



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Genetic Testing for Myotonic Dystrophy

Effective Date 11/15/2010
Next Review Date 11/15/2012
Coverage Policy Number 0271

Table of Contents

Coverage Policy	1
General Background	2
Coding/Billing Information	5
References	5
Policy History	8

Hyperlink to Related Coverage Policies

Comparative Genomic Hybridization Testing
(Chromosomal Microarray Analysis)
Genetic Counseling
Genetic Testing of Heritable Disorders
Preimplantation Genetic Diagnosis

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers genetic testing for myotonic dystrophy types 1 (DM1) and/or 2 (DM2) as medically necessary for ANY of the following indications:

- diagnostic testing when there are clinical features that are suggestive of DM1 or DM2
- predictive testing in an asymptomatic individual \geq age 18 when a first- or second-degree* relative has been diagnosed with DM1 or DM2
- prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when one parent has been diagnosed with DM1 or DM2

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half-siblings.

CIGNA does not cover genetic testing for DM1 or DM2 in the general population because such screening is considered not medically necessary or of unproven benefit.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or licensed or certified genetic counselor.

General Background

Myotonic dystrophy types 1 (DM1) and 2 (DM2) are forms of muscular dystrophy. DM1 may be referred to as Steinert syndrome, dystrophia myotonica, myotonia atrophica, myotonia dystrophica, Steinert disease, or Steinert myotonic dystrophy syndrome. DM2 may also be referred to as proximal myotonic myopathy (PROMM), myotonic myopathy, and proximal Ricker syndrome. Myotonic dystrophy is the most common adult form of muscular dystrophy. These conditions are multisystem disorders that affect skeletal muscle and smooth muscle, as well as the eye, heart, endocrine system and central nervous system (CNS). They share the same core diagnostic criteria and multiorgan involvement but there are clinical aspects that are specific to each type (Botta, et al., 2006).

DM1 is suspected in adults with the following clinical features (Bird, 1999/2007):

- muscle weakness, particularly of the distal leg, hand, neck and face
- myotonia or sustained muscle contraction, which often manifests as the inability to quickly release a hand grip (i.e., grip myotonia) and which can be demonstrated by tapping a muscle with a reflex hammer (i.e., percussion myotonia)
- observation of posterior subcapsular cataracts that are detectable as red and green iridescent opacities on slit lamp examination

In neonates, DM1 may be suspected when there is some combination of hypotonia, facial muscle weakness, generalized weakness, positional malformations (including club foot), and respiratory insufficiency.

There are three overlapping forms of DM1 (Bird, 1999/2007):

- Mild DM1: Individuals with mild DM1 may have only cataract, mild myotonia, (i.e., sustained muscle contraction) or diabetes mellitus. These individuals may have a normal or minimally shortened life span.
- Classic DM1: The age of onset for classic DM1 is generally in the 20s and 30s and less commonly after age 40 years. At times, it may be evident in childhood with subtle signs such as myotonic facies and myotonia observe. The predominant symptom is distal muscle weakness, leading to foot drop/gait disturbance and difficulty with tasks that require fine dexterity. Some individuals may have ophthalmoplegia, and others may exhibit dysarthria with nasal speech. Eventually, cataracts may be observed by slit lamp examination in nearly all affected individuals. Cardiac conduction defects may occur. Rarely, this form will progress to the point of wheelchair confinement. Women with DM1 are at risk for complications during pregnancy.
- Congenital DM1: This form often presents before birth as polyhydramnios and reduced fetal movement. After delivery, main features include severe generalized weakness, hypotonia and respiratory compromise. Mortality from respiratory failure is high. A gradual increase in motor function may occur in surviving infants. As in the classic form, progressive myopathy may eventually occur. In 50–60% of affected individuals, mental retardation may be present.

