

## ***Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies***

**Effective:** April 1, 2021

**Next Review:** January 2022

**Last Review:** February 2021

### **IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

### **DESCRIPTION**

The inherited peripheral neuropathies are the most common inherited neuromuscular disease. Genetic testing has been suggested as a way to diagnose specific inherited peripheral neuropathies.

### **MEDICAL POLICY CRITERIA**

Genetic testing for an inherited peripheral neuropathy, including panel testing of multiple peripheral neuropathy genes, is considered **investigational** for all indications, including but not limited to confirming a clinical diagnosis of an inherited peripheral neuropathy.

*NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.*

### **CROSS REFERENCES**

None

### **BACKGROUND**

The inherited peripheral neuropathies are a clinically and genetically heterogeneous group of

disorders. The estimated prevalence is roughly one in 2,500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.<sup>[1]</sup>

Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary myelinopathies, depending upon which portion of the nerve fiber is affected. Further anatomic classification includes fiber type (e.g. motor versus sensory, large versus small), and gross distribution of the nerves affected (e.g. symmetry, length-dependency).

The inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies, and other miscellaneous, rare types (e.g. hereditary brachial plexopathy, hereditary sensory autonomic neuropathies). Other hereditary metabolic disorders, such as Friedreich's ataxia, Refsum's disease, and Krabbe's disease, may be associated with motor and/or sensory neuropathies but typically have other predominating symptoms. This policy will focus on the hereditary motor and sensory neuropathies and hereditary neuropathy with liability to pressure palsies.

A genetic etiology of a peripheral neuropathy is generally 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.<sup>[2]</sup> A family history of at least three generations with details on health issues, cause of death, and age at death should be collected.

## HEREDITARY MOTOR AND SENSORY NEUROPATHIES

The majority of inherited polyneuropathies are variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurological findings to the classic picture with pes cavus and "stork legs" to a severe polyneuropathy with respiratory failure.<sup>[3]</sup> CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies.<sup>[4]</sup> In addition, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different inheritance patterns. A 2015 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the five most commonly represented subtypes.<sup>[5]</sup>

CMT subtypes are characterized by variants in one of several myelin genes, which lead to abnormalities in myelin structure, function, or upkeep. There are seven 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).<sup>[6]</sup> CMT type 2 is associated with about 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 (adapted from Bird, 2015<sup>[6]</sup>)**

Locus Name	Gene	Protein Product	Prevalence (if known)
<b>CMT type 1</b>			
CMT1A	<i>PMP22</i>	Peripheral myelin protein 22	70-80% of CMT1
CMT1B	<i>MPZ</i>	Myelin P0 protein	10-12% of CMT1
CMT1C	<i>LITAF</i>	Lipopolysaccharide-induced tumor necrosis factor- $\alpha$ factor	$\approx$ 1% of CMT1

