

DRAFT Medical Coverage Policy | Genetic Testing for Duchenne and Becker Muscular Dystrophy



EFFECTIVE DATE: 01|01|2024

POLICY LAST UPDATED: 10|02|2023

OVERVIEW

Variants in the Duchenne muscular dystrophy (*DMD*) gene, which encodes the protein dystrophin, may result in a spectrum of X-linked muscle diseases, including the progressive diseases Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) and dilated cardiomyopathy. Genetic testing can confirm a diagnosis of a dystrophinopathy and distinguish the less from more severe forms, as well as identify female carriers at risk.

This policy addresses the following test(s):

- Genomic Unity® DMD Analysis (Variantyx Inc) CPT code 0218U

MEDICAL CRITERIA

Medicare Advantage Plans and Commercial Products

Genetic Testing for DMD gene variants may be considered medically necessary under the following conditions:

- In a male with signs and symptoms of a dystrophinopathy in order to confirm the diagnosis and direct treatment.
- For at-risk female relatives*
 - To confirm or exclude the need for cardiac surveillance.
 - For preconception testing to determine the likelihood of an affected offspring in a woman considering pregnancy.

*At-risk females are defined as first- and second-degree female relatives and include the proband's mother, female siblings of the proband, female offspring of the proband, the proband's maternal grandmother, maternal aunts, and their offspring.

- For at-risk male offspring*
 - To confirm or exclude the need for medical cardiac surveillance.

*An at-risk male is defined as an asymptomatic male offspring of a female carrier or an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy

PRIOR AUTHORIZATION

Medicare Advantage Plans and Commercial Products

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See Related Policies section.

POLICY STATEMENT

Medicare Advantage Plans and Commercial Products

Genetic testing for DMD gene variants may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the above criteria are met.

Genetic testing for DMD gene variants in all other situations is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products.

Commercial Products

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate section of the Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable laboratory testing and not medically necessary/not covered benefits/coverage.

BACKGROUND

Dystrophinopathies

The dystrophinopathies include a spectrum of muscle diseases. The mild end of the spectrum includes asymptomatic increases in serum concentration of creatine phosphokinase and clinical symptoms such as muscle cramps with myoglobinuria and/or isolated quadriceps myopathy. The severe end of the spectrum includes progressive muscle diseases that lead to substantial morbidity and mortality. When skeletal muscle is primarily affected, the disease is classified as Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD); when the heart is primarily affected, the disease is classified as DMD-associated dilated cardiomyopathy (left ventricular dilation and heart failure).

Duchenne Muscular Dystrophy

DMD, the most common muscular dystrophy, is a severe childhood X-linked recessive disorder that results in significant disability due to skeletal myopathy and cardiomyopathy. The disease is characterized by progressive, symmetric muscle weakness and gait disturbance resulting from a defective dystrophin gene. According to a 2022 systematic review and meta-analysis, the global prevalence of DMD is estimated at 4.8 cases (95% confidence interval [CI], 3.6 to 6.3) per 100,000 people. Approximately one-third of DMD cases arise from de novo variants and have no known family history. Infant males with DMD are often asymptomatic. Manifestations may be present as early as the first year of life in some patients, but clinical manifestations most often appear during preschool, from years 2 to 5. Affected children present with gait problems, calf hypertrophy, positive Gower sign, and difficulty climbing stairs. The affected child's motor status may plateau between 3 and 6 years of life with deterioration beginning at 6 to 8 years. Most patients will be wheelchair-bound by ages 9 to 12 years but will retain preserved upper-limb function until a later period. Cardiomyopathy occurs after 18 years of age. Late complications are cardiorespiratory (eg, decreased pulmonary function as a result of respiratory muscle weakness and cardiomyopathy). These severe complications commonly appear in the second decade of life and eventually lead to death. Few individuals with DMD survive beyond the third decade.

Becker Muscular Dystrophy

BMD is characterized by later onset skeletal muscle weakness. Individuals remain ambulatory into their 20s. Despite the milder skeletal muscle involvement, heart failure from cardiomyopathy is a common cause of morbidity and the most common cause of death in these patients, with a mean age of death in the mid-40s. According to a 2022 systematic review and meta-analysis, the global prevalence of BMD is estimated at 1.6 cases (95% CI, 1.1 to 2.4) per 100,000 people.