DM2 is generally less heterogeneous in its presentation than DM1. The clinical course of DM2 is generally more favorable as compared to DM1 (Udd, et al., 2006). The onset of symptoms of DM2 is generally in the third decade. The most common symptoms are muscle weakness and pain, although there have been reports of myotonia in the first decade. Unlike DM1, which can present in adulthood or during infancy or childhood with variable severe congenital features, DM2 has not been reported to be associated with developmental abnormalities and severe childhood symptoms (Dalton, et al., 2006/2007). No congenital form has yet been described in the literature (Botta, et al., 2006).

DM2 should be suspected in individuals with the following clinical features (Dalton, et al., 2006/2007): muscle weakness, myotonia, posterior subcapsular cataracts that are detectable as nonspecific vacuoles and opacities on direct ophthalmoscopy or as pathognomonic posterior subcapsular red and green iridescent opacities on slit lamp examination, cardiac conduction defects or progressive cardiomyopathy, hypogammaglobulinemia, insulin

insensitivity that can appear clinically as impaired normalization of glucose on a glucose tolerance test despite normal or elevated serum insulin concentrations, and primary gonadal failure in males.

There is no specific treatment for the progressive weakness in individuals with myotonic dystrophy. Management may include consultation with a physiatrist, occupational therapy, or physical therapy for evaluation for orthoses and assistive devices. Electrocardiogram (ECG), Holter monitoring and an echocardiogram should be performed to evaluate syncope, palpitations and other symptoms of potential cardiac origin. When cardiac symptoms or ECG evidence of arrhythmia are present, consultation with a cardiologist is strongly recommended because fatal arrhythmias can occur prior to other symptoms.

The nonmolecular tests that were used in the past to establish the diagnosis of DM1 and DM2 currently play little role in diagnosis. To the extent that they are still used, they are primarily employed when molecular testing of either myotonic dystrophy protein kinase (DMPK) gene or the gene encoding zinc finger protein 9 (ZNF9), are normal and other myopathies are under consideration. These tests may include: electromyography (EMG), serum creatine kinase concentration, and muscle biopsy (Bird, 1999/2007; Dalton, et al., 2006/2007). Muscle biopsy cannot distinguish between the two types of myotonic dystrophy. The diagnosis of myotonic dystrophy is confirmed by molecular genetic testing. The DMPK gene is the only gene associated with DM1. ZNF9 is the only gene known to be associated with DM2. Both types of myotonic dystrophy are inherited in an autosomal dominant manner. Offspring of an individual with an expanded allele have a 50% chance of inheriting the mutant allele.

Molecular genetic testing detects mutations in nearly 100% of affected individuals with DM1 and is clinically available. Essentially, 100% of individuals with DM1 have an increased number (i.e., an expansion) of the cholesterol triglyceride trinucleotide repeat in the DMPK gene. Direct analysis of the cytosine-thymidine-guanine (CTG) repeat expansions is so sensitive and specific that the combination of southern blot and polymerase chain reaction (PCR) can detect all DM1 mutations without false-positives (International Myotonic Dystrophy Consortium [IDMC], 2000).

In 2000, allele sizes for DM1 were established by the second IDMC. Normal alleles contain 5–35 CTG repeats. Mutable normal alleles contain 35–49 CTG repeats. Individuals with CTG expansions in the permutation range have not been reported to have symptoms, but their children are at increased risk of inheriting a larger repeat size and thus having symptoms. Full penetrance alleles, which contain > 50 CTG repeats, are associated with disease manifestations. The number of CTG repeats does not reliably predict the age of onset, the rate of disease progression or the severity of symptoms for any individual patient. However, it has been noted that at-risk offspring may inherit repeat lengths considerably longer than those of the parent, which may result in occurrence of increasing disease severity and decreasing age of onset (Bird, 1999/2007). Genetic testing for DM1 is performed by PCR analysis and Southern blot analysis (Bird, 1999/2007).

The clinical uses of molecular genetic testing for DM1 and DM2 include the following (Dalton, et al., 2006/2007; Bird, 1999/2007):

- diagnostic testing
- predictive testing
- prenatal testing
- preimplantation genetic diagnosis (PGD)

Because diagnostic gene test results have direct implications for other family members (siblings and children), genetic counseling should be made available to the person who had the gene test and also to any other interested family members. In addition, individuals who have asymptomatic testing should always have genetic counseling with a qualified counselor to assure that the subject understands risks and benefits of testing (IDMC, 2000; Dalton, et al., 2006/2007).