Locus Name	Gene	Protein Product	Prevalence (if known)
CMT1D	<i>EGR2</i>	Early growth response protein 2	
CMT1E	<i>PMP22</i>	Peripheral myelin protein 22 (sequence changes)	≈1% of CMT1
<b>CMT type 2</b>			
CMT2A1	<i>KIF1B</i>	Kinesin-like protein KIF1B	
CMT2A2	<i>MFN2</i>	Mitofusin-2	20% of CMT2
CMT2B	<i>RAB7A</i>	Ras-related protein Rab-7	
CMT2B1	<i>LMNA</i>	Lamin A/C	
CMT2B2	<i>MED25</i>	Mediator of RNA polymerase II transcription subunit 25	
CMT2C	<i>TRPV4</i>	Transient receptor potential cation channel subfamily V member 4	
CMT2D	<i>GARS</i>	Glycyl-tRNA synthetase	3% of CMT2
CMT2E/1F	<i>NEFL</i>	Neurofilament light polypeptide	4% of CMT2
CMT2F	<i>HSPB1</i>	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein-1	5% of CMT2
CMT2I/2J	<i>MPZ</i>	Myelin P0 protein	
CMT2L	<i>HSPB8</i>	Heat-shock protein beta-8	
CMT2N	<i>AARS</i>	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	<i>DYNC1H1</i>	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	<i>LRSAM1</i>	E3 ubiquitin-protein ligase LRSAM1	
CMT2S	<i>IGHMBP2</i>	DNA-binding protein SMUBP-2	
CMT2T	<i>DNAJB2</i>	DnaJ homolog subfamily B member 2	
CMT2U	<i>MARS</i>	Methionine--tRNA ligase, cytoplasmic	
<b>CMT type 4</b>			
CMT4A	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	<i>MTMR2</i>	Myotubularin-related protein 2	
CMT4B2	<i>SBF2</i>	Myotubularin-related protein 13	
CMT4C	<i>SH3TC2</i>	SH3 domain and tetratricopeptide repeats-containing protein 2	
CMT4D	<i>NDRG1</i>	Protein NDRG1	
CMT4E	<i>EGR2</i>	Early growth response protein 2	
CMT4F	<i>PRX</i>	Periaxin	
CMT4H	<i>FGD4</i>	FYVE, RhoGEF and PH domain-containing protein 4	
CMT4J	<i>FIG4</i>	Phosphatidylinositol 3, 5-biphosphate	
<b>X-linked CMT</b>			
CMTX1	<i>GJB1</i>	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX2	<i>Xp22.2</i>	Unknown	
CMTX3	<i>Xq26</i>	Unknown	
CMTX4	<i>AIFM1</i>	Apoptosis-inducing factor 1	
CMTX5	<i>PRPS1</i>	Ribose-phosphate pyrophosphokinase 1	
CMTX6	<i>PDK3</i>	Pyruvate dehydrogenase kinase isoform 3	

## CMT1

Charcot-Marie-Tooth 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 individuals usually become symptomatic between age five and 25 years, and lifespan is not shortened. Less than 5% of individuals 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.

The largest proportion of CMT1 cases are due to variants in *PMP22*. CMT1A involves duplication of the gene *PMP22*. *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.<sup>[7]</sup> Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype whereas three normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype.<sup>[8]</sup>

## **CMT2**

Charcot-Marie-Tooth 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.<sup>[8]</sup> 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.

## **CMT4**

Charcot-Marie-Tooth type 4 (CMT4) 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

## **CMTX1**

Charcot-Marie-Tooth X type 1 (CMTX1) is characterized by a moderate to severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.<sup>[9]</sup> Sensorineural deafness and central nervous system symptoms also occur in some families. CMTX1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (*Cx32*) detects about 90% of cases of CMTX1, which is available on a clinical basis.<sup>[9]</sup>

## **HEREDITARY NEUROPATHY WITH LIABILITY TO PRESSURE PALSIES**

In hereditary neuropathy with liability to pressure palsies (HNPP), also called tomaculous neuropathy, inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression/entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some authors report presentation as early as birth or as late as the seventh decade of life.<sup>[10]</sup> The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for under diagnosis of the disease.<sup>[10]</sup> An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination.<sup>[11]</sup> 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.<sup>[11]</sup> 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 in which variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients and the remaining 20% of patients have point variants and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point variants in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.<sup>[12]</sup> Studies have also reported that the point variant frequency may vary considerably by ethnicity.<sup>[13]</sup> About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.<sup>[14]</sup>

## TREATMENT

Currently there is no effective therapy for the inherited peripheral neuropathies. A systematic review of exercise therapies for CMT including nine studies described in 11 articles reported significant improvements in functional activities and physiological adaptations with exercise.<sup>[15]</sup> 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, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.<sup>[16]</sup> Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.<sup>[6]</sup>