Female Carriers

Females heterozygous for a *DMD* disease-associated variant can manifest symptoms of the disease. An estimated 2.5% to 7.8% of female carriers are manifesting carriers who develop symptoms ranging from mild muscle weakness to a rapidly progressive DMD-like muscular dystrophy. Female carriers are at increased risk for dilated cardiomyopathy and need routine cardiac surveillance and treatment. Most heterozygous women do not show severe myopathic features of DMD, possibly due to compensation by a normal X chromosome with inactivation of the mutated *DMD* gene in the affected X chromosome. In some cases, this compensation can be reversed by a nonrandom or skewed inactivation of the X chromosome, resulting in greater expression of the affected X chromosome and some degree of myopathic features. Other mechanisms of manifesting female carriers include X chromosome rearrangement involving the *DMD* gene and complete or partial absence of the X chromosome (Turner syndrome).

Clinical Diagnosis

Duchenne Muscular Dystrophy

Suspicion of DMD should be considered irrespective of family history; it is most commonly triggered by the observation of abnormal muscle function in a male child, the detection of an increase in serum creatine kinase tested for unrelated indications, or detection of increased serum transaminases (aspartate aminotransferase and alanine aminotransferases). Clinical examination by a neuromuscular specialist for DMD includes visual inspection of mechanical function such as running, jumping, climbing stairs, and getting up from the floor. Common presenting symptoms include abnormal gait with frequent falls, difficulties rising from the floor or tip-toe walking, and pseudohypertrophy of the calves. A clinical examination may reveal decreased or lost muscle reflexes and, commonly, a positive Gower sign. An elevation of serum creatine kinase, at least 10 to 20 times normal levels (between 5000 IU/L and 150000 IU/L), is nonspecific to DMD but is always present in affected patients. Electromyography and nerve conduction studies were traditional parts of the assessment of neuromuscular disorders, but these tests may not be necessary for assessment of DMD. An open skeletal muscle biopsy is needed when a test for deletions or duplications of the *DMD* gene is negative. The biopsy will provide general signs of muscular dystrophy, including muscle fiber degeneration, muscle regeneration, and increased content of connective tissue and fat. Dystrophin analysis of a muscle biopsy will always be abnormal in affected patients but is not specific to DMD.

Becker Muscular Dystrophy

BMD is clinically similar to DMD but is milder and has a later onset. BMD presents with progressive symmetric muscle weakness, often with calf hypertrophy, although the weakness of quadriceps femoris may be the only sign. Activity-induced cramping may be present in some individuals, and flexion contractures of the elbows may be present late in the course. Neck flexor muscle strength is preserved, which differentiates BMD from DMD. Serum creatine kinase shows moderate-to-severe elevation (5 to 100 times the normal level).

Molecular Diagnosis

DMD is the only gene of which variants are known to cause DMD, BMD, and *DMD*-associated cardiomyopathy. Molecular genetic testing of *DMD* can establish the diagnosis of a dystrophinopathy without muscle biopsy in most patients with DMD and BMD.

The dystrophinopathies are X-linked recessive and penetrance is complete in males. The gene that codes for dystrophin is the largest known human gene. A molecular confirmation of DMD and BMD is achieved by confirming the presence of a pathogenic variant in this gene by a number of available assays. The large size of the dystrophin gene results in a complex variant spectrum with over 5000 reported disease-associated variants, as well as a high spontaneous de novo variant rate.

Treatment

There is no cure for DMD or BMD. Treatment is aimed at controlling symptoms to improve quality of life. However, the natural history of the disease can be changed by strategies such as corticosteroid therapy, proper nutrition, or rehabilitative interventions. Glucocorticoids were shown in a 1991 randomized controlled trial (RCT) to prolong the period of independent ambulation by 3 years. The goal of this therapy is to

preserve ambulation and minimize later respiratory, cardiac, and orthopedic complications. Glucocorticoids work by decreasing inflammation, preventing fibrosis, improving muscle regeneration, improving mitochondrial function, decreasing oxidative radicals, and stopping abnormal apoptosis pathways. Bone density measurement and immunization are prerequisites for corticosteroid therapy initiation, which typically begins at 2 to 5 years of age, although there has been no demonstrated benefit of therapy before 5 years of age.

