
Medical Policy



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***Current Policy Effective Date: 7/1/23**
(See policy history boxes for previous effective dates)

Title: Genetic Testing for Myotonic Dystrophy

Description/Background

Muscular dystrophy refers to a group of more than 30 inherited diseases that cause progressive muscle weakness and muscle loss. Myotonic dystrophy (DM) is a type of muscular dystrophy and has 2 forms, type 1 (DM1) and type 2 (DM2). It is the most common form of adult-onset muscular dystrophy.¹

DM1

DM1, also known as Steinert's disease, is estimated to affect 1 in 20,000 individuals worldwide. Prevalence appears to be regional and may be as high as 1 in 10,000 (Iceland), to 1 in 100,000 (in certain areas of Japan). It is inherited in an autosomal dominant manner. DM1 is caused by expansion of a cytosine-thymine-guanine trinucleotide repeat in the *DMPK* gene, located on chromosome 19. CTG repeat lengths of up to 34 are considered normal. Repeat lengths between 35 and 49, although abnormal, do not result in an expression of symptoms; however, children of these individuals are at increased risk of larger repeats (anticipation). With DM1, repeats may exceed 5,000.^{2,3} The length of the CTG repeat expansion is moderately correlated with disease severity.

DM1 is a multi-system disorder that potentially affects brain, skeletal and smooth muscles, eyes, heart, gastrointestinal tract, lungs and endocrine system. It is one of the most variable inherited human disorders, as the expression ranges from asymptomatic adults to severely affected neonates. Clinical findings have been categorized into 3 phenotypes; however, there is not absolute distinction between them, as they are more of a continuum.

- Mild DM1 (adult-onset) is the most prevalent form and may include premature cataracts, baldness and mild myotonia; life span is normal.
- Classic DM1 (adult-onset) may include cataracts; distal weakness involving dorsiflexors of the leg and long finger flexors of the arms; myotonia of the hand, neck and face; gastrointestinal symptoms; fatigue; cardiac conduction abnormalities. Adults may have a shortened life span.

- Congenital DM1 may present in utero as polyhydramnios. At birth, presentation may include hypotonia, severe generalized weakness, clubfoot and respiratory insufficiency. Mortality from respiratory failure is high. In surviving infants, there is gradual improvement in motor function. Eventually, progressive myopathy ensues in about the second decade of life. Intellectual disability is found in up to 60% of these individuals.^{2,5}

The European Journal of Human Genetics (2012) delineates an additional category of Juvenile DM1. This form resembles a classic form; however, it is more clearly associated with cognitive and behavioral abnormalities, such as difficulties in learning and socialization. Muscle involvement may be minimal.

In addition to the clinical findings, progression may include development of endocrinopathies, including hyperinsulinism; thyroid dysfunction; diabetes mellitus; testicular atrophy and infertility.²

DM2

DM2, also known as proximal myotonic myopathy (PROMM), proximal myotonic dystrophy and Ricker syndrome, was first described in 1994 after discovering who were thought to have DM1 did not have the CTG expansion. They instead have a cytosine-cytosine-thymine-guanine repeat expansion on chromosome 3, in the *CNBP (ZNF9)* gene. On normal alleles, there are 11 to 26 tetranucleotide repeats; on pathogenic alleles, the number of repeats ranges from 75 to more than 11,000. There is no definite correlation between repeat length and disease severity. Though less well studied than DM1, reports from Europe suggest the prevalence of DM2 is similar to DM1, while in the United States anecdotal evidence suggests that DM2 occurs less frequently than DM1.⁴

In general, DM2 is a less severe disease than DM1. Presentation onset ranges from the second to the seventh decades, often presenting with myotonia, weakness or cataracts. Weakness predominantly involves the proximal muscles; whereas distal muscles are most affected in DM1. Prominent early involvement of neck flexors, finger flexors and later hip girdle muscles and sparing of facial and hand intrinsic muscles should suggest the diagnosis of DM2. A challenge to diagnosis is that DM2 in its mildest form can be difficult to recognize.^{4,5}

Regulatory Status:

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer LDTs must be licensed by 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.

Medical Policy Statement

Genetic testing for the presence of myotonic dystrophy Type I (DM1) and Type 2 (DM2) has been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions:

Genetic testing for DM1 (*DMPK* gene) and DM2 (*CNBP / ZNF9* gene) are considered established when the following are met:

- The member displays clinical features suggestive of myotonic dystrophy Type 1 (DM1) or Type 2 (DM2); **and**
The result of the test will directly impact the treatment being delivered; **OR**
 - The member is at risk of inheriting the mutation; **OR**
 - For prenatal diagnosis or preimplantation genetic diagnosis of DM1 or DM2
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CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

81187

81234

81239

S3853

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Prior (2009), on behalf of the American College of Medical Genetics, reported:

“...CTG-repeat expansion mutations account for >99% of cases of DM1. The analytical sensitivity and specificity of tests that effectively detect and measure the CTG repeat in the 3’ UTR of the *DMPK1* gene approaches 100%. However, the DM1 mutation can be carried by asymptomatic or minimally affected individuals who have relatively small expansions, in the range of approximately 50 to 100 repeats. Therefore, factors such as age, family history, penetrance, and variable expressivity preclude an accurate

determination of the clinical sensitivity and specificity of the test in individuals with one or both alleles in the range of 50 to 100 repeats. For CTG repeats larger than this range, the clinical sensitivity and specificity are high and expected to approach 100%. Allele sizes of 35 to 49 CTG repeats (premutation alleles) are rare and have been mostly ascertained through their symptomatic offspring, which expanded >50 repeats.”