Supportive treatment for HNPP can include transient bracing (e.g., a wrist splint or ankle-foot orthosis) which may become permanent in some cases of foot drop.<sup>[17]</sup> Prevention of HNPP manifestations can be accomplished by wearing protective padding (e.g., elbow or knee pads) to prevent trauma to nerves during activity. Some authors report that vincristine should also be avoided in HNPP patients.<sup>[8, 17]</sup> Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit.<sup>[18]</sup> Attarian (2014) reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of three already approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A.<sup>[19]</sup> The study demonstrated the safety and tolerability of the drug. Mandel (2015) included this randomized controlled trial and three other trials, one of ascorbic acid and two of PXT3003, in a meta-analysis.<sup>[20]</sup>

## REGULATORY STATUS

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service. Such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

## EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature<sup>[21]</sup> is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent
2. Clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease
3. Clinical utility of the test, i.e., how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This review focuses on the clinical validity and utility of genetic testing. Most of the published data available for the clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the *PMP22* gene in the diagnosis of Charcot-Marie-Tooth (CMT) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively.

### CLINICAL VALIDITY

The clinical sensitivity of the diagnostic test for CMT and HNPP can be dependent on variable factors such as the age or family history of the patient. A general estimation of the clinical sensitivity was presented in a report by Aretz (2010) on hereditary motor and sensory neuropathy and HNPP with a variety of analytic methods (MLPA, multiplex amplicon quantification [MAQ], qPCR, Southern blot, FISH, PFGE, dHPLC, high-resolution melting, restriction analysis and direct sequencing).<sup>[22]</sup> The clinical sensitivity (i.e., proportion of positive tests if the disease is present) for the detection of deletions/duplications to *PMP22* was reported to be about 50% and 1% for point variants. The clinical specificity (i.e., proportion of negative tests if the disease is not present) was reported to be nearly 100%.

An evidence-based review by England (2009) on the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathies concluded that genetic testing was established as useful for the accurate diagnosis and classification of hereditary polyneuropathies in patients with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype.<sup>[3]</sup> Six studies included in the review showed that when the test for CMT1A duplication was restricted to patients with clinically probable CMT1 (i.e., autosomal dominant, primary demyelinating polyneuropathy), the yield is 54% to 80% as compared to testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathy where the yield was only 25% to 59% (average of 43%).

### Sequential Testing

Given the genetic complexity of CMT, many commercial and private laboratories evaluate CMT with a testing algorithm based on patients' presenting characteristics. For the evaluation of clinical validity of genetic testing for CMT, we included studies that evaluated patients with clinically suspected CMT who were evaluated with a genetic testing algorithm that was described in the study.

Saporta (2011) reported results from genetic testing of 1,024 patients with clinically suspected CMT who were evaluated at a single institution's CMT clinic from 1997 to 2009.<sup>[4]</sup> Patients who were included were considered to have CMT if they had a sensorimotor peripheral neuropathy and a family history of a similar condition. Patients without a family history of neuropathy were considered to have CMT if their medical history, neurophysiological testing, and neurological examination were typical for CMT1, CMT2, CMTX, or CMT4. There were 787 patients with clinically diagnosed CMT; of those, 527 (67%) had a specific genetic diagnosis as a result of their visit. Genetic testing decisions were left up to the treating clinician, and the authors noted that decisions about which genes to test changed over the course of the study period. The majority (98.2%) of those with clinically-diagnosed CMT1 had a genetic diagnosis, and of all of the patients with a genetic diagnosis, the majority (80.8%) had clinically-diagnosed CMT1. The authors characterize several clinical phenotypes of CMT based on clinical presentation and physiologic testing.

