Clinical Policy Title: Genetic testing for Duchenne muscular dystrophy

Clinical Policy Number: CCP.1282

Effective Date: February 1, 2017
Initial Review Date: January 18, 2017
Most Recent Review Date: January 8, 2019
Next Review Date: January 2020

Related policies:
CCP.1002 Maternal genetic testing
CCP.1271 Genetic and genomic testing criteria
CCP.1252 Genetic testing for hereditary cardiomyopathy

ABOUT THIS POLICY: AmeriHealth Caritas has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas’ clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of “medically necessary,” and the specific facts of the particular situation are considered by AmeriHealth Caritas when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas’ clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas’ clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas will update its clinical policies as necessary. AmeriHealth Caritas’ clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas considers the once-per-lifetime use of genetic testing for Duchenne or Becker muscular dystrophy (DMD gene mutations) to be clinically proven and, therefore, medically necessary when all of the following criteria are met (Birnkrant, 2018):

- The test is ordered by the treating specialist (e.g., neurologist, medical geneticist, developmental-behavioral pediatrician, or neuromuscular subspecialist).
- For one of the following clinical indications:
  - Diagnostic testing for symptomatic members (e.g., characteristic features of dystrophinopathy, elevated serum creatine kinase levels, with or without a family history consistent with X-linked inheritance), and no previous DMD gene testing.

1 For example, progressive symmetric muscle weakness (proximal greater than distal), calf hypertrophy, positive Gower maneuver, early onset of symptoms, delayed motor milestones, gait problems, or learning difficulties.
- Carrier screening for asymptomatic at-risk individuals with a family history consistent with X-linked inheritance.
- Prenatal testing for at-risk pregnancies when a DMD gene mutation has been identified in mother or sibling.

- The test is analytically and clinically valid.
- Pre- and post-test genetic counseling accompanies testing.
- Available genetic testing options based on the minimal number of genes needed to establish a diagnosis, including:
  - Known familial mutation analysis.
  - DMD deletion/duplication analysis with no known mutation.
  - DMD genome sequencing if no mutations are detected by DMD deletion/duplication analysis and no previous full sequencing analysis of DMD has been performed.

Limitations:

The following uses of genetic testing for Duchenne muscular dystrophy are not medically necessary:
- Newborn screening, subject to state and local requirements (Birnkrant, 2018; Health Resources & Services Administration, 2018).
- Repeat testing of the same genetic panel or targeted gene testing.

Alternative covered services:

Routine primary and specialist medical and surgical care as indicated by the diagnosed condition.

Background

Duchenne muscular dystrophy is a dystrophinopathy caused by a genetic mutation in the DMD gene that provides instructions for making the protein dystrophin, which helps stabilize and protect muscle fibers in skeletal and cardiac muscle and may play a role in chemical signaling within cells (Genetic Home Reference, 2018). Mutations in the DMD gene either alter the structure or function of dystrophin, or prevent any functional dystrophin from being produced, resulting in progressive weakness and atrophy of skeletal and heart muscles (National Institutes of Health, 2017). Most DMD gene mutations are inherited in an X-linked recessive pattern and, therefore, predominately affect males, but approximately one-third of mutations occurs de novo (Wilson, 2017). A smaller portion of affected females may present with a classic dystrophinopathy or be asymptomatic carriers (Genetic Home Reference, 2018).

Muscle weakness associated with Duchenne muscular dystrophy usually appears by age 3 or 4 years and begins in the hips, pelvis, upper legs, and shoulders (National Institutes of Health, 2017). Another dystrophinopathy, Becker muscular dystrophy, is associated with less severe symptoms that start later in childhood and progress more slowly. Current treatment is supportive, consisting of controlling symptoms and related complications caused by severe progressive muscle weakness and atrophy, and
maximizing quality of life. Clinical trials of genomic therapy for Duchenne muscular dystrophy are ongoing.

A prompt and accurate diagnosis has implications for the individual and family members with respect to prenatal testing, family planning, treatment eligibility, and disease surveillance. Clinical findings (phenotype), laboratory findings suggestive of dystrophinopathy (e.g., serum creatine phosphokinase concentration), and a positive family history warrant diagnostic confirmation (Darras, 2018). Carrier testing may be needed to identify blood relatives who are at risk of passing on the disease and are at risk for developing related conditions (e.g., DMD-associated cardiomyopathy). A skeletal muscle biopsy may be performed by western blot of muscle protein extract or by immunohistochemistry to detect the presence or absence of dystrophin in muscle tissue.