“Indications for genetic testing: This test is often used for symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member. The test is also useful for prenatal diagnosis for at-risk pregnancies after ultrasound evidence of fetal hypotonia, reduced fetal movements, positional abnormalities, and/or polyhydramnios. The testing is also extremely helpful in identifying individuals who are asymptomatic or exhibit equivocal symptoms, such as cataracts. No new mutations have been described in DM, which is consistent with the linkage disequilibrium data.”³

Kamsteeg (2012) stated:

“Detection of a repeat expansion in the *DMPK* gene and the *CNBP* gene is fast, inexpensive and reliable. Both the clinical sensitivity and the clinical specificity are >99% (Eurogentest clinical utility gene cards).”⁵

No specific treatment exists for the progressive weakness in individuals with DM1. However, a definitive diagnosis leads to appropriate supportive care. Evaluation by a physiatrist, physical therapist and occupational therapist is of value in constructing a treatment plan for maximum mobility and identifying appropriate assistive devices. Pain management evaluation is valuable for disabling pain. Pharmacotherapy may include mexiletine, carbamazepine and anti-spasticity agents. Increased weakness in DM1 has been associated with both hypothyroidism and statins, thus some strength may return if these factors are eliminated.²

Prevention of secondary complications include appropriate anesthesia care, prevention of life-threatening arrhythmias and continued physical activity and weight management. Surveillance may include cardiac monitoring, annual fasting glucose levels and a bi-annual ophthalmologic examination. Statins may increase muscle pain and weakness. Several anesthetic agents (vecuronium, succinylcholine, propofol and doxorubicin) are associated with increased surgical complications in individuals with DM1. Lifestyle risk factors associated with more severe phenotypes of DM1 include smoking, obesity, illicit drug use and excessive alcohol intake.²

Bird (2020), in the review of Myotonic Dystrophy 1, states that molecular genetic testing detects pathogenic variants in nearly 100% of affected individuals.²

Schoer (2020), in the review of Myotonic Dystrophy 2, states that the detection rate of a *CNBP* CCTG expansion is more than 99% with the combination of routine PCR, Southern blot analysis and the PCR repeat-primed assay.⁶

SUPPLEMENTAL INFORMATION

Clinical Practice Guidelines and Position Statements

American College of Medical Genetics

Technical standards and guidelines for myotonic dystrophy type 1 testing, 2009³

Indications for genetic testing: symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member. The test is also useful for prenatal diagnosis for at-risk pregnancies after ultrasound evidence of fetal hypotonia, reduced fetal movements, positional abnormalities and/or polyhydramnios.

International Myotonic Dystrophy Consortium (IDMC)

Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2, 2012⁵

"...because of the disease characteristics in DM1 and DM2, appropriate molecular testing and reporting is very important for the optimal counseling in myotonic dystrophy."

"...the clinical challenge in DM1 lies in supplying optimal care for this multisystem disease, whereas in DM2 it is also a diagnostic challenge to recognize the disease. Detection of a repeat expansion in the *DMPK* gene and the *CNBP* gene is fast, inexpensive and reliable. Both the clinical sensitivity and the clinical specificity are >99% (Eurogentest clinical utility gene cards: <http://www.eurogentest.org>)."

European Neuromuscular Centre (ENMC)

140th International Workshop, 2006¹⁴:

Myotonic Dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management

Indications for genetic DM2 testing

Increasing numbers of patients without the full range of multi-organ symptoms associated with myotonic dystrophy have been verified with DM2 mutation. In the single patient, none of the common clinical key features: proximal weakness, myotonia, cataracts, elevated CK-values or established family history is absolutely mandatory for DM2 disease:

The threshold for genetic testing of DM2 based on clinical findings should generally be lower than that usually required for DM1 genetic testing, especially if testing is started with the screening/exclusion test of the normal alleles at the DM2 locus.

248th ENMD International Workshop, 2019:¹⁵

Myotonic dystrophies: Molecular approaches for clinical purposes, framing a European molecular research network

(No new recommendations regarding testing.)

Government Regulations

National:

There is no national coverage determination (NCD) on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation

Local Coverage Article: Billing and Coding MoIDx: Molecular Diagnostic Tests (MDT) (A57772)

Original Effective Date: 11/01/2019

Revision Effective Date: 10/01/2020

Codes 81187, 81234 and 801239 are listed in the Group 1 Codes list.