Rudnik-Schoneborn (2016) reported results from genetic testing of 1,206 index patients and 124 affected relatives who underwent genetic testing at a single reference laboratory from 2001 to 2012.<sup>[23]</sup> Patients were referred by neurologic or genetic centers throughout Germany, and were grouped by age at onset (early infantile [ $<2$  years], childhood [2 to 10 years], juvenile [10 to 20 years], adult [20 to 50 years], and late adult [ $>50$  years]), and by electroneurographic findings. Molecular genetic methods changed over the time period of the study, and testing was tiered depending on patient features and family history. Of the 674 index patients with a demyelinating CMT phenotype on nerve conduction studies, 343 (51%) had a genetic diagnosis; of the 340 index patients with an axonal CMT phenotype, 45 (13%) had a genetic diagnosis; and of the 192 with HNPP, 67 (35%) had a genetic diagnosis. The most common genetic diagnoses differed by nerve conduction phenotype: of the 429 patients genetically identified with demyelinating CMT (index and secondary), 89.3% were detected with *PMP22* del/dup (74.8%), *GJB1/Cx32* (8.9%), or *MPZ/P0* (5.6%) variant analysis. In contrast, of the 57 patients genetically identified with axonal CMT (index and secondary), 84.3% were detected with *GJB1/Cx32* (42.1%), *MFN2* (33.3%), or *MPZ/P0* (8.8%) analysis.

Gess (2013) reported on sequential testing for CMT-related genes from 776 patients with genetic testing at a single center for suspected inherited peripheral neuropathies from 2004 to 2012.<sup>[24]</sup> Most patients (n=624) were treated in the same center. The test strategy varied based on electrophysiologic data and family history. The yield of genetic testing was 66% (233/355) in patients with CMT1, 35% (53/151) in patients with CMT2, and 64% (53/83) in patients with HNPP. Duplications on chromosome 17 were the most common variants in CMT1 (77%), followed by *GJB1* (13%) and *MPZ* (8%) variants among those with positive genetic tests. For CMT2 patients, *GJB2* (30%) and *MFN2* (23%) variants were most common among those with positive genetic tests.

Ostern (2013) reported on a retrospective analysis of cases of CMT diagnostic testing referred to a single reference laboratory in Norway from 2004 to 2010.<sup>[25]</sup> Genetic testing was stratified based on clinical information supplied on patient requisition forms based on age of onset of symptoms, prior testing, results from motor NCV, and patterns of inheritance. The

study sample included 435 index cases, of a total of 549 CMT cases tested (other tests were for at risk family members or other reasons). Patients were grouped based on whether they had symptoms of polyneuropathy, classical CMT, with or without additional symptoms or changes on imaging, or if they had atypical features or the physician suspected an alternative diagnosis. Among the cases tested, 72 (16.6%) were found to be variant positive, all of whom had symptoms of CMT. Most (69/72, 95.8%) of the positive molecular genetic findings were *PMP22* region duplications or sequence variants in *MPZ*, *GJB1*, or *MFN2* genes.

Murphy (2012) reported on the yield of sequential testing for CMT-related gene variants from 1,607 patients with testing sent to a single center.<sup>[26]</sup> Of the 916 patients seen in the authors' clinic, 601 (65.6%) had a clinical diagnosis of CMT (425 CMT, 46 HNPP), CMT1 (56.5%) and 115 had CMT2 (27.1%). Of those with CMT, 266 (62.6%) received a genetic diagnosis. Of the patients with a positive genetic test, variants in four genes (*PMP22* duplication, and *GJB1*, *MPZ*, and *MFN2*) represented 92% of all variants.

### Panel Testing

Several studies have evaluated broader panel tests for hereditary peripheral neuropathies. Hoyer (2014) reported the yield of testing with next-generation sequencing (NGS) with a custom panel including 32 CMT genes and 19 other genes associated with inherited neuropathies among 81 families with CMT.<sup>[27]</sup> Pathogenic or likely pathogenic gene variants were identified in 37 (46%) of families. Of the 38 families with CMT1, 55% (21/38) had certain or likely pathogenic genotypes identified (11 copy number variants, ten point variants). Of the 33 families with CMT2, 36% (12/33) had certain or likely pathogenic genotypes identified.

Frasquet (2020) reported on the results of genetic testing, including NGS and Sanger sequencing of the *SORD* gene, in 163 patients (from 108 families) with distal hereditary motor neuropathies in Spain.<sup>[28]</sup> The most commonly identified genetic variants were in the *HSPB1* (10.4%), *GARS1* (9.8%), *BICD2* (8.0%), and *DNAJB2* (6.7%) genes, while *SORD* variants accounted for 3.1%. A genetic diagnosis was found for 37/108 (34.2%) of the families.