Chromosomal microarray analysis (CMA), a method of genetic testing, has been proposed to be used in genetic testing including various forms of myotonia. CMA is an emerging method of genetic testing that is also referred to as array comparative genomic hybridization, array CGH, or aCGH. The testing method can identify small deletions and duplications of the subtelomeres, each pericentromeric region and other chromosome regions. CMA is an emerging method of genetic testing that is also referred to as array comparative genomic

hybridization, array CGH, or aCGH. The testing method can identify small deletions and duplications of the subtelomeres, each pericentromeric region and other chromosome regions. There is a lack of evidence in the medical literature that supports the use of this testing for these conditions. The clinical utility and the specific patients who are appropriate for CMA testing have not yet been determined. The use of this testing method in patients with DM1 and DM2 is still preliminary and is not yet recommended.

Prenatal Testing and Preimplantation Genetic Diagnosis (PGD)

The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy. Decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made before pregnancy (Bird, 1999/2007; Dalton, et al., 2006/2007). The overlapping ranges, as well as the uncertainty regarding somatic mosaicism and in utero instability of the expanded CTG repeat, make it impossible to predict accurately whether the fetus will have congenital or adult onset DM1 (Bird, 1999/2007). Although the prenatal diagnosis is based on direct detection of the mutation, analysis of DNA from both parents may be required to exclude maternal contamination in the fetal DNA sample and, in some cases, to verify the PCR results.

Preimplantation genetic diagnosis (PGD) refers to genetic testing of an early embryo resulting from in vitro fertilization. The testing is performed before implantation. PGD has recently been used as an alternative to prenatal testing with amniocentesis or chorionic villus sampling (CVS) techniques for detecting single gene disorders in embryos that have been identified as being at high risk for inheriting the gene disorder. PGD is available for families in which DM1 has been diagnosed in one of the parents.

Professional Societies/Organizations

The American College of Medical Genetics (ACMG) published technical standards and guidelines for myotonic dystrophy type 1 testing (Prior, 2009). The guidelines note that testing indications include: symptomatic confirmatory diagnostic testing and predictive testing, after the identification of the mutation in an affected family member. The testing may also be used for prenatal testing for at-risk pregnancies.

The International Myotonic Dystrophy Consortium (IDMC) established nomenclature and genetic testing guidelines for DM1. The IDMC guidelines note that as the correlation between expansion size and symptom severity is not absolute, it is not appropriate to offer a prediction of prognosis based on the expansion size. The testing guidelines include the following indications for genetic testing (IDMC, 2000):

- Confirmatory or symptomatic testing:
 - To confirm the clinical diagnosis: The gene test will increase the physician's confidence in diagnosing a patient with typical symptoms.
 - To clarify an uncertain clinical diagnosis: The gene test will be useful for individuals in whom DM1 is part of a wider differential diagnosis.
- Asymptomatic or preclinical testing:
 - To determine which relative of a proband has the DM1 gene mutation: This information is important in genetic counseling.
 - To modify the a priori risk of inheriting the DM1 allele
- Testing of minors:
 - Unless there is a medically compelling reason, minors (children under the legal age) should not be tested. This is to ensure that the person tested fully understands the risks and benefits of testing.
 - Exceptions might be appropriate in the case of a symptomatic minor for whom confirmatory testing is necessary and for prenatal testing.
 - If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk.
- Prenatal testing:
 - If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk.
 - If a parent is at 50% risk and asymptomatic, the best approach is a two-step process by which the at-risk parent is tested first and prenatal testing done subsequently (if still necessary).