Codes 81187, 81234 and 81239 have fees on the 2021 Clinical Laboratory Fee Schedule. An assigned fee is not a guarantee of coverage.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

Genetic Testing for Duchenne and Becker Muscular Dystrophy

References

1. US Department of Health and Human Services, National Institutes of Health, Muscular Dystrophy. <https://www.nichd.nih.gov/health/topics/musculardys> Accessed 1/30/23.
2. Bird T.D. Myotonic dystrophy type 1. Gene Reviews. Funded by the NIH. Developed at the University of Washington, Seattle. Initial posting: September 17, 1999. Last revision: March 25, 2021. <https://www.ncbi.nlm.nih.gov/books/NBK1165/> Accessed 1/30/23.
3. Prior T.W. Technical standards and guidelines for myotonic dystrophy type 1 testing. On behalf of the American College of Medical Genetics (ACGM) Laboratory Quality Assurance Committee. Genetics in Medicine, Vol 11, Number 7, July 2009.
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5. Kamsteeg E.J. et al. Best practice guidelines and recommendations on the molecular diagnosis of myotonic dystrophy types 1 and 2. European Journal of Human Genetics (2012) 20, 1203-1208.

6. Schoser B. Myotonic dystrophy type 2. Gene Reviews. Funded by the NIH. Initial Posting: September 21, 2006. Last Revision: March 19, 2020. <https://www.ncbi.nlm.nih.gov/books/NBK1466/> Accessed 1/30/23.
7. Day, J., et al. Myotonic dystrophy type 2: molecular, diagnostic and clinical spectrum, *Neurology*, 2003, Vol. 60, No. 4, pp. 657-664.
8. Kakourou, A., et al., Preimplantation genetic diagnosis for myotonic dystrophy type 1 in the UK, *Neuromuscular Disorders*, 2008, Vol. 18, No. 2, pp. 131-136.
9. Martorell, L., et al., Prenatal diagnosis in myotonic dystrophy type 1. Thirteen years of experience: implications for reproductive counseling in DM1 families, *Prenatal Diagnosis*, 2007, Vol. 27, No. 1, pp. 68-72.
10. Meola, G., et al. Myotonic dystrophy type 2: an update on clinical aspects, genetic and pathomolecular mechanism. *Journal of Neuromuscular Diseases* 2 (2015) S59-S71.
11. Pavicevic, D.S., et al. Molecular genetics and genetic testing in myotonic dystrophy type 1. *BioMed Research International*, Vol 2013, Article ID 391821.
12. Salehi, L., et al. Risk Prediction for Clinical Phenotype in Myotonic Dystrophy Type 1 Data from 2,650 Patients, *Genetic Testing*, 2007, Vol. 11, No. 1, pp. 84-90.
13. Udd B. Myotonic dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management. *Neuromuscular Disorders* 16 (2006) 403-413.
14. Udd B., et al. Myotonic dystrophy type 2 (DM2) and related disorders report of the 180th ENMC workshop including guidelines on diagnostics and management 3-5 December 2010, Naarden, The Netherlands. *Neuromuscul Disord.* 2011 Jun;21(6):443-50.
15. Wansink DG, et al. 248th ENMC International Workshop: Myotonic dystrophies: Molecular approaches for clinical purposes, framing a European molecular research network, Hoofddorp, the Netherlands, 11–13 October 2019. *Neuromuscular Disorders* 2020 (30): 521-531. [https://www.nmd-journal.com/article/S0960-8966\(20\)30083-3/fulltext](https://www.nmd-journal.com/article/S0960-8966(20)30083-3/fulltext) Accessed 1/30/23.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/16/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
5/20/04	5/20/04	6/29/04	Joint policy established
11/1/07	8/21/07	11/1/07	Routine maintenance
3/1/09	12/9/08	12/21/08	Routine maintenance
1/1/12	10/11/11	11/9/11	Routine maintenance, code update, 81404 added and 88299 deleted.
11/1/13	8/22/13	8/27/13	Routine maintenance
7/1/16	4/19/16	5/23/16	Routine maintenance, updated references and rationale, policy statement changed to include coverage for DM2 testing. Added CPT code 81401.
7/1/17	4/18/17	4/18/17	Routine maintenance Updated Medicare and Medicaid sections.
7/1/18	4/17/18	4/17/18	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance: MPS and inclusions clarified.
7/1/19	4/16/19		Routine maintenance Codes 81187, 81234, 81239 added Codes 81401, 81404 removed Medicare section updated; Medicaid section deleted; Description and Rationale updated.
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance. Ref 15 added
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (jf) Vendor Managed: NA

Next Review Date: 2nd Qtr, 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR MYOTONIC MUSCULAR DYSTROPHY

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Policy criteria apply.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.