

**LETTER OF MEDICAL NECESSITY**

**CMT Advanced Evaluation – Comprehensive**

**Instructions for Healthcare Provider:**

1. This letter template is being provided as a tool for clinicians to assist communication with payers.
2. Include specific patient information in the letter for this tool to be effective. The areas that must be edited/deleted are indicated in grey on the template
3. Print the template on the physician’s letterhead, **NOT** Athena letterhead. There should be no Athena branding on the letter.

[LMN: Charcot-Marie-Tooth (CMT) Advanced Evaluation – Comprehensive (03.04.22)]

<Date>

ATTN: <Medical Director/ Physician Name>, MD

 <Institution/Insurance Company>

  <Street Address>

 <City>**,** <State> <Zip>

RE: <Patient Name>

DOB: <MM/DD/YYYY>

Member ID: <Insurance ID Number>

Group #: <Enter Group #>

Dear Doctor <Medical Director/ Physician Name>:

I am writing this letter on behalf of my patient <Patient Name> to request coverage for the CMT Advanced Evaluation – Comprehensive, a genetic test with a 2-step approach for obtaining a molecular diagnosis for Charcot-Marie-Tooth disease (CMT). The test begins by evaluating *PMP22* duplication or deletion, as *PMP22* duplication is the most common cause of CMT.[1](#_ENREF_1) If results are negative, then testing is performed for deletions in *GJB1*, and next-generation sequencing (NGS) is performed to detect variants in 23 genes. This letter documents the medical necessity for CMT Advanced Evaluation – Comprehensive in light of my patient’s medical history. Results from the test will be used to guide appropriate medical care management for the patient.

I have determined that this test is medically necessary because of the following aspects of this patient’s history:

<Patient name> is a <age>-year-old <gender> with a suspected diagnosis of Charcot-Marie-Tooth disease. Symptoms and clinical findings are consistent with this diagnosis.

1. <Symptom #1 with ICD-10 code>

2. <Symptom #2 with ICD-10 code>

<Consider indicating symptoms that support diagnosis, such as distal limb weakness and results from peripheral nerve ultrasound. Consider indicating whether any electrodiagnostic studies were performed, and whether results were informative.>

<Consider adding any relevant family history (or lack thereof) or other personal history, such as information on disease onset and progression.>

**Rationale for Testing**

Charcot-Marie-Tooth disease (CMT) is the most common inherited peripheral neuropathy, affecting approximately 1 in 2,500 individuals.[1](#_ENREF_1) CMT comprises motor and sensory polyneuropathies that are predominantly caused by peripheral nerve demyelination or axonal degradation.[1](#_ENREF_1) The mode of inheritance can be autosomal dominant (ie, 1 copy of a pathogenic variant causes disease), autosomal recessive (2 copies of a pathogenic variant are required to cause disease), or X-linked (lack of male-to-male transmission).[1](#_ENREF_1) Together, neurophysiology and the mode of inheritance broadly classify CMT into types (eg, CMT1 for autosomal dominant demyelinating CMT). Each of these classifications contains subtypes defined by a variant in a particular gene; consequently, genetic testing is required to obtain a definitive molecular diagnosis that accurately classifies the patient’s specific CMT subtype.[1-3](#_ENREF_1)

The diagnosis and classification of CMT is traditionally performed using clinical evaluation of phenotype, determination of family history, neurophysiology (eg, nerve conduction) studies, and nerve biopsy.[4](#_ENREF_4) However, several factors can lead to an inaccurate diagnosis. Different genetic mutations can cause a similar phenotype, or a genotype may cause different phenotypes.[5](#_ENREF_5) Also, family history may be lacking or unclear, and the clinical phenotypes of family members may vary.[4](#_ENREF_4),[5](#_ENREF_5) Lastly, nerve conduction studies may be affected by factors such as age, duration of disease, and the severity of symptoms.[4](#_ENREF_4) For reasons such as these, a joint Practice Parameter by the American Academy of Neurology (AAN), American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), and American Academy of Physical Medicine and Rehabilitation (AAPMR) recommends genetic testing for the accurate diagnosis and classification of hereditary neuropathies.[5](#_ENREF_5)