Summary

Myotonic dystrophy types 1 (DM1) and 2 (DM2) are multisystem disorders that affects skeletal and smooth muscle as well as the eye, heart, endocrine system, and central nervous system. Molecular genetic testing for these conditions includes: confirmatory or diagnostic testing; predictive testing of asymptomatic relatives of the proband who are \geq age 18; and prenatal and preimplantation genetic diagnosis testing which, if a parent has already been diagnosed with DM1 or DM2, can be used to assess fetal risk.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

CPT[®]* Codes	Description
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892	Molecular diagnostics; enzymatic digestion
83894	Molecular diagnostics; separation by gel electrophoresis (eg, agarose, polyacrylamide)
83896	Molecular diagnostics; nucleic acid probe, each
83897	Molecular diagnostics; nucleic acid transfer (eg, Southern, Northern), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912	Molecular diagnostics; interpretation and report

HCPCS Codes	Description
S3853	Genetic testing for myotonic muscular dystrophy

ICD-9-CM Diagnosis Codes	Description
359.21	Myotonic muscular dystrophy
359.29	Other specified myotonic disorder
728.87	Muscle weakness, (generalized)
V17.89	Family history of, Other musculoskeletal diseases

Experimental/Investigational/Unproven/Not Covered:

ICD-9-CM Diagnosis Codes	Description
V82.6	Multiphasic screening
V82.71	Screening for genetic disease carrier status

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

References

1. Arsenault ME, Prevost C, Lescault A, Laberge C, Puymirat J, Mathieu J. Clinical characteristics of myotonic dystrophy type 1 patients with small CTG expansions. *Neurology*. 2006 Apr 25;66(8):1248-50.
2. Bick DP, Lau EC. Preimplantation genetic diagnosis. *Pediatr Clin North Am*. 2006 Aug;53(4):559-77.
3. Bird TD. Myotonic dystrophy type 1. Gene Reviews. Funded by the NIH. Developed at the University of Washington, Seattle. Initial posting: September 17, 1999. Last revision: November 15, 2007. Accessed September 16, 2010. Available at URL address: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=myotonic-d>
4. Botta A, Bonifazi E, Vallo L, Gennarelli M, Garrè C, Salehi L, et al. Italian guidelines for molecular analysis in myotonic dystrophies. *Acta Myol*. 2006 Jun;25(1):23-33.
5. Brunner H, Jansen G, Nillesen W, Nelen M, de Die C, Howeler C, et al. Brief report: reverse mutation in myotonic dystrophy. *N Engl J Med*. 1993 Feb 18;328(7):476-80.
6. Dalton JC, Ranum LPW, Day JW. Myotonic dystrophy type 2. Gene Reviews. Funded by the NIH. Developed at the University of Washington, Seattle. Initial Posting: September 21, 2006. Last Revision: April 23, 2007. Accessed September 16, 2010. Available at URL address: <http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=myotonic-d2>
7. Dean NL, Tan SL, Ao A. The development of preimplantation genetic diagnosis for myotonic dystrophy using multiplex fluorescent polymerase chain reaction and its clinical application. *Mol Hum Reprod*. 2001 Sep;7(9):895-901.
8. De Temmerman N, Sermon K, Seneca S, De Rycke M, Hilven P, Lissens W, et al. Intergenerational instability of the expanded CTG repeat in the DMPK gene: studies in human gametes and preimplantation embryos. *Am J Hum Genet*. 2004 Aug;75(2):325-9.
9. European Molecular Genetics Quality Network (EMQN). EMQN Best Practice Guidelines and Recommendations on Myotonic Dystrophy types 1 and 2. 3/9/2010. Accessed October 8, 2010. Available at URL address: <http://www.emqn.org/emqn/Best+Practice>
10. Fokstuen S, Myring J, Evans C, Harper PS. Presymptomatic testing in myotonic dystrophy: genetic counselling approaches. *J Med Genet*. 2001 Dec;38(12):846-50.
11. Genetics home reference. Myotonic dystrophy. Reviewed: November 2006; Published: October 12, 2007. Accessed September 16, 2010. Available at URL address: <http://ghr.nlm.nih.gov/condition=myotonicdystrophy>
12. International Myotonic Dystrophy Consortium (IDMC). New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). *Neurology*. 2000;54:1218–1221.
13. Krajewski KM, Shy ME. Genetic testing in neuromuscular disease. *Neurol Clin*. 2004 Aug;22(3):481-508, v.
14. Manning M, Hudgins L. Array-based technology and recommendations for utilization in medical genetics practice for detection of chromosomal abnormalities. ACMG practice guideline. 2010. Accessed September 16, 2010. Available at URL address: http://www.acmg.net/AM/Template.cfm?Section=Practice_Guidelines&Template=/CM/HTMLDisplay.cfm&ContentID=5760
15. Mathews KD. Muscular dystrophy overview: genetics and diagnosis. *Neurol Clin*. 2003 Nov;21(4):795-816.

