Myotonic Dystrophy Type 1 Genetic Testing

Introduction
Myotonic Dystrophy type 1 (DM1) genetic testing is addressed by this guideline.

Procedures addressed
The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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<th>Procedures addressed by this guideline</th>
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What is Myotonic Dystrophy Type 1

Definition
Myotonic dystrophy type 1 (DM1) affects multiple body systems and is characterized by myotonia (prolonged muscle contraction), muscle weakness and wasting, and cataracts.¹

Incidence and Prevalence
DM1 affects approximately 1 in 20,000 people.¹ The condition is considered to be nearly 100% penetrant, meaning that essentially every person with an expanded repeat mutation will show some features of DM1.¹

Symptoms
DM1 can range from mild to severe and can be grouped into three overlapping categories:¹

- **Mild DM1**: The most mild myotonia with cataracts, but lifespan is typically normal.
- **Classic DM1**: More significant myotonia with physical disability in adulthood and possibly shortened lifespan. Heart conduction abnormalities are common, as well as cataracts, balding, and muscle weakness.
- Congenital DM1: The most severe form causes general weakness at birth, with respiratory insufficiency. Intellectual disability may be present and lifespan is shortened. Polyhydramnios and reduced fetal movement may be noted in pregnancy.

**Cause**

DM1 is caused by expansion of a CTG trinucleotide repeat in the myotonic dystrophy protein kinase (DMPK) gene. The number of CTG repeats that an individual has is reasonably correlated with the severity of their disease:

- 5-34 repeats: Normal range. Individuals do not have DM1.
- 35-49 repeats: Premutation range. Individuals have not been reported to have symptoms, but the repeats are thought to be unstable and can expand in future generations.
- 50-150 repeats: Mild DM1
- 100-1000 repeats: Classic DM1
- More than 1000 repeats: Congenital DM1

**Inheritance**

DM1 is an autosomal dominant condition. A person with an affected parent has a 50% risk to also be affected with DM1. The number of CTG repeats in the DMPK gene can expand from one generation to the next, a phenomenon called anticipation. Therefore, children and grandchildren of an affected individual have an increased risk for a more severe form of myotonic dystrophy and/or an earlier age of onset than their affected relatives. Anticipation can occur with maternal or paternal inheritance; however, it is more commonly seen when inherited from the mother.

**Diagnosis**

DM1 should be suspected in adults who present with the following:

- Muscle weakness (especially in leg, hands, neck, and face)
- Myotonia (for example, difficulty quickly releasing a gripped hand)
- Posterior subcapsular cataracts

DM1 should be suspected in newborns who present with the following:

- Hypotonia (low muscle tone)
- Weakness in facial muscles
- General muscle weakness
- Positional malformations
- Respiratory problems
If DM1 is suspected, confirmation can be obtained with molecular testing to detect CTG expansions in the DMPK gene. DMPK testing has greater than a 99% detection rate for those with DM1.

Predictive testing may be considered for at-risk relatives if there is a known mutation in DMPK previously identified in the family.\(^1,2\) Children at-risk for DM1 can present with conduction defects and arrhythmias at an early age, when other signs of myopathy may not be apparent. Confirming or ruling out a DM1 mutation guides cardiac screening and anticipatory management of other symptoms.\(^2\)

Non-molecular testing currently is not used for diagnostic purposes, but can be used if molecular testing finds no repeat expansions in DMPK and other neuromuscular disorders are being considered. Such non-molecular testing may include:\(^1,2\)

- Electromyography (EMG)
- Serum CK concentration
- Muscle biopsy

**Treatment**

No cure currently exists for DM1, so treatment is focused on managing the specific symptoms with which an individual presents. Physical and/or occupational therapy can help strengthen muscles and provide appropriate assistive devices. One may consult a cardiologist as well, if the individual presents with cardiac symptoms.\(^1\)

Screening and prevention strategies may include: \(^1,2\)

- Annual cardiac screening for conduction abnormalities and cardiac management
- Avoidance of specific medications, such as statins, that can increase weakness
- Identify risk for malignant hyperthermia with the use of anesthesia medications (uncommon complication)

**Survival**

Affected individuals are most likely to die from respiratory failure or cardiovascular problems. Larger CTG repeat expansions are correlated with both an earlier age of onset, and shorter expected lifespan.\(^1\)

- Mild DM1: 60 years – normal lifespan
- Classic DM1: 48 – 55 years
- Congenital DM1: 45 years
Test Information

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Testing for DM1 may include targeted analysis to detect repeat expansions in DMPK, characterization of repeat expansions in DMPK, or known familial mutation analysis.

Trinucleotide repeat expansion

Characterization of repeat lengths in DMPK are as follows:¹

- 5-34 CTG repeats: Normal range
- 35-49 CTG repeats: Premutation, meaning the individual is asymptomatic. However, his or her children are at an increased risk for presenting with symptoms
- 50 or more CTG repeats: Full-penetrance alleles, meaning the individual will show symptoms of this condition

Known familial mutation analysis

Known familial mutation analysis is performed when a causative mutation has been identified in a close relative of the individual requesting testing.