The AAN/AANEM/AAPMR also recommend that traditional clinical evaluation be used to guide the genetic testing profile to achieve the highest yield,[5](#_ENREF_5) although any of the aforementioned factors can prove problematic when attempting to select the appropriate genes for testing. There are multigene panels that test for a limited number of genes based on traditional evaluation, but a comprehensive multigene panel, such as the CMT Advanced Evaluation – Comprehensive, may be especially useful for patients who lack informative electrodiagnostic testing and/or family history. Comprehensive multigene panels that simultaneously assess multiple candidate genes using NGS technology have been increasingly adopted by physicians as the preferred method for genetic diagnosis in patients with CMT.[6](#_ENREF_6) NGS provides a lower-cost and high-throughput platform compared with traditional genetic analysis using Sanger sequencing.[7](#_ENREF_7) Comprehensive (52- to 81-gene) multigene panels have been shown to approximately double the diagnostic yield, ranging from 27% to 40%, when compared with 12% to 23% using traditional Sanger sequencing in patients with hereditary peripheral neuropathies.[8](#_ENREF_8),[9](#_ENREF_9)

Although the AAN/AANEM/AAPMR recommend selective gene testing based on traditional clinical evaluation,[5](#_ENREF_5) other diagnostic algorithms have been used or proposed that involve analysis for either single, select (notably, *PMP22* duplications/deletions, *GJB1*, *MPZ*, and *MFN2*), or numerous gene variants, with varying approaches on panel size and sequence of testing.[4](#_ENREF_4),[6](#_ENREF_6),[10-14](#_ENREF_10) An advantage of initial analysis with a comprehensive multigene NGS panel is the simplification of the diagnostic algorithm, which results in improved decision-making processes in neuropathy care.[4](#_ENREF_4) For example, use of these panels avoids the additional time involved in sequential and/or repeat testing.[12](#_ENREF_12),[15](#_ENREF_15) Also, since an estimated 20% of all CMT patients have negative or unknown family history, there is a substantial need for genetic tests that can effectively diagnose apparently sporadic cases of CMT.[1](#_ENREF_1) Studies have shown that a molecular diagnosis can be achieved in 19% to 22% of sporadic CMT cases using comprehensive multigene panels.[9](#_ENREF_9),[16](#_ENREF_16)

Comprehensive multigene panels are also advantageous in their abilities to prevent misdiagnoses. One example is the misdiagnosis of CMT as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), which can occur in cases of inherited neuropathies with atypical features or unknown family history.[2](#_ENREF_2),[17](#_ENREF_17) One study identified 3.2% of patients initially diagnosed with CIDP as having CMT based on genetic analysis of *PMP22* and either a 76-gene or 127-gene NGS panel in *PLP22*-negative patients.[18](#_ENREF_18) CMT patients with an incorrect diagnosis for an inflammatory neuropathy, such as CIDP, are often unresponsive to their prescribed immunosuppressive therapy, resulting in healthcare waste.[2](#_ENREF_2)

The ability of comprehensive multigene panels to provide a definitive diagnosis is valuable for informing a patient’s prognosis and clinical management. Genetic testing informs prognosis because clinical presentation varies across subtypes of CMT. For example, CMT1D, caused by variants in *EGR2,* is characterized by a severe phenotype involving cranial neuropathy, in contrast to the more moderate phenotype typical of CMT1A (caused by *PMP22* duplication or variant).[3](#_ENREF_3) While there is currently no treatment for CMT that alters the disease course, an individual’s symptoms guide the consideration of supportive treatments (eg, ankle foot orthoses and other assistive devices) and surgical interventions.[12](#_ENREF_12) Thus, knowledge of the patient’s expected clinical presentation may facilitate coordination of care.

In summary, genetic testing is required to obtain a definitive molecular diagnosis that accurately classifies the patient’s specific CMT subtype. The CMT Advanced Evaluation – Comprehensive panel demonstrates clinical utility by simplifying and improving the diagnosis of CMT subtype, thereby informing the most appropriate clinical management for my patient. Therefore, I am requesting that <Patient Name> be approved for the CMT Advanced Evaluation – Comprehensive test (Test Code 4001; CPT codes 81324(1) [without reflex], 81448(1) [with reflex]) offered by Athena Diagnostics®.

I hope you will support this letter of medical necessity for <Patient Name>. Please feel free to contact me at <Physician Phone> if you have additional questions.

