle biopsy may be used for diagnosis when molecular testing does not find a mutation.[2]

DMD deletion/duplication testing is the best first diagnostic test, which detects genetic changes in about 65-80% of probands with a pathogenic mutation.[1] DMD sequence analysis will identify about 20-35% of DMD genetic changes.[1] DMD deletion/duplication or sequence 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]

Management

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] Ataluren is an investigational drug that may provide benefit in individuals with nonsense mutations. "The interim results of the STRIDE Registry indicate the benefit of long-term treatment of nmDMD [nonsense mutation DMD] patients with ataluren as used in routine clinical practice in slowing disease progression."[3] 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.

Antisense oligonucleotides (ASO) targeted to the dystrophin pre-messenger RNA to skip out-of-frame variants (US FDA-approved therapies) include: Eteplirsen (exon skip 51 amenable), Golodirsen (exon skip 53 amenable), Viltolarsen (exon skip 53 amenable), and Casimersen (exon skip 45 amenable).[1] Other therapies are under investigation.[1]

Survival

There has been improvement in survival for males with DMD, however survival beyond the third decade is rare with a median survival of 24 years.[1] Ventilated individuals have a median survival of 27 years.[1] Heart failure from dilated cardiomyopathy is the main cause of death for individuals with BMD.[1,4] The mean age of death for individuals with BMD is in the mid-40's.[1,4] For individuals with BMD and minimal cardiac disease or well-controlled cardiac disease, the life span can be normal or near normal.[4]

Test Information

Introduction

Testing of the DMD gene may include known familial mutation analysis, deletion/duplication analysis, and/or next generation sequencing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Special Considerations

If genetic testing does not identify a DMD pathogenic mutation, "skeletal muscle biopsy of individuals with suspected DMD or BMD is warranted for western blot and immunohistochemistry studies of dystrophin. Skeletal muscle biopsy continues to be used only rarely in the diagnosis of dystrophinopathies."[1]

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to DMD testing.

American Academy of Pediatrics

The American Academy of Pediatrics (AAP, 2008) guidelines on cardiac care addressed screening for DMD/BMD carriers.[5]

"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."

"Carrier 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."

"Carriers should be screened with a complete cardiac evaluation at a minimum of every 5 years starting at 25 to 30 years of age."

- "Treatment of cardiac disease is similar to that outlined for boys with DMD or BMD."

American College of Medical Genetic and Genomics

The American College of Medical Genetics and Genomics Professional Practice and Guidelines Committee (ACMG, 2018) stated:[6]

"DCM is a common complication of neuromuscular disease such as Duchenne or Becker muscular dystrophy. Genetic testing is important in mothers of individuals with Duchenne or Becker to determine carrier status because carrier females may develop DCM in the third to fifth decade of life."

Center for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC, 2018) selected the Care Considerations Working Group and created guidelines for diagnosis and management of DMD:[2]

"Because approximately 70% of individuals with DMD have a single-exon or multi-exon deletion or duplication in the dystrophin gene, dystrophin gene deletion and duplication testing is usually the first confirmatory test. Testing is best done by multiplex ligation-dependent probe amplification (MLPA) or comparative genomic hybridisation array, since use of multiplex PCR can only identify deletions. Identification of the boundaries of a deletion or duplication mutation by MLPA or comparative genomic hybridisation array might indicate whether the mutation is predicted to preserve or disrupt the reading frame.

If deletion or duplication testing is negative, genetic sequencing should be done to screen for the remaining types of mutations that are attributed to DMD (approximately 25–30%). These mutations include point mutations (nonsense or missense), small deletions, and small duplications or insertions, which can be identified using next-generation sequencing.

- Finally, 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."

Criteria

Introduction

Requests for DMD testing are reviewed using these criteria.

DMD Known Familial Mutation Analysis

Genetic Counseling:

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

Previous Genetic Testing:

No previous genetic testing of DMD by a method that would detect the familial variant, AND

Diagnostic Testing for Symptomatic At-Risk Individuals:

DMD mutation identified in 1st, 2nd, or 3rd degree biologic relative(s), OR

Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At-Risk Individuals:

DMD mutation identified in 1st, 2nd, or 3rd degree biologic relative(s), OR

- Prenatal Testing for At-Risk Pregnancies:

DMD mutation identified in mother or sibling

DMD Deletion/Duplication Analysis

Genetic Counseling:

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

Previous Testing:

No previous deletion/duplication analysis of DMD, and

- If sequence analysis of DMD was performed, no mutations detected, AND
- Diagnostic Testing for Symptomatic Individuals:

Progressive symmetric muscle weakness (proximal greater than distal)—e.g., leg, pelvic and shoulder girdle muscles, and calf hypertrophy, and positive Gower maneuver, or

Elevated serum CK concentration, and

Progressive symmetric muscle weakness (proximal greater than distal)-e.g., leg, pelvic and shoulder girdle muscles, or

Calf hypertrophy, or

Positive Gower maneuver, or

Male gender, or

Onset of symptoms by early adulthood (usually by adolescence), or

Delayed motor milestones, or

Gait problems; waddling gait or

Learning difficulties, or

Quadriceps weakness; activity-induced cramping, or

- Family history consistent with X-linked inheritance, OR

Carrier Screening and Predictive Testing for Presymptomatic/Asymptomatic At-Risk Individuals:

DMD or BMD diagnosed in 1st or 2nd degree family member and no known mutation at time of testing, AND

- Family history consistent with X-linked inheritance

DMD Sequencing

Genetic Counseling:

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

- Previous testing:

No mutations detected by deletion/duplication analysis in DMD, and

- No previous full sequencing analysis of DMD

References

Introduction

These references are cited in this guideline.

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