Clinical Policy Title: Genetic tests for Duchenne muscular dystrophy

Clinical Policy Number: 02.01.23

Effective Date: February 1, 2017
Initial Review Date: January 18, 2017
Most Recent Review Date: January 18, 2017
Next Review Date: January 2018

Related policies:

CP# 02.01.01 Maternal genetic testing
CP# 02.01.02 Genetic testing for breast and ovarian cancer
CP# 02.01.03 Array comparative genomic hybridization testing
CP# 02.01.13 Pharmacogenetic testing for warfarin
CP# 02.01.07 Genetic testing for cystic fibrosis
CP# 02.01.08 Familial polyposis gene testing
CP# 02.01.10 COLARIS® test for Lynch syndrome
CP# 02.01.11 Afirma™ gene expression classifier for indeterminate thyroid nodules
CP# 02.01.12 Corus coronary artery disease (CAD) for genomic expression
CP# 02.01.14 Gene expression profile testing for breast cancer
CP# 05.01.04 Molecular analysis for targeted therapy of non-small cell lung cancer

ABOUT THIS POLICY: AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania’s 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 Pennsylvania 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 Pennsylvania’s 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 Pennsylvania’s clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania’s clinical policies are not guarantees of payment.

Coverage policy

AmeriHealth Caritas Pennsylvania considers the once-per-lifetime use of genetic testing for Duchenne muscular dystrophy to be clinically proven and, therefore, medically necessary when the following criteria are met:

- Serum creatine kinase is elevated.
• The test results will directly impact management (i.e., as a result of the test, effective
treatment may be offered that will alter the course of disease or outcomes).
• The test is an analytically and clinically valid test (i.e., supported by peer-reviewed published research).
• Test is ordered by a trained professional (e.g., neurologist, medical geneticist,
developmental-behavioral pediatrician, neuromuscular subspecialist) who will ensure face-
to-face genetic consult or counseling by appropriately trained professionals to accompany testing.
• The test results will be discussed with the patient or guardian including the limitations of the testing method, the risks and benefits of either continuing or stopping the therapy based on the test.
• There is a care-coordinating, multidisciplinary team available for genetic and behavioral counseling for a tiered evaluation, which includes (a.) a primary care provider and (b.) a geneticist (who is a physician or a licensed genetic counselor).
• The patient or guardian has a desire for engagement with the integrated multidisciplinary team that is documented in the clinical record.
• Consideration has been given to standard diagnostic evaluation and use of tiered panel or targeted test sequence for minimal number of genes to establish the diagnosis.

Limitations:

All other uses of genetic testing for Duchenne muscular dystrophy are not medically necessary.

Repeat uses of genetic testing for Duchenne muscular dystrophy are not medically necessary.

Alternative covered services:

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

Background

Duchenne muscular dystrophy (DMD) is a serious X-linked, heritable skeletal muscular dysfunction that typically afflicts young male children four to five years of age. The condition is estimated to have a prevalence of one in 3600 — 6000 (<0.03 percent) live male births. It is manifest clinically as a delayed or failed ability to walk or climb stairs accompanied by repeated falls. It is characterized by “Gower’s sign,” a peculiar pushing up of the body by the arms and hands from a squat position that reflects the muscular weakness of the hips, pelvis and legs. In time the disease progresses to involve the muscles of the upper extremities and chest, causing physical enfeeblement and debility.

The condition is intimately related to a diminished level of dystrophin, a protein essential to the development of language in the brain. As such, retarded development of speech is a frequent diagnostic
sign in dystrophic individuals. Mutations of the genetic code at the location of the dystrophin protein (Xp21.2-p21.1, which is the short arm of the X chromosome between positions 21.2 and 21.1) are held responsible for the muscular breakdown and physical deterioration associated with DMD.

The DMD Care Considerations Working Group is a national body created by the U.S. Centers for Disease Control and Prevention (CDC) that is tasked with study and action toward earlier diagnosis and treatment of DMD. The organization has emphasized the need for proactive clinical multidisciplinary intercession when the disease is suspected because the muscular defects of DMD are often irreversible and demand treatment at as early an age as possible.

**Searches**

AmeriHealth Caritas Pennsylvania searched PubMed and the databases of:
- UK National Health Services Centre for Reviews and Dissemination.
- Agency for Healthcare Research and Quality’s National Guideline Clearinghouse and other evidence-based practice centers.
- The Centers for Medicare & Medicaid Services (CMS).