New therapeutic trials require accurate diagnoses of these disorders, especially when the therapy is targeted at specific pathogenic variants. Exon-skipping is a molecular therapy aimed at skipping the transcription of a targeted exon to restore a correct reading frame using antisense oligonucleotides. Exon-skipping may result in a DMD protein without the mutated exon and a normal, nonshifted reading frame. Exon-skipping may also restore DMD protein function so that the treated patient's phenotypic expression more closely resembles BMD. Several therapies are currently in clinical trials. Exon-skipping therapies using antisense oligonucleotides approved by the U.S. Food and Drug Administration include: eteplirsen (Exondys 51) for treatment for patients who have a confirmed variant of the dystrophin gene amenable to exon 51 skipping, golodirsen (Vyondys 53), and viltolarsen (Viltepso) for patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. These approvals were based on improvements in the surrogate outcome of increased dystrophin production in skeletal muscle and benefits in clinical outcomes have not yet been established.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

For individuals who are male and have signs and symptoms of a dystrophinopathy who receive genetic testing for Duchenne muscular dystrophy (*DMD*) gene variants to confirm diagnosis without biopsy, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or Becker muscular dystrophy (BMD). Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Virtually all males with DMD or BMD have identifiable *DMD* disease-associated variants, indicating a high clinical sensitivity for genetic testing. The clinical utility of *DMD* gene testing can be established for the index case to confirm the diagnosis without a muscle biopsy, to initiate effective treatment, and to distinguish between DMD and the less severe BMD. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are female and are a relative of a patient with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine carrier status, the evidence includes case series and database entries describing screening and results of types of variants found in patients with clinical signs of DMD or BMD. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for the clinical validity for testing for a known familial variant are lacking but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in at-risk female relatives is lacking. However, the chain of evidence is strong, because determination of carrier status in a female for a *DMD* familial variant necessitates or eliminates the need for routine cardiac surveillance and can indicate the likelihood of an affected offspring in women considering children. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are asymptomatic male offspring of a female *DMD* familial variant carrier or an asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy who receive targeted *DMD* testing for a known familial variant to determine *DMD* status, the evidence includes case series

and database entries. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, morbid events, quality of life, medication use, and resource utilization. Published data for clinical validity of testing for a known familial variant are lacking, but validity is expected to be high. Direct evidence on the clinical utility of *DMD* gene testing in asymptomatic male offspring of a female *DMD* familial variant carrier or male sibling of a patient with a *DMD*-associated dystrophinopathy is also lacking. However, the chain of evidence is strong, because detection of the *DMD* familial variant necessitates or eliminates the need for increased medical surveillance or cardiac surveillance in an asymptomatic male offspring of a female carrier or the asymptomatic male sibling of a patient with a *DMD*-associated dystrophinopathy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following CPT code is medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above is met;

The following code(s) can be used for Genomic Unity® DMD Analysis;

0218U Neurology (muscular dystrophy), DMD gene sequence analysis, including small sequence changes, deletions, duplications, and variants in non-uniquely mappable regions, blood or saliva, identification and characterization of genetic variants.

RELATED POLICIES

Biomarker Testing Mandate

Proprietary Laboratory Analysis (PLA)

