BlueCross BlueShield Federal Employee Program.

# FEP Medical Policy Manual

## FEP 2.04.89 Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

### Annual Effective Policy Date: April 1, 2024

### Original Policy Date: April 2018

### Related Policies:

None

# Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

## Description

## Description - Intro

The inherited peripheral neuropathies are a heterogeneous group of diseases that may be inherited in an autosomal dominant, autosomal recessive, or X-linked dominant manner. These diseases can generally be diagnosed based on clinical presentation, nerve conduction studies, and family history. Genetic testing has been used to diagnose specific inherited peripheral neuropathies.

Peripheral neuropathies can be subdivided into 2 major categories: primary axonopathies and primary myelinopathies, depending on which portion of the nerve fiber is affected. The further anatomic classification includes fiber type (eg, motor vs. sensory, large vs. small) and gross distribution of the nerves affected (eg, symmetry, length-dependency).

Inherited peripheral neuropathies are divided into hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies (HNPP), and other miscellaneous, rare types (eg, hereditary brachial plexopathy, hereditary sensory, autonomic neuropathies). Other hereditary metabolic disorders, such as Friedreich ataxia, Refsum disease, and Krabbe disease, may be associated with motor and/or sensory neuropathies but typically have other predominating symptoms. This evidence review focuses on hereditary motor and sensory neuropathies and HNPP.

A genetic etiology of peripheral neuropathy is typically suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course.[2,] A family history of at least 3 generations with details on health issues, the cause of death, and age at death should be collected.

# Charcot-Marie-Tooth Disease

## Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure.[3,] CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with inherited neuropathies.[4,]Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and inheritance patterns. A 2016 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the 5 most commonly represented subtypes.[5,]

CMT subtypes are characterized by variants in 1 of several myelin genes, which lead to abnormalities in myelin structure, function, or upkeep. There are 7 subtypes of CMT, with type 1 and 2 representing the most common hereditary peripheral neuropathies.

Most cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. Most cases are CMT type 1 (approximately 40% to 50% of all CMT cases, with 78% to 80% of those due to *PMP22* variants).[6,] CMT type 2 is associated with 10% to 15% of CMT cases, with 20% of those due to *MFN2* variants.

A summary of the molecular genetics of CMT is outlined in Table 1.

### Table 1. Molecular Genetics of CMT Variants

| Locus | Gene | Protein Product | Prevalence (if known) |
|---|---|---|---|
| CMT type 1 | | | |
| CMT1A | *PMP22* | Peripheral myelin protein 22 | 50% of CMT1 |
| CMT1B | *MPZ* | Myelin P0 protein | 25% of CMT1 |
| CMT1C | *LITAF* | Lipopolysaccharide-induced tumor necrosis factor-a factor | |
| CMT1D | *EGR2* | Early growth response protein 2 | |
| CMT1E | *PMP22* | Peripheral myelin protein 22 (sequence changes) | |
| CMT1F/2E | *NEFL* | Neurofilament light polypeptide | |
| CMT1G | *PMP2* | Peripheral myelin protein 2 | |
| CMT type 2 | | | |
| CMT2A1 | *KIF1B* | Kinesin-like protein KIF1B | |
| CMT2A2A/B | *MFN2* | Mitofusin-2 | |
| CMT2B | *RAB7A* | Ras-related protein Rab-7 | |
| CMT2B1 | *LMNA* | Lamin A/C | |
| CMT2B2 | *PNKP* | | |
| CMT2C | *TRPV4* | Transient receptor potential cation channel subfamily V member 4 | |
| CMT2D | *GARS1* | Glycyl-tRNA synthetase | |
| CMT2F | *HSPB1* | Heat-shock protein beta-1 | |
| CMT2G | *LRSAM1* | E3 ubiquitin-protein ligase LRSAM1 | |

