Charcot-Marie-Tooth Neuropathy Testing

Introduction

Testing for Charcot-Marie-Tooth disease 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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### Procedures addressed by this guideline

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### What is Charcot-Marie-Tooth Hereditary Neuropathy

#### Definition

Charcot-Marie-Tooth Hereditary Neuropathy (CMT) is a group of inherited genetic conditions characterized by chronic motor and sensory polyneuropathy. The key finding in CMT is symmetric, slowly progressive distal motor neuropathy of the arms and legs, usually beginning in the first to third decade and resulting in weakness and atrophy of the muscles in the feet and/or hands. This is expressed as distal muscle weakness and atrophy, weak ankle dorsiflexion, depressed tendon reflexes, and pes cavus foot deformity (i.e. high arched feet).

#### Diagnosis

The clinical diagnosis of CMT in a symptomatic person is based on characteristic findings of peripheral neuropathy on medical history and physical examination. CMT needs to be distinguished from the following entities: systemic disorders with neuropathy, other types of hereditary neuropathy, distal myopathies, hereditary sensory neuropathies (HSN), and acquired disorders.

Molecular genetic testing can be used to establish a specific diagnosis, which aids in understanding the prognosis and risk assessment for family members.
Prevalence

CMT is the most common inherited neurological disorder. The prevalence of all CMT types is 1 in 2,500.\(^1\)

Types and subtypes

As more genes causing CMT were identified and as the overlap of neuropathy phenotypes and modes of inheritance became apparent, the previous alphanumeric classification system proved unwieldy and inadequate. In 2018, Magy et al proposed a gene-based classification of inherited neuropathies, which includes a comprehensive list of CMT-associated genes and correlation with the alphanumeric classification.\(^5\) An additional advantage of this classification system is that a patient's findings can be described in terms of mode of inheritance, neuropathy type, and gene.

More than 80 different genes are associated with CMT and establishing a specific genetic cause of CMT hereditary neuropathy can aid in discussions of prognosis.\(^1\)

Inheritance

CMT can be inherited in an autosomal dominant, autosomal recessive, or an X-linked manner.\(^1\)

Test information

Introduction

Testing for CMT may include gene sequencing, deletion/duplication analysis, or panel testing.

Genetic testing

There are various methods used to test for mutations in genes which can cause CMT neuropathy.

- Single gene analysis
- Deletion/duplication analysis, particularly for the 1.5-Mb duplication at 17p11.2 that includes PMP22
- Panel testing using next-generation sequencing (NGS)
CMT panel testing

CMT multi-gene panels include a wide variety of genes associated with CMT neuropathy. Multi-gene panels may also include genes believed to be associated with CMT neuropathy but with a lower impact on risk than recognized syndromes. Results for such genes are of less clear value because there often are not clear management recommendations for mutation-positive individuals.

Under certain circumstances, technologies used in multi-gene testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multi-gene test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted.

Multi-gene tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

Since genes can be easily added or removed from multi-gene tests over time by a given lab, medical records must document which genes were included in the specific multi-gene test used from each patient, and in which labs they were performed.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to CMT testing.

American Academy of Neurology

Evidence-based guidelines from the American Academy of Neurology (2009; reaffirmed in 2013) recommend testing for CMT, but with a tiered approach:

- “Genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies.”
  - This is considered a level A recommendation which is defined as “established as effective, ineffective or harmful (or established as useful/predictive or not useful/predictive) for the given condition in the specified population.”

- “Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype. Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 mutation screening.”
  - This is considered a level C recommendation which is defined as “possibly effective, ineffective or harmful (or possibly useful/predictive or not useful/predictive) for the given condition in the specified population.”
• “There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype.”
  
  o This is considered a level U recommendation which is defined as “data inadequate or conflicting; given current knowledge, treatment (test, predictor) is unproven.”