16. Medvescek C. The pros and cons of genetic testing. The Muscular Dystrophy Association. QUEST. 2003 May/Jun;10(3). Accessed September 16, 2010. Available at URL address: <http://www.mda.org/publications/Quest/q103testing.html>
17. National Center for Biotechnology Information. Microarrays: chipping away at the mysteries of science and medicine. Revised: July 27, 2007. Accessed September 16, 2010. Available at URL address: <http://www.ncbi.nlm.nih.gov/About/primer/microarrays.html>
18. Muscular Dystrophy Association (MDA). Facts About Myotonic Muscular Dystrophy. August 2005; updated Dec 2009. Accessed September 16, 2010. Available at URL address: <http://www.mda.org/publications/fa-mmd-qa.html>
19. National Human Genome Research Institute. Learning About Myotonic Dystrophy. Last Reviewed: July 2010. Accessed September 16, 2010. Available at URL address: <http://www.genome.gov/25521207>
20. National Institute of Neurological Disorders and Stroke (NINDS). National Institutes of Health (NIH). Muscular Dystrophy: Hope through Research. Last updated August 24, 2010. Accessed September 16, 2010. Available at URL address: http://www.ninds.nih.gov/disorders/md/detail_md.htm
21. Prior TW; American College of Medical Genetics (ACMG) Laboratory Quality Assurance Committee. Technical standards and guidelines for myotonic dystrophy type 1 testing. Genet Med. 2009 Jul;11(7):552-5.
22. Redman J, Fenwick R, Fu Y, Pizzuti A, Caskey C. Relationships between parental trinucleotide GCT repeat length and severity of myotonic dystrophy in offspring. JAMA. 1993 Apr 21;269(15):1960-5.
23. Savic D, Rakocvic-Stojanovic V, Keckarevic D, Culjkovic B, Stojkovic O, Mladenovic J, et al. 250 CTG repeats in DMPK is a threshold for correlation of expansion size and age at onset of juvenile-adult DM1. Hum Mutat. 2002;19(2):131-139.
24. Shaffer LG, Beaudet AL, Brothman AR, Hirsch B, Levy B, Martin CL, et al.; Working Group of the Laboratory Quality Assurance Committee of the American College of Medical Genetics. Microarray analysis for constitutional cytogenetic abnormalities. Genet Med. 2007 Sep;9(9):654-62.
25. Smith CO, Bennett RL, Bird TD. Myotonic Dystrophy: Making an Informed Choice About Genetic Testing. University of Washington Medical Center. Funded by the National Institute on Disability and Rehabilitation Research, a division of the U. S. Department of Education. 2000 Aug.
26. Thornhill AR, Snow K. Molecular diagnostics in preimplantation genetic diagnosis. J Mol Diagn. 2002 Feb;4(1):11-29.
27. Udd B, Meola G, Krahe R, Thornton C, Ranum LP, Bassez G, et al. 140th ENMC International Workshop: Myotonic Dystrophy DM2/PROMM and other myotonic dystrophies with guidelines on management. Neuromuscul Disord. 2006 Jun;16(6):403-13. Epub 2006 May 8.

Policy History

Pre-Merger Organizations	Last Review Date	Policy Number	Title
CIGNA HealthCare	12/15/2007	0271	Genetic Testing for Myotonic Dystrophy Type 1

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.