| Locus | Gene | Protein Product | Prevalence (if known) |
|---|---|---|---|
| CMT2H/2K | *GDAP1* | Ganglioside-induced differentiation-associated protein 1 | |
| CMT2I/ J | *MPZ* | Myelin P0 protein | |
| CMT2L | *HSPB8* | Heat-shock protein beta-8 | |
| CMT2M | *DNM2* | Dynamin 2 | |
| CMT2N | *AARS1* | Alanyl-tRNA synthetase, cytoplasmic | |
| CMT2O | *DYNC1H1* | Cytoplasmic dynein 1 heavy chain 1 | |
| CMT2P | *LRSAM1* | E3 ubiquitin-protein ligase LRSAM1 | |
| CMT2Q | *DHTKD1* | Dehydrogenase E1 And Transketolase Domain Containing 1 | |
| CMT2R | *TRIM2* | Tripartite Motif Containing 2 | |
| CMT2S | *IGHMBP2* | DNA-binding protein SMUBP-2 | |
| CMT2T | *MME* | Membrane Metalloendopeptidase | |
| CMT2U | *MARS1* | Methionine-tRNA ligase, cytoplasmic | |
| CMT2V | *NAGLU* | N-Acetyl-Alpha-Glucosaminidase | |
| CMT2W | *HARS1* | Histidyl-TRNA Synthetase 1 | |
| CMT2X | *SPG11* | Spastic paraplegia 11 | |
| CMT2Y | *VCP* | Valosin Containing Protein | |
| CMT2Z | *MORC2* | Microrchidia Family CW-Type Zinc Finger 2 | |
| CMT type 4 | | | |
| CMT4A | *GDAP1* | Ganglioside-induced differentiation-associated protein 1 | |
| CMT4B1 | *MTMR2* | Myotubularin-related protein 2 | |
| CMT4B2 | *SBF2* | Myotubularin-related protein 13 | |
| CMT4B3 | *SBF1* | SET Binding Factor 1 | |
| CMT4C | *SH3TC2* | SH3 domain and tetratricopeptide repeats-containing protein 2 | |
| CMT4D | *NDRG1* | Protein NDRG1 | |
| CMT4E | *EGR2* | Early growth response protein 2 | |
| CMT4F | *PRX* | Periaxin | |
| CMT4H | *FGD4* | FYVE, RhoGEF, and PH domain-containing protein 4 | |
| CMT4J | *FIG4* | Phosphatidylinositol 3, 5-biphosphate | |
| X-linked CMT | | | |
| CMTX3 | *Xq26* | Unknown | |
| CMTX4 | *AIFM1* | Apoptosis-inducing factor 1 | |
| CMTX5 | *PRPS1* | Ribose-phosphate pyrophosphokinase 1 | |

| Locus | Gene | Protein Product | Prevalence (if known) |
|---|---|---|---|
| CMTX6 | *PDK3* | Pyruvate dehydrogenase kinase isoform 3 | |

Adapted from Bird (2022).[6,]
CMT: Charcot-Marie-Tooth.

## CMT Type 1

CMT1 is an autosomal dominant, demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity, bilateral foot drop, and palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve. Affected people usually become symptomatic between ages 5 and 25 years, and their lifespan is not shortened. Less than 5% of people become wheelchair-dependent. CMT1 is inherited in an autosomal dominant manner. The CMT1 subtypes (CMT 1A-E) are separated by molecular findings and are often clinically indistinguishable. CMT1A accounts for 70% to 80% of all CMT1, and about two-thirds of probands with CMT1A have inherited the disease-causing variant, and about one-third have CMT1A as the result of a de novo variant.

CMT1A involves duplication of the *PMP22* gene. *PMP22* encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal *PMP22* gene dosage effects.[7,] Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) result in the most severe phenotype, whereas 3 normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.[6,]

## CMT Type 2

CMT2 is a non-demyelinating (axonal) peripheral neuropathy characterized by distal muscle weakness and atrophy, mild sensory loss, and normal or near-normal nerve conduction velocities. Clinically, CMT2 is similar to CMT1, although typically less severe.[6,] The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

## X-Linked CMT

CMT X type 1 is characterized by a moderate-to-severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.[8,] Sensorineural deafness and central nervous system symptoms also occur in some families. CMT X type 1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (Cx32), which is available on a clinical basis, detects about 90% of cases of CMT X type 1.

## CMT Type 4

CMT type 4 is a form of hereditary motor and sensory neuropathy that is inherited in an autosomal recessive fashion and occurs secondary to myelinopathy or axonopathy. It occurs more rarely than the other forms of CMT neuropathy, but some forms may be rapidly progressive and/or associated with severe weakness.