Peer Reviewed Literature

DiVincenzo et al. [2014] described their experience testing more than 17,000 patients for CMT using a commercially available comprehensive panel of 14 genes. Overall, they identified a mutation in 18.5% of patients. Notably they state that “Among patients with a positive genetic finding in a CMT-related gene, 94.9% were positive in one of four genes (PMP22, GJB1, MPZ, or MFN2). The results of our study in a population in over 17,000 individuals support the initial genetic testing of four genes (PMP22, GJB1, MPZ, and MFN2) followed by an evaluation of rarer genetic causes in the diagnostic evaluation of CMT.”

Dohrne et al. [2017] examined over 600 patients with either a CMT phenotype, hereditary sensory neuropathy, familial amyloid neuropathy, or small fiber neuropathy using a NGS multigene panel. At least one putative pathogenic mutation was identified in 121 cases (19.8%), with the most frequently affected genes PMP22, GJB1, MPZ, SH3TC2, and MFN2. Likely or known pathogenic variants in HINT1, HSPB1, NEFL, PRX, IGHHBP2, NDRG1, TTR, EGR2, FIG4, GDAP1, LMNA, LRSAM1, POLG, TRPV4, AARS, BIC2, DHTKD1, FGD4, HK1, INF2, KIF5A, PDK3, REEP1, SBF1, SBF2, SCN9A, and SPTLC2 were detected with a declining frequency. One pathogenic variant in MPZ was identified after being previously missed by Sanger sequencing. The authors conclude that panel-based NGS “is a useful, time- and cost-effective approach to assist clinicians in identifying the correct diagnosis and enable causative treatment considerations”.

Bacquet et al [2018] compared the diagnostic yield of targeted NGS with their previous step-wise Sanger sequencing strategy. A cohort of 123 unrelated patients affected with diverse forms of inherited peripheral neuropathies including CMT (23% CMT1, 52% CMT2), distal hereditary motor neuropathy (9%), hereditary sensory and autonomic neuropathy (7%), and intermediate CMT (6.5%) were evaluated using an 81-gene NGS panel. Pathogenic variants were identified in 49 of 123 patients (~40%). In this cohort, the most frequently mutated genes were: MFN2, SH3TC2, GDAP1, NEFL, GAN, KIF5A and AARS, respectively. “Panel-based NGS was more efficient in familial cases than in sporadic cases (diagnostic yield 49% vs 19%, respectively). NGS-based search for copy number variations, allowed the identification of three duplications in three patients and raised the diagnostic yield to 41%. This yield is two times higher than the one obtained previously by gene Sanger sequencing screening. The impact of panel-based NGS screening is particularly important for demyelinating CMT (CMT1) subtypes, for which the success rate reached 87% (36% only for axonal CMT2).” While NGS panels were able to identify causal variants in a shorter and more cost-effective time, the authors caution that this...
approach, “leads to the identification of numerous variants of unknown significance, which interpretation requires interdisciplinary collaborations between molecular geneticists, clinicians and (neuro) pathologists.”

**Expert-authored review**

In an expert-authored review, the following step-wise genetic testing strategy is recommended:

- **Step 1:** “Single-gene testing for PMP22 duplication/deletion is recommended as the first test in all probands with CMT. PMP22 duplication (a 1.5-Mb duplication at 17p11.2 that includes PMP22) accounts for as much as 50% of all CMT.”

- **Step 2:** “A multigene panel that includes the seven most commonly involved genes (i.e., GDAP1, GJB1, HINT1, MFN2, MPZ, PMP22, and SH3CT2) as well as some or all of the other CMT-associated genes is most likely to identify the genetic cause of the neuropathy at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype.”

- **Step 3:** “Comprehensive genomic testing - which does not require the clinician to determine which gene(s) are likely involved – may be considered if a genetic cause has not been identified in Step 1 and Step 2. Exome sequencing is most commonly used; genome sequencing is also possible. Exome array (when clinically available) may be considered if exome sequencing is nondiagnostic.”

- “Given the complexity of the genetics of CMT, health care providers should consider referring at-risk relatives to a neurogenetics center or genetic counselor specializing in neurogenetics.”

- “For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.”

**Comprehensive CMT panels**

Comprehensive CMT panels test most known genes related to CMT simultaneously, but this is not usually necessary or cost-effective, and therefore not recommended as first line tests."
Criteria

Introduction

Requests for CMT testing are reviewed using these criteria.