Drew (2015) reported results of whole exome sequencing for 110 patients with inherited peripheral neuropathies who had previously had negative genetic testing for variants in common genes associated with peripheral neuropathies.<sup>[29]</sup> The authors identified 41 missense sequence variants in genes known to be associated with inherited peripheral neuropathies, nine of which were considered pathogenic, 12 of which were considered novel variants potentially implicated in the disease, and 20 of which were considered polymorphisms.

DiVincenzo (2014) reported the variant detection rate for 14 hereditary peripheral neuropathy-associated genes in a cohort of 17,880 patients with CMT disease who were referred to a commercial genetic testing laboratory.<sup>[30]</sup> Test methods included Sanger sequencing assay (n=100,102 assays), NGS assays (n=2,338), and MLPA assays (n=21,990). The genes evaluated include *PMP22*, *GJB1*, *MPZ*, *MFN2*, *SH3TC2*, *GDAP1*, *NEFL*, *LITAF*, *GARS*, *HSPB1*, *FIG4*, *EGR2*, *PRX*, and *RAB7A*. Of the patient cohort, 18.5% (n=3,312) had a genetic abnormality detected. Among those with a genetic abnormality in a CMT-related gene, 94.9% were positive in one of four genes (*PMP22*, *GJB1*, *MPZ*, *MFN2*). Duplications (56.7%) or deletions (21.9%) in the *PMP22* gene were the most common finding, followed by *GJB1* variants (6.7%).

### Genotype-Phenotype Correlations



There is significant clinical variability within and across subtypes of CMT. Therefore, some studies have evaluated genotype-phenotype correlations within CMT cases.

Sanmaneechai (2015) characterized genotype-phenotype correlations in patients with CMT1B in terms of variants in the *MPZ* gene in a cohort of 103 patients from 71 families.<sup>[31]</sup> Patients underwent standardized clinical assessments and clinical electrophysiology. There were 47 different *MPZ* variants and three characteristic ages of onset, infantile (age range 0 to 5 years), childhood (age range 6 to 20 years), and adult (age  $\geq$  21 years). Specific variants clustered by age group, with only two variants found in more than one age group.

Considerable variability of phenotype has been observed within families with CMT2A.<sup>[32]</sup> Choi (2007) reported on genotype-phenotype correlations between *MFN2* variants and CMT2A symptoms in 160 families with CMT2A, 36 of which had *MFN2* variants.<sup>[33]</sup> Among patients with *MFN2* variants, disease severity was correlated with age of onset, but specific associations between genotype and disease severity are not reported.

Karadima (2015) investigated the association of *PMP22* variants and clinical phenotypes in 100 Greek patients referred for genetic testing for HNPP.<sup>[34]</sup> In the 92 index cases the frequency of *PMP22* deletions was 47.8% and the frequency of *PMP22* “micromutations” was 2.2%. Variant-negative patients were more likely to have an atypical phenotype (41%), absent family history (96%), and nerve conduction study findings not fulfilling HNPP criteria (80.5%).

## CLINICAL UTILITY

The clinical utility of genetic testing for the hereditary peripheral neuropathies depends on how the results can be used to improve patient management. Published data for the clinical utility of genetic testing for the inherited peripheral neuropathies is lacking.

The likelihood that genetic testing for this condition will alter patient management is low. Given the diagnosis of an inherited peripheral neuropathy can generally be made clinically and the inherited peripheral neuropathies have no specific therapy, the incremental benefit of a genetic confirmation of these disorders is not known. Some specific medications for CMT are under investigation, but their use is not well-established. Although there are differences in prognosis for different forms of CMT, whether different prognosis leads to choices in therapy that lead to different outcomes is uncertain.

## PRACTICE GUIDELINE SUMMARY

### AMERICAN ACADEMY OF NEUROