

# Genetic testing for Duchenne muscular dystrophy

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Next review date: 5/2025

Policy contains: DMD-associated dilated cardiomyopathy; X-linked dystrophinopathy; Duchenne muscular dystrophy; Becker muscular dystrophy.

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## Coverage policy

Once-per-lifetime genetic testing for Duchenne or Becker muscular dystrophy (*DMD* gene mutations) is clinically proven and, therefore, may be 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).
- The test is ordered 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.
  - 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.
  - Testing to assess candidacy for U.S. Food and Drug Administration-approved gene therapies for Duchenne muscular dystrophy.
- The test is analytically and clinically valid.
- Pre- and post-test genetic counseling accompanies testing.

- Available genetic testing options are 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.

For any determinations of medical necessity for medications, refer to the applicable state-approved pharmacy policy.

### Limitations

The following uses of genetic testing for Duchenne muscular dystrophy are considered experimental/investigational and not clinically proven:

- Newborn screening, subject to state and local requirements (Birnkrant, 2018; Health Resources & Services Administration, 2023).
- 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. This gene 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 (Genetics Home Reference, 2016). 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, 2023). 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 (Genetics Home Reference, 2016).

Long-term outcomes for persons diagnosed with Duchenne muscular dystrophy are poor. A meta-analysis (n = 2,283) of persons with the disease found the average age at death was 22.0 years, slightly higher for those born since 1990 (28.1 years) (Broomfield, 2021).

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, 2023). 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. The U.S. Food and Drug Administration (2021) has approved several antisense oligonucleotide gene therapies for Duchenne muscular dystrophy for use in persons with confirmed genetic mutations.

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, 2022). 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, 2022):

- 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.

## 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.

A 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.

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, which was deleted from the policy). 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, 2023). 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 to 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.

In 2020, we identified no new relevant information to add to the policy.

In 2021, we updated the references and added an indication to the coverage section to test for candidacy for available gene therapies.

In 2022, we updated the references and identified no new relevant research for the policy. We modified the coverage indication addressing candidacy for U.S. Food and Drug Administration-approved antisense oligonucleotide gene therapies to account for the expanding list of targeted gene therapies for Duchenne muscular dystrophy.

In 2023, we updated the references and identified no new relevant research for the policy.

In 2024, we added a guideline for testing for dystrophinopathies, including Duchenne muscular dystrophy, written by European experts. This guideline included testing recommendation criteria similar to the Centers for Disease Control and Prevention, and classified recommendations into levels of testing:

- Level 1 (deletion/duplication testing); an initial screen that detects most variants, and should be the first test offered;
- Level 2 (small variants detection); Sanger sequencing is recommended; and
- Level 3 (RNA analysis); Sanger sequencing or TaqMan assay can be used (Fratter, 2020).

We added a systematic review of 11 studies (n = 1,416,123) using creatine kinase tests for neonatal screening. Sensitivity in 10 of 11 studies exceeded 81%, and specificity was close to 100% (de Freitas Nakata, 2021).

We added a systematic review of seven studies (n = 99 families at risk) that showed accuracy of non-invasive pre-natal testing for Duchenne muscular dystrophy was 100% in all but one study (95%). Authors note that ensuring informed parental consent, providing detailed guidelines, and arranging genetic counseling are essential (Zaninovic, 2023).

## References

On October 27, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. 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 the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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## Policy updates

1/2017: initial review date and clinical policy effective date: 2/2017

1/2019: Policy references updated and added policy changes related to medical necessity criteria, tiered testing, carrier testing, and newborn screening. Policy ID changed from CP #02.01.23 to CCP.1282.

1/2020: Policy references updated.

1/2021: Policy references updated and coverage amended.

1/2022: Policy references updated. Coverage modified.

1/2023: Policy references updated.

1/2024: Policy references updated.