We conducted searches on November 3, 2016. Search terms were: “Duchenne muscular dystrophy,” “genetic testing,” and “DMD Working Group.”

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**

Okubo (2016) noted that the diagnosis of DMD is traditionally not easily made because of the large size of the dystrophin gene, its complex mutational spectrum and the number of tests patients must undergo for diagnosis. The authors applied a high-throughput method using Ion Torrent next generation sequencing (NGS) technology to 67 cases with known dystrophin abnormalities and diagnosed 92 percent of patients with DMD in a single analysis. In contrast, 50 percent of duplications were correctly identified when using alternative testing methods (i.e., multiplex ligation-dependent probe amplification or MLPA). Small insertions in consecutive bases could not be detected. The authors estimated that Ion Torrent sequencing could diagnose approximately 92 percent of DMD patients, and that the results
clearly indicate that NGS technology is suitable for routine clinical practice to provide comprehensive genetic information that may direct expedient therapy.

In a review of the of diagnosis of DMD, Zatz (2016) described the evolution from the detection of deletions in the dystrophin gene by Southern blot, followed by multiplex analysis of the most common deleted exons by polymerase chain reaction (PCR):

“In the 1990’s, the use of microsatellite markers throughout the genome led to the mapping of novel neuromuscular dystrophy (NMD) genes. In addition, microsatellite markers within and flanking the dystrophin gene, allowed us to improve DMD carrier detection tests by segregation analysis, particularly in familial cases in which no deletion had been detected in the dystrophin gene. In the mid 1990’s semi-automated Sanger sequencing equipment opened the possibility to again expand and improve genetic testing. . . . A recent new improvement in 2013-2014 was the acquisition of NGS equipment (MiSeq and HiSeq, Illumina) and standardization of its methodology. NGS, based on a panel of 80 genes, increased significantly the efficacy of NMD diagnosis, with molecular alterations being identified in approximately 73 percent of the cases.”

Aartsma-Rus (2015) described an algorithm for diagnosis of DMD using muscle biopsy with immunohistochemistry and/or western blot analysis to show the presence or absence of dystrophin as the initial step. However, because a genetic diagnosis is still required when absence of dystrophin is shown in a muscle biopsy, and because a muscle biopsy is an invasive procedure, the standards of care for DMD diagnosis suggest bypassing a muscle biopsy and using only genetic testing to diagnose DMD. For most patients, muscle biopsies are never required.

The authors observed that the use of MLPA and array comparative genome hybridization (aCGH) may be chosen; but if no whole-exon deletions or duplications are found using MLPA, it is still possible that the patient has a small mutation in one of the 79 exons (20 percent of patients have small mutations). These can be identified using Sanger sequencing of individual exons, which is labor-intensive and more expensive than MLPA or aCGH. The authors further opined that Sanger sequencing will be in short order be replaced by more efficient and less expensive NGS techniques such as whole-exome sequencing (WES) for the genetic diagnosis of DMD.

Wang (2014) studied 26 patients of whom 21 had known large deletion/duplications and 5 did not have detectable large deletion/duplications by multiplex ligation-dependent probe amplification technology (MLPA). The authors noted that historically approximately 30 percent of patients with DMD do not receive a molecular diagnosis because of the complex mutational spectrum and the large size of the gene, but NGS with the Illumina HiSeq 2000 sequencer using paired read 100 bp sequencing is far more efficacious. They applied whole dystrophin gene analysis by NGS to the five patients who did not have detectable large deletion/duplications and to five randomly chosen patients from the 21 who did have large deletion/duplications. Five small mutations were identified in the first five patients, of which four
variants were previously unreported, and the deleted or duplicated exons and the breakpoints in the five large deletion/duplication patients were precisely identified. The authors concluded that whole dystrophin gene sequencing by NGS is a useful tool for the genetic diagnosis of Duchenne and Becker muscular dystrophies.

Wei (2014) noted that traditional diagnostic MLPA plus Sanger sequencing require multiple steps to fulfill the diagnosis of DMD. The authors described a series of 89 patients, 18 female carriers and 245 non-DMD patients who were evaluated using targeted NGS. Compared with traditional methods, NGS yielded 99.99 percent specificity and 98.96 percent sensitivity for detection of copy number variations, and 100 percent accuracy for the identification of single-nucleotide variation mutations. They also noted that NGS was able to detect partial deletions/duplications, thus offering precise personal DMD gene information for gene therapy, and opined that NGS is suitable for routine clinical practice, with shorter turnaround time, higher accuracy, and better insight into comprehensive genetic information (detailed breakpoints) for ensuing gene therapy.