Known Familial Mutation Analysis

- Previous Genetic Testing:
  - No previous genetic testing for the familial mutation, and
  - Pathogenic CMT-related mutation in a 1st or 2nd degree biologic relative, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), or
  - Electrodiagnostic studies consistent with a peripheral neuropathy

PMP22 Deletion/Duplication Analysis

- Previous Genetic Testing:
  - No previous PMP22 deletion/duplication analysis, and
  - No known CMT-related mutation in the member's family, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), AND

- The member does not have a known underlying cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy, known mutation), AND

- Member’s electrodiagnostic studies are consistent with a primary demyelinating neuropathy
CMT Neuropathy Multigene Panel

When a multi-gene panel is being requested and will be billed with the appropriate CPT panel code, 81448, the panel will be considered medically necessary when the following criteria are met:

- Previous Genetic Testing:
  - No previous CMT neuropathy multi-gene panel testing, and
  - No known CMT-related mutation in the member’s family, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Distal muscle weakness and atrophy, or
  - Weak ankle dorsiflexion (e.g. foot drop), or
  - Distal sensory loss, or
  - Depressed or absent tendon reflexes, or
  - Foot deformity (e.g. high arches, hammer toes, pes cavus), AND

- The member does not have a known underlying cause for their neuropathy (e.g. diabetic neuropathy, vitamin B12 deficiency, chronic inflammatory demyelinating polyneuropathy, known mutation), AND

- The panel includes the genes with the highest diagnostic yield for the member’s suspected CMT neuropathy subtype, AND

- Member’s electrodiagnostic studies are consistent with an axonal neuropathy or combined axonal and demyelinating neuropathy (e.g., CMT1 is NOT the most likely diagnosis), OR

- Member’s electrodiagnostic studies are consistent with a primary demyelinating neuropathy (e.g., CMT1 is the most likely diagnosis) and PMP22 deletion/duplication analysis was previously performed and was negative

Billing and reimbursement considerations

- When separate procedure codes will be billed for individual CMT-related genes (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), the entire panel will be approved if the above criteria are met. However, the laboratory will be redirected to the use of an appropriate panel CPT code, 81448, for billing purposes.

- The billed amount should not exceed the list price of the test.

- Broad CMT neuropathy panels may not be medically necessary when a narrower panel is available and more appropriate based on the clinical findings.
• Genetic testing is only necessary once per lifetime. Therefore, a single gene included in a panel or a multi-gene panel may not be reimbursed if testing has been performed previously. Exceptions may be considered if technical advances in testing demonstrate significant advantages that would support a medical need to retest.

• If a panel was previously performed and an updated, larger panel is being requested, only testing for the medically necessary, previously untested genes will be reimbursable. Therefore, only the most appropriate procedure codes for those additional genes will be considered for reimbursement.

• If the laboratory will not accept redirection to 81448 due to their panel not sequencing at least 5 genes, the medical necessity of each billed component procedure will be assessed independently.
  
  o In general, only a limited number of panel components that are most likely to explain the member’s presentation will be reimbursable. The remaining individual components will not be reimbursable.
  
  o When the test is billed with multiple stacked codes, only sequencing of the following genes may be considered for reimbursement, based on electrodiagnostic findings and the family history:

    ▪ Primary demyelinating neuropathy with negative PMP22 deletion/duplication analysis (CMT1 suspected): MPZ, PMP22, LITAF (SIMPLE) and EGR2.
    
    ▪ Primary axonal neuropathy (CMT2 suspected): MFN2, MPZ and HSPB1 (HSP27). If there is no evidence of male-to-male transmission in the family, GJB1 (for CMTX) is also reimbursable.
    
    ▪ Combined axonal and demyelinating neuropathy (intermediate CMT suspected): DNM2, YARS, MPZ, and GNB4.

**Benefit exclusion**

**Exclusions and other considerations**

Testing unaffected individuals (e.g. carrier testing, predictive testing, presymptomatic testing, etc) is a BCBSAZ benefit exclusion and, therefore, not eligible for reimbursement.

**References**

**Introduction**

These references are cited in this guideline.