## Hereditary Neuropathy with Liability to Pressure Palsies

The largest proportion of CMT1 cases are due to variants in *PMP22*. In HNPP (also called tomaculous neuropathy), inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression or entrapment. Patients with HNPP rarely present symptoms before the second or third decade of life. However, some have reported presentation as early as birth or as late as the seventh decade of life.[9,] The prevalence is estimated at 16 persons per 100,000, although some authors have indicated a potential for underdiagnosis of the disease.[9,] An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination.[10,] HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode.[10,] Poor recovery usually involves a history of prolonged pressure on a nerve, but, in these cases, the remaining symptoms are typically mild.

*PMP22* is the only gene for which a variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have single nucleotide variants (SNVs) and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. SNVs in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.[11,] Studies have also reported that the SNV frequency may vary considerably by ethnicity.[12,] About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.[13,]

## Treatment

Currently, there is no therapy to slow the progression of neuropathy for inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with functional activities and physiological adaptations with exercise.[14,] Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, the use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.[15,] Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended for patients with CMT.[6,]

Supportive treatment for HNPP can include transient bracing (eg, wrist splint or ankle-foot orthosis), which may become permanent in some cases of foot drop.[16,] Prevention of HNPP manifestations can be accomplished by wearing protective padding (eg, elbow or knee pads) to prevent trauma to nerves during activity. Some have reported that vincristine should also be avoided in HNPP patients.[6,16,] Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but a 2013 trial in humans did not demonstrate significant clinical benefit.[17,] Attarian et al (2014) reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of 3 approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A.[18,] The trial demonstrated the safety and tolerability of the drug. Mandel et al (2015) included this randomized controlled trial and 3 other trials (1 of ascorbic acid, 2 of PXT3003) in a meta-analysis.[19,]

## Molecular Genetic Testing

Multiple laboratories offer individual variant testing for genes involved in hereditary sensory and motor neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation sequencing followed by deletion/duplication analysis (ie, with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in *MFN2,* whole gene or select exome sequence analysis is typically used to identify SNVs, in addition to or followed by deletion or duplication analysis for the detection of large deletions or duplications.

Aretz et al (2010) reported a general estimation of the clinical sensitivity of CMT variant testing for hereditary motor and sensory neuropathy and HNPP using a variety of analytic methods (multiplex ligation-dependent probe amplification, multiplex amplicon quantification, quantitative polymerase chain reaction, Southern blot, fluorescence in-situ hybridization, pulsed-field gel electrophoresis, denaturing high-performance liquid chromatography, high-resolution melting, restriction analysis, direct sequencing).[20,] The clinical sensitivity (ie, the proportion of positive tests if the disease is present) for the detection of deletions/duplications or mutations to *PMP22* was about 50% and 1%, respectively, for single nucleotide variants. The clinical specificity (ie, the proportion of negative tests if the disease is not present) was nearly 100%.

A number of genetic panel tests for the assessment of peripheral neuropathies are commercially available. For example, GeneDx (Gaithersburg, MD) offers an Axonal CMT panel, which uses next-generation sequencing and exon array comparative genomic hybridization. The genes tested include *AARS*, *AIFM1*, *BSCL2*, *DNAJB2*, *DNM2*, *DYNC1H1*, *GAN*, *GARS*, *GDAP1*, *GJB1*, *GNB4*, *HARS*, *HINT1*, *HSPB1*, *HSPB8*, *IGHMBP2*, *INF2, KIF5A, LMNA*, *LRSAM1*, *MFN2*, *MME*, *MORC2*, *MPZ*, *NEFL*, *PLEKHG5, PRPS1*, *RAB7A*, *SLC12A6, TRIM2, TRPV4, and YARS*.[21,] InterGenetics (Athens, Greece) offers a next-generation sequencing panel for neuropathy that includes 42 genes involved in CMT, along with other hereditary neuropathies. Fulgent Clinical Diagnostics Lab offers a broader next-generation sequencing panel for CMT that includes 48 genes associated with CMT and other neuropathies and myopathies.

# OBJECTIVE

The objective of this evidence review is to evaluate whether genetic testing in individuals with suspected inherited motor and sensory peripheral neuropathy improves health outcomes.

# POLICY STATEMENT

Genetic testing is considered **medically necessary** when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms, but a definitive diagnosis cannot be made without genetic testing.

Genetic testing for an inherited peripheral neuropathy is considered **investigational** for all other indications.