PUBLISHED

Provider Update, November 2023

REFERENCES

1. Verma S, Anziska Y, Cracco J. Review of Duchenne muscular dystrophy (DMD) for the pediatricians in the community. *Clin Pediatr (Phila)*. Nov 2010; 49(11): 1011-7. PMID 20724320
2. Salari N, Fatahi B, Valipour E, et al. Global prevalence of Duchenne and Becker muscular dystrophy: a systematic review and meta-analysis. *J Orthop Surg Res*. Feb 15 2022; 17(1): 96. PMID 35168641
3. Darras BT, Miller DT, Urion DK. Dystrophinopathies. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. *GeneReviews*. Seattle, WA: University of Washington; 2014.
4. Yoon J, Kim SH, Ki CS, et al. Carrier woman of Duchenne muscular dystrophy mimicking inflammatory myositis. *J Korean Med Sci*. Apr 2011; 26(4): 587-91. PMID 21468271
5. Soltanzadeh P, Friez MJ, Dunn D, et al. Clinical and genetic characterization of manifesting carriers of DMD mutations. *Neuromuscul Disord*. Aug 2010; 20(8): 499-504. PMID 20630757
6. Bonilla E, Schmidt B, Samitt CE, et al. Normal and dystrophin-deficient muscle fibers in carriers of the gene for Duchenne muscular dystrophy. *Am J Pathol*. Dec 1988; 133(3): 440-5. PMID 3059802
7. Yoshioka M, Yorifuji T, Mituyoshi I. Skewed X inactivation in manifesting carriers of Duchenne muscular dystrophy. *Clin Genet*. Feb 1998; 53(2): 102-7. PMID 9611069
8. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol*. Jan 2010; 9(1): 77-93. PMID 19945913
9. Mah JK, Selby K, Campbell C, et al. A population-based study of dystrophin mutations in Canada. *Can J Neurol Sci*. May 2011; 38(3): 465-74. PMID 21515508
10. Griggs RC, Moxley RT, Mendell JR, et al. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. *Clinical Investigation of Duchenne Dystrophy Group*. *Arch Neurol*. Apr 1991; 48(4): 383-8. PMID 2012511
11. Abbs S, Tuffery-Giraud S, Bakker E, et al. Best practice guidelines on molecular diagnostics in Duchenne/Becker muscular dystrophies. *Neuromuscul Disord*. Jun 2010; 20(6): 422-7. PMID 20466545

12. Food and Drug Administration (FDA). FDA News Release: FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. 2016; <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm521263.htm>. Accessed January 30, 2023.
13. Food and Drug Administration. VYONDYS 53 (golodirsen) Prescribing Information. 2019 https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/211970s000lbl.pdf Accessed January 29, 2023.
14. Food and Drug Administration. VILTEPSO (viltolarsen) Prescribing Information. 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212154Orig1s000lbl.pdf. Accessed January 28, 2023.
15. Monaco AP, Bertelson CJ, Liechti-Gallati S, et al. An explanation for the phenotypic differences between patients bearing partial deletions of the DMD locus. *Genomics*. Jan 1988; 2(1): 90-5. PMID 3384440
16. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, et al. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve*. Aug 2006; 34(2): 135-44. PMID 16770791
17. Ross LF, Saal HM, David KL, et al. Technical report: Ethical and policy issues in genetic testing and screening of children. *Genet Med*. Mar 2013; 15(3): 234-45. PMID 23429433
18. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. Mar 2018; 17(3): 251-267. PMID 29395989
19. Fratter C, Dalgleish R, Allen SK, et al. EMQN best practice guidelines for genetic testing in dystrophinopathies. *Eur J Hum Genet*. Sep 2020; 28(9): 1141-1159. PMID 32424326

CLICK THE ENVELOPE ICON BELOW TO SUBMIT COMMENTS

This medical policy is made available to you for informational purposes only. It is not a guarantee of payment or a substitute for your medical judgment in the treatment of your patients. Benefits and eligibility are determined by the member's subscriber agreement or member certificate and/or the employer agreement, and those documents will supersede the provisions of this medical policy. For information on member-specific benefits, call the provider call center. If you provide services to a member which are determined to not be medically necessary (or in some cases medically necessary services which are non-covered benefits), you may not charge the member for the services unless you have informed the member and they have agreed in writing in advance to continue with the treatment at their own expense. Please refer to your participation agreement(s) for the applicable provisions. This policy is current at the time of publication; however, medical practices, technology, and knowledge are constantly changing. BCBSRI reserves the right to review and revise this policy for any reason and at any time, with or without notice. Blue Cross & Blue Shield of Rhode Island is an independent licensee of the Blue Cross and Blue Shield Association.