The DMD gene is large with many potential genetic mutations, and multiple genetic tests may be required to find a mutation. Molecular genetic testing approaches include (Darras, 2018):

- Single-gene testing to detect the majority of more clinically distinct pathogenic variants through deletion/duplication analysis of DMD or sequence analysis.
- Multi-panel testing to detect DMD and other genes of interest, particularly with less clinically distinct presentations, through sequence analysis, deletion/duplication analysis, or other non-sequencing-based tests.
- Comprehensive genomic testing, including exome sequencing, genome sequencing, and exome array (where available), particularly for atypical presentations or when other genetic testing approaches are indeterminate.

**Searches**

AmeriHealth Caritas searched PubMed and the databases of:

- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality.
- The Centers for Medicare & Medicaid Services.

We conducted searches on November 1, 2018. Search terms were: “dystrophin/genetics” (MeSH), “muscular dystrophy, Duchenne/diagnosis” (MeSH), and “muscular dystrophy, Duchenne/genetics” (MeSH), and free text terms “Duchenne muscular dystrophy” and “genetic testing.”

We included:

- **Systematic reviews**, which pool results from multiple studies to achieve larger sample sizes and greater precision of effect estimation than in smaller primary studies. Systematic reviews use predetermined transparent methods to minimize bias, effectively treating the review as a scientific endeavor, and are thus rated highest in evidence-grading hierarchies.
- **Guidelines based on systematic reviews**.
• **Economic analyses**, such as cost-effectiveness, and benefit or utility studies (but not simple cost studies), reporting both costs and outcomes — sometimes referred to as efficiency studies — which also rank near the top of evidence hierarchies.

**Findings**

Low-quality evidence from case series of persons with known dystrophin abnormalities supports the feasibility and utility of next-generation sequencing technology over alternative testing methods (e.g., multiplex ligation-dependent probe amplification or Sanger sequencing) for identifying more comprehensive genetic information (Okubo, 2016; Wang, 2014; Wei, 2014). Next-generation sequencing offers a shorter turnaround time, higher accuracy, and more precise information on partial gene deletions and duplications for directing both current therapy and eligibility for gene therapy.

The Centers for Disease Control and Prevention consensus group recommends evaluation by a neuromuscular specialist who can assess the individual in the context of the clinical presentation (Bushby, 2010). Serum genetic diagnosis is always necessary after a positive biopsy diagnosis of Duchenne muscular dystrophy, but a muscle biopsy is not necessary if a genetic diagnosis is secured first.

**Policy updates:**

Duchenne muscular dystrophy, Pompe disease, and spinal muscular atrophy challenge traditional screening criteria (Ross, 2017). Duchenne muscular dystrophy does not present in infancy and lacks effective treatment. Pompe disease and spinal muscular atrophy may not present until adulthood, and safety and efficacy of long-term intrathecal treatment for spinal muscular atrophy is unknown. The potential reproductive benefit and improved research recruitment do not justify a public health screening program for these three conditions.

In 2019, we added one guideline update from the Centers for Disease Control and Prevention (Birnkrant, 2018, update of Bushby, 2010). In the majority of cases, neuromuscular signs and symptoms suggestive of Duchenne muscular dystrophy and, to a far lesser extent, elevated serum enzyme levels (e.g., creatine kinase) may prompt genetic screening. The screening algorithm should begin with testing for the most common genetic or known variants and proceed to more comprehensive genetic testing if the initial test results are negative, reserving muscle biopsy for indeterminate genetic test results.