# POLICY GUIDELINES

This policy addresses the hereditary motor and sensory peripheral neuropathies, of which peripheral neuropathy is the primary clinical manifestation. A number of other hereditary disorders may have neuropathy as an associated finding but typically have other central nervous system or other systemic findings. Examples include Refsum disease, various lysosomal storage diseases, and mitochondrial disorders.

## Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual"s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

# FDA REGULATORY STATUS

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests 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.

# RATIONALE

## Summary of Evidence

For individuals with suspected inherited motor and sensory peripheral neuropathy who receive testing for genes associated with inherited peripheral neuropathies, the evidence includes case-control and genome-wide association studies. Relevant outcomes are test validity, symptoms, and change in disease status. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies (HNPP), the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and HNPP was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Academy of Neurology

In 2009, the American Academy of Neurology (AAN) and 2 other specialty societies published an evidence-based, tiered approach for the evaluation of distal symmetric polyneuropathy and suspected hereditary neuropathies, which concluded the following (see Table 2).[3,]

**Table 2. Recommendations on Distal Symmetric Polyneuropathy and Suspected Hereditary Neuropathies**

| Recommendation | LOE[a] |
|---|---|
| "Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies" | A |
| "Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype" | C |
| "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 screening" | |
| "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" | U |

CMT: Charcot-Marie-Tooth; HNPP: hereditary neuropathy with liability to pressure palsies; LOE: level of evidence.

[a] Grade A: established as effective, ineffective, or harmful for the given condition in the specified population; grade C: possibly effective, ineffective, or harmful for the given condition in the specified population; grade U: data inadequate or conflicting; given current knowledge.

The AAN website indicates the recommendations were reaffirmed on January 22, 2022, and indicated an update is in progress.

## American Academy of Family Physicians

In 2020, the American Academy of Family Physicians recommended genetic testing for a patient with suspected peripheral neuropathy, if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology and diseases such as diabetes, toxic medications, thyroid disease, vitamin deficiency, and vasculitis can be ruled out.[32,]

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

# REFERENCES


1. Burgunder JM, Schls L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. Eur J Neurol. Feb 2011; 18(2): 207-217. PMID 20500522
2. Alport AR, Sander HW. Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. Continuum (Minneap Minn). Feb 2012; 18(1): 13-38. PMID 22810068
3. 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. Jan 13 2009; 72(2): 185-92. PMID 19056666
4. Saporta AS, Sottile SL, Miller LJ, et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. Jan 2011; 69(1): 22-33. PMID 21280073
5. Cornett KM, Menezes MP, Bray P, et al. Phenotypic Variability of Childhood Charcot-Marie-Tooth Disease. JAMA Neurol. Jun 01 2016; 73(6): 645-51. PMID 27043305
6. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews. Seattle, WA: University of Washington; 2023.
7. Stankiewicz P, Lupski JR. The genomic basis of disease, mechanisms and assays for genomic disorders. Genome Dyn. 2006; 1: 1-16. PMID 18724050
8. Abrams CK. GJB1 Disorders: Charcot Marie Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2020.
9. Meretoja P, Silander K, Kalimo H, et al. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. Neuromuscul Disord. Dec 1997; 7(8): 529-32. PMID 9447611
10. Celik Y, Kiliner C, Hamamcioğlu MK, et al. Hereditary neuropathy with liability to pressure palsies in a Turkish patient (HNPP): a rare cause of entrapment neuropathies in young adults. Turk Neurosurg. Jan 2008; 18(1): 82-4. PMID 18382985
11. Taioli F, Cabrini I, Cavallaro T, et al. Inherited demyelinating neuropathies with micromutations of peripheral myelin protein 22 gene. Brain. Feb 2011; 134(Pt 2): 608-17. PMID 21252112
12. Bissar-Tadmouri N, Parman Y, Boutrand L, et al. Mutational analysis and genotype/phenotype correlation in Turkish Charcot-Marie-Tooth Type 1 and HNPP patients. Clin Genet. Nov 2000; 58(5): 396-402. PMID 11140841
13. Dubourg O, Mouton P, Brice A, et al. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord. Mar 2000; 10(3): 206-8. PMID 10734269
14. Sman AD, Hackett D, Fiatarone Singh M, et al. Systematic review of exercise for Charcot-Marie-Tooth disease. J Peripher Nerv Syst. Dec 2015; 20(4): 347-62. PMID 26010435
15. Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. Adv Exp Med Biol. 2009; 652: 207-24. PMID 20225028
16. Chrestian N. Hereditary neuropathy with liability to pressure palsies. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. Gene Reviews. Seattle, WA: University of Washington; 2020.
17. Lewis RA, McDermott MP, Herrmann DN, et al. High-dosage ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A: results of a randomized, double-masked, controlled trial. JAMA Neurol. Aug 2013; 70(8): 981-7. PMID 23797954
18. Attarian S, Vallat JM, Magy L, et al. An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A. Orphanet J Rare Dis. Dec 18 2014; 9: 199. PMID 25519680
19. Mandel J, Bertrand V, Lehert P, et al. A meta-analysis of randomized double-blind clinical trials in CMT1A to assess the change from baseline in CMTNS and ONLS scales after one year of treatment. Orphanet J Rare Dis. Jun 13 2015; 10: 74. PMID 26070802