Sincerely,

<Physician Name>, MD

NPI #: <Physician NPI#>

Contact information:

< Address>

<City>**,** <State>, <Zip>

Contact Phone No.: <phone number>

The CPT codes provided are based on AMA guidelines and are for informational purposes only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

**References**

**1.** Gutmann L, Shy M. Update on Charcot-Marie-Tooth disease. *Curr Opin Neurol*. 2015;28(5):462-467. doi:10.1097/WCO.0000000000000237

**2.** Rossor AM, Polke JM, Houlden H, et al. Clinical implications of genetic advances in Charcot-Marie-Tooth disease. *Nat Rev Neurol*. 2013;9(10):562-571. doi:10.1038/nrneurol.2013.179

**3.** Bassam BA. Charcot-Marie-Tooth disease variants-classification, clinical, and genetic features and rational diagnostic evaluation. *J Clin Neuromuscul Dis*. 2014;15(3):117-128. doi:10.1097/cnd.0000000000000020

**4.** Klein CJ. Charcot-Marie-Tooth Disease and Other Hereditary Neuropathies. *Continuum (Minneap Minn)*. 2020;26(5):1224-1256. doi:10.1212/con.0000000000000927

**5.** England JD, Gronseth GS, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2009;72(2):185-192. doi:10.1212/01.wnl.0000336370.51010.a1

**6.** Pipis M, Rossor AM, Laura M, et al. Next-generation sequencing in Charcot-Marie-Tooth disease: opportunities and challenges. *Nat Rev Neurol*. 2019;15(11):644-656. doi:10.1038/s41582-019-0254-5

**7.** Sun H, Shen XR, Fang ZB, et al. Next-generation sequencing technologies and neurogenetic diseases. *Life (Basel)*. 2021;11:1-17. doi:10.3390/life11040361

**8.** Høyer H, Busk Ø L, Holla Ø L, et al. Hereditary peripheral neuropathies diagnosed by next-generation sequencing. *Tidsskr Nor Laegeforen*. 2015;135(20):1838-1844. doi:10.4045/tidsskr.14.1002

**9.** Bacquet J, Stojkovic T, Boyer A, et al. Molecular diagnosis of inherited peripheral neuropathies by targeted next-generation sequencing: molecular spectrum delineation. *BMJ Open*. 2018;8:e021632. doi:10.1136/bmjopen-2018-021632

**10.** Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *J Neurol Neurosurg Psychiatry*. 2012;83(7):706-710. doi:10.1136/jnnp-2012-302451

**11.** Østern R, Fagerheim T, Hjellnes H, et al. Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies. *BMC Med Genet*. 2013;14:94. doi:10.1186/1471-2350-14-94

**12.** Hoyle JC, Isfort MC, Roggenbuck J, et al. The genetics of Charcot-Marie-Tooth disease: current trends and future implications for diagnosis and management. *Appl Clin Genet*. 2015;8:235-243. doi:10.2147/tacg.S69969

**13.** Nam SH, Hong YB, Hyun YS, et al. Identification of genetic causes of inherited peripheral neuropathies by targeted gene panel sequencing. *Mol Cells*. 2016;39(5):382-388. doi:10.14348/molcells.2016.2288

**14.** Rudnik-Schöneborn S, Tölle D, Senderek J, et al. Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. *Clin Genet*. 2016;89(1):34-43. doi:10.1111/cge.12594

**15.** Høyer H, Braathen GJ, Busk Ø L, et al. Genetic diagnosis of Charcot-Marie-Tooth disease in a population by next-generation sequencing. *Biomed Res Int*. 2014;2014:210401. doi:10.1155/2014/210401

**16.** Yoshimura A, Yuan JH, Hashiguchi A, et al. Genetic profile and onset features of 1005 patients with Charcot-Marie-Tooth disease in Japan. *J Neurol Neurosurg Psychiatry*. 2019;90(2):195-202. doi:10.1136/jnnp-2018-318839

**17.** Campagnolo M, Taioli F, Cacciavillani M, et al. Sporadic hereditary neuropathies misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: pitfalls and red flags. *J Peripher Nerv Syst*. 2020;25(1):19-26. doi:10.1111/jns.12362

**18.** Hauw F, Fargeot G, Adams D, et al. Charcot-Marie-Tooth disease misdiagnosed as chronic inflammatory demyelinating polyradiculoneuropathy: an international multicentric retrospective study. *Eur J Neurol*. 2021;28(9):2846-2854. doi:10.1111/ene.14950