Carrier testing of female relatives of a boy or man with a genetically confirmed diagnosis should be offered to inform family planning decisions. Newborn screening for Duchenne muscular dystrophy is not included in the Recommended Uniform Screening Panel (Health Resources & Services Administration, 2018). Emerging gene therapies that depend on genetic testing results may prove to be more effective if initiated before symptom onset, but currently routine newborn screening is not recommended. To conform with the updated guideline recommendations, we added neuromuscular signs and symptoms suggestive of Duchenne muscular dystrophy to the criteria for medical necessity, and statements for
tiered testing, carrier testing, and newborn screening to the policy. The policy ID was changed from CP #02.01.23 to CCP.1282.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Birnkrant (2018) for the Centers for Disease Control and Prevention</td>
<td><strong>Key points:</strong></td>
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<td></td>
<td>- Suggestive signs and symptoms, and less commonly developmental delay or elevated serum enzymes, should prompt referral to a neuromuscular specialist, with input from a geneticist or genetic counsellor, to avoid diagnostic delay.</td>
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<tr>
<td>Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management</td>
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<td></td>
<td>- Screening algorithm begins with multiplex ligation-dependent probe amplification or comparative genomic hybridization array to detect dystrophin gene deletion and duplication that occurs in approximately 70% of affected individuals.</td>
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<td></td>
<td>- If negative, perform next-generation sequencing to screen for the remaining types of mutations, including point mutations (nonsense or missense), small deletions, and small duplications or insertions.</td>
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<td>- If non-confirmatory, then perform a muscle biopsy sample for the presence of dystrophin protein by immunohistochemistry of tissue cryosections or by western blot of a muscle protein extract.</td>
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<td>- Perform carrier testing for female relatives of a boy or man with genetically confirmed diagnosis to inform reproductive choices, including preimplantation genetic diagnosis or prenatal genetic testing through chorionic villus or amniotic fluid sampling.</td>
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<td></td>
<td>- In confirmed carriers, perform medical assessment and follow up of cardiac status.</td>
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<td></td>
<td>- Newborn screening is not included on the Recommended Uniform Screening Panel, but emerging therapies may be more effective if initiated before symptom onset.</td>
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<tr>
<td>Ross (2017)</td>
<td><strong>Key points:</strong></td>
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<tr>
<td>A historical and current review of newborn screening for neuromuscular disorders from around the world: lessons for the United States</td>
<td></td>
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<tr>
<td></td>
<td>- Duchenne muscular dystrophy, Pompe disease, and spinal muscular atrophy challenge traditional screening criteria.</td>
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<td>- Duchenne muscular dystrophy does not present in infancy and lacks effective treatment.</td>
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<td>- Pompe disease and spinal muscular atrophy may not present until adulthood, and safety and efficacy of long-term intrathecal treatment for spinal muscular atrophy is unknown.</td>
</tr>
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<td></td>
<td>- The potential reproductive benefit and improved research recruitment do not justify a public health screening program.</td>
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<td>Okubo (2016)</td>
<td><strong>Key points:</strong></td>
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<td>Genetic diagnosis of Duchenne/Becker muscular dystrophy using next-generation sequencing: validation analysis of DMD mutations</td>
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<td></td>
<td>- Applied next generation sequencing technology to 67 cases with known dystrophin gene abnormalities: 37 with deletions/duplications and 30 with small mutations or short insertions/deletions.</td>
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<td>- Next generation sequencing diagnosed 92% of patients with Duchenne muscular dystrophy in a single analysis versus 50% using alternative testing methods (e.g., multiplex ligation-dependent probe amplification or Sanger sequencing), in which</td>
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small insertions in consecutive bases could not be detected.

### Key points:

- A comparison of the diagnostic performance of whole dystrophin gene analysis using next generation sequencing with the Illumina HiSeq 2000 sequencer using paired read 100 bp sequencing in 26 patients; 21 had known large deletion/duplications and five did not have detectable large deletion/duplications based on multiplex ligation-dependent probe amplification technology.
- In the five patients who did not have detectable large deletions, next generation sequencing identified five deleted or duplicated exons, of which four variants were previously unreported.

### Key points:

- Series of 89 patients, 18 female carriers, and 245 patients with non-Duchenne muscular dystrophy who were evaluated using targeted next-generation sequencing.
- Next-generation sequencing yielded 99.99% specificity and 98.96% sensitivity for detection of copy number variations, and 100% accuracy for the identification of single-nucleotide variation mutations.
- Next-generation sequencing offers shorter turnaround time, higher accuracy, and better insight into comprehensive genetic information (detailed breakpoints) for ensuing gene therapy.

### References

**Professional society guidelines/other**


**Peer-reviewed references:**


**Centers for Medicare & Medicaid Services National Coverage Determinations:**

No National Coverage Determinations identified as of the writing of this policy.

**Local Coverage Determinations:**

L35160 MolDX: Molecular Diagnostic Tests (MDT).

L36256 MolDX: Molecular Diagnostic Tests (MDT).
L35025 MolDX: Molecular Diagnostic Tests (MDT).

L36807 MolDX: Molecular Diagnostic Tests (MDT).

Below are the most commonly submitted codes for the service(s)/item(s) subject to this policy. This is not an exhaustive list of codes. Providers are expected to consult the appropriate coding manuals and bill accordingly.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
<th>Comments</th>
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<tbody>
<tr>
<td>81161</td>
<td>DMD (dystrophin) (e.g., Duchenne/Becker muscular dystrophy) deletion analysis, and duplication analysis, if performed</td>
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<table>
<thead>
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<tbody>
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<td>R74.8</td>
<td>Abnormal serum enzyme level, unspecified</td>
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<tr>
<td>Z84.81</td>
<td>Family history of carrier of genetic disease</td>
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<table>
<thead>
<tr>
<th>HCPCS Level II Code</th>
<th>Description</th>
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<tr>
<td>N/A</td>
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