20. Aretz S, Rautenstrauss B, Timmerman V. Clinical utility gene card for: HMSN/HNPP HMSN types 1, 2, 3, 6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA); HNPP. Eur J Hum Genet. Sep 2010; 18(9). PMID 20512157
21. GeneDx. Charcot-Marie-Tooth Panel. https://www.genedx.com/tests/detail/charcot-marie-tooth-panel-888 Accessed November 17, 2023.
22. Rudnik-Schneborn S, Tlle 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. Jan 2016; 89(1): 34-43. PMID 25850958
23. Gess B, Schirmacher A, Boentert M, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord. Aug 2013; 23(8): 647-51. PMID 23743332
24. stern 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. Sep 21 2013; 14: 94. PMID 24053775
25. 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. Jul 2012; 83(7): 706-10. PMID 22577229
26. Ucha Cavalcanti EB, Santos SCL, Martins CES, et al. Charcot-Marie-Tooth disease: Genetic profile of patients from a large Brazilian neuromuscular reference center. J Peripher Nerv Syst. Sep 2021; 26(3): 290-297. PMID 34190362
27. Antoniadi T, Buxton C, Dennis G, et al. Application of targeted multi-gene panel testing for the diagnosis of inherited peripheral neuropathy provides a high diagnostic yield with unexpected phenotype-genotype variability. BMC Med Genet. Sep 21 2015; 16: 84. PMID 26392352
28. DiVincenzo C, Elzinga CD, Medeiros AC, et al. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. Mol Genet Genomic Med. Nov 2014; 2(6): 522-9. PMID 25614874
29. Volodarsky M, Kerkhof J, Stuart A, et al. Comprehensive genetic sequence and copy number analysis for Charcot-Marie-Tooth disease in a Canadian cohort of 2517 patients. J Med Genet. Apr 2021; 58(4): 284-288. PMID 32376792
30. Sanmaneechai O, Feely S, Scherer SS, et al. Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain. Nov 2015; 138(Pt 11): 3180-92. PMID 26310628
31. Karadima G, Koutsis G, Raftopoulou M, et al. Mutational analysis of Greek patients with suspected hereditary neuropathy with liability to pressure palsies (HNPP): a 15-year experience. J Peripher Nerv Syst. Jun 2015; 20(2): 79-85. PMID 26110377
32. Castelli G, Desai KM, Cantone RE. Peripheral Neuropathy: Evaluation and Differential Diagnosis. Am Fam Physician. Dec 15 2020; 102(12): 732-739. PMID 33320513


## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| March 2018 | New policy | Genetic testing for inherited motor and sensory neuropathies may be considered medically necessary when the disease is suspected. Genetic testing for an inherited peripheral neuropathy is considered investigational for all other indications. |
| March 2019 | Replace policy | Policy updated with literature review through December 6, 2018; no references added. Policy statements unchanged. |
| March 2020 | Replace policy | Policy updated with literature review through November 11, 2019; no references added. Policy statement unchanged. |
| March 2021 | Replace policy | Policy updated with literature review through November 11, 2020; no references added. Policy statements unchanged. |
| March 2022 | Replace policy | Policy updated with literature review through November 15, 2021; references added. Policy statements unchanged. |
| March 2023 | Replace policy | Policy updated with literature review through November 21, 2022; no new references added. Policy statements unchanged. |
| March 2024 | Replace policy | Policy updated with literature review through November 17, 2023; no new references added. Policy statements unchanged. |