Analysis for known familial mutations is typically performed by trinucleotide repeat expansion analysis.

Guidelines and Evidence

Introduction

This section includes relevant guidelines and evidence pertaining to genetic testing for DM1.

European Federation of Neurological Societies (EFNS)

Guidelines from the European Federation of Neurological Societies (EFNS, 2011) address the molecular diagnosis of myotonic dystrophy and other neurogenetic disorders. They state:³

- "In patients with certain distinctive phenotypes, and a suggestive family history, a molecular diagnosis can be made without additional investigations, this includes a male patient with muscular dystrophy, whose uncle had a similar phenotype, a patient with the typical presentation of a myotonic dystrophy or of a facio-scapulohumeral dystrophy. In such cases, an analysis of the respective gene should be performed without a muscle biopsy (level B)."
European Molecular Genetics Quality Network (EMQN)

Guidelines established at the European Molecular Genetics Quality Network (EMQN) Best Practice Meeting in 2008 state the following:4

- “Muscle biopsies of patients with congenital DM1 may reveal only variability in fiber size and centralization of nuclei. However, none of the characteristics found in muscle biopsies of patients with classical or adult-onset DM1 myotonic dystrophy are present. Therefore, in order to confirm a clinical suspicion of congenital DM1, the diagnosis can only be established by DNA analysis.”

International Myotonic Dystrophy Consortium

Eighty-three myotonic dystrophy researchers gathered at the second International Myotonic Dystrophy Consortium (1999) meeting and produced the following consensus-based guidelines:5

- "Direct analysis of the CTG repeat expansion has sensitivity and specificity, such that the combination of Southern blot and polymerase chain reaction (PCR) can detect all DM1 mutations without false positives...The gene test will increase the physician’s confidence in diagnosing a patient with typical symptoms."
- "The gene test will be useful for individuals in whom DM1 is part of a wider differential diagnosis."
- "If a parent has already been diagnosed with DM1, prenatal testing can be used to assess fetal risk."

Myotonic Dystrophy Foundation (MDF)

Over 65 medical experts on myotonic dystrophy from the US, Canada, the UK, and Western Europe worked on a project organized by the Myotonic Dystrophy Foundation (MDF) from 2015-2017. The goal was to develop consensus-based recommendations, which included the following:6

- “DM1 via molecular genetic testing as the first line of investigation for any patient suspected of having DM1. Muscle biopsy should no longer be performed as a diagnostic test when there is clear clinical suspicion of DM1. Patients with more than 50 CTG repeats in the 3’ untranslated region of the DMPK gene on chromosome 19 are considered to have DM1.”

Consensus-based recommendations were also developed for children (MDF, 2019) and included the following:7

- “If DM1 is suspected clinically, a definitive diagnosis can be made via a genetic test. A family history and a single symptom or sign consistent with DM1 should prompt genetic testing... Arriving at a definite genetic diagnosis of DM1 in children and adolescents is very important in managing the presenting problem and to ensure proper monitoring and precautionary measures.”
Criteria
Introduction
Requests for DM1 testing are reviewed using these criteria.

Known familial mutation analysis

- Genetic Counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous DMPK gene analysis performed that would have identified the known familial mutation, AND
- Presymptomatic Testing for Asymptomatic Individuals:
  - 18 years of age or older, and
  - Known disease-causing mutation in DMPK gene identified in 1st degree relative(s), OR
- Diagnostic Testing for Symptomatic Individuals:
  - Known disease-causing mutation in DMPK gene identified in 1st degree relative(s), AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

DMPK repeat analysis

- Genetic counseling:
  - Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - No previous repeat analysis of DMPK performed, AND
- Individual has a clinical suspicion of myotonic dystrophy type 1 based on the following:
  - Infant with one or more of the following without a known etiology:
    - Hypotonia
    - Weakness in facial muscles (e.g. ptosis, eyelid closure, weak smile, inverted upper lip, thin face, dull facial expression)
    - General muscle weakness
    - Positional malformations
\begin{itemize}
  \item Respiratory problems, or
    \begin{itemize}
      \item Individual with one or more of the following without a known etiology:
        \begin{itemize}
          \item Muscle weakness (especially in leg, hands, neck, and face)
          \item Weakness in facial muscles (e.g. ptosis, eyelid closure, weak smile, inverted upper lip, thin face, dull facial expression)
          \item Myotonia (for example, difficulty quickly releasing a gripped hand), AND
        \end{itemize}
    \end{itemize}
  \item Family history is consistent with autosomal dominant inheritance (including simplex cases), AND
  \item Rendering laboratory is a qualified provider of service per the Health Plan policy
\end{itemize}

References

Introduction

These references are cited in this guideline.


6. The Myotonic Dystrophy Foundation. Consensus-based Care Recommendations for Adults with Myotonic Dystrophy Type I (Published September 25, 2018). Available at: https://www.myotonic.org/mdf-releases-dm1-care-recommendations