Bushby (2010) reported the results of the CDC assessment of the diagnosis of DMD. The authors advocated that diagnosis should be done by a neuromuscular specialist who can assess the child clinically and can rapidly access and interpret appropriate investigations in the context of the clinical presentation. They wrote that testing for a DMD mutation in a blood sample is always necessary even if DMD is first confirmed by the absence of dystrophin protein expression on muscle biopsy. Genetic testing after a positive biopsy diagnosis of DMD is mandatory. A muscle biopsy is not necessary if a genetic diagnosis is secured first.

Summary of clinical evidence:

<table>
<thead>
<tr>
<th>Citation</th>
<th>Content, Methods, Recommendations</th>
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<tbody>
<tr>
<td>Okubo (2016)</td>
<td>Genetic diagnosis of Duchenne/Becker muscular dystrophy using next-generation sequencing: validation analysis of DMD mutations</td>
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<tr>
<td></td>
<td>• Noted that the diagnosis of DMD is traditionally not easy because of the large size and complexity of the dystrophin gene.</td>
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<td>• Applied NGS technology to 67 cases with known dystrophin abnormalities and diagnosed 92 percent of patients with DMD in a single analysis.</td>
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<td>• Estimated that Ion Torrent sequencing could diagnose approximately 92 percent of DMD patients and is suitable for routine clinical.</td>
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<td>Zatz (2016)</td>
<td>Neuromuscular disorders: genes, genetic counseling and therapeutic trials.</td>
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<td></td>
<td>• Described the evolution of detection of deletions in the dystrophin gene.</td>
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<td></td>
<td>• Initially microsatellite markers throughout the genome led to the mapping of NMD genes and to improved DMD carrier identification.</td>
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<td></td>
<td>• Sanger sequencing led to NGS equipment (MiSeq and HiSeq, Illumina) and increased efficacy of NMD diagnosis.</td>
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<td>Reference</td>
<td>Key points:</td>
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| Wang (2014)     | • Historically approximately 30 percent of patients with DMD do not receive a molecular diagnosis because of the complexity and size of the dystrophic genes.  
• NGS with the Illumina HiSeq 2000 sequencer using paired read 100 bp sequencing was found to be more efficacious.  
• Authors applied whole dystrophin gene analysis by NGS to five patients who did not have detectable large deletion.  
• Five small mutations were identified in the five patients, of which four variants were previously unreported.  
• The authors concluded that whole dystrophin gene sequencing by NGS is a useful tool for the genetic diagnosis of Duchenne and Becker muscular dystrophies. |
| Aartsma-Rus (2015) | • Created an algorithm for diagnosis of DMD using muscle biopsy with immunohistochemistry and/or western blot analysis.  
• Acknowledged that the standard of care for DMD diagnosis suggests only genetic testing to diagnose DMD.  
• Opined that Sanger sequencing will eventually be replaced by NGS and WES. |
| Wei (2014)      | • Series of 89 patients, 18 female carriers and 245 non-DMD patients who were evaluated using targeted NGS.  
• NGS yielded 99.99 percent specificity and 98.96 percent sensitivity for detection of copy number variations, and 100 percent accuracy for the identification of single-nucleotide variation mutations.  
• Also noted that NSG was able to detect partial deletions/duplications, thus offering precise personal DMD gene information for gene therapy.  
• Concluded that NGS is suitable for routine clinical practice, with shorter turnaround time, higher accuracy, and better insight into comprehensive genetic information (detailed breakpoints) for ensuing gene therapy. |
| Bushby (2010)   | • Assessment of the CDC work on diagnosis of DMD.  
• Recommended that diagnosis should be done by a neuromuscular specialist who can assess the child for care.  
• Concluded that testing for a DMD mutation in a blood sample is always necessary even if DMD is first confirmed by the absence of dystrophin protein expression on muscle biopsy.  
• Concluded that genetic testing after a positive biopsy diagnosis of DMD is mandatory.  
• Concluded that muscle biopsy is not necessary if a genetic diagnosis is secured first. |
References

Peer-reviewed references:


CMS National Coverage Determinations (NCDs):

No NCDs identified as of the writing of this policy.

Local Coverage Determinations (LCDs):

No LCDs identified as of the writing of this policy.

Commonly submitted codes

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.

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<td>DMD(dystrophin) (eg., Duchenne/Becker muscular dystrophy) deletion analysis,</td>
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and duplication analysis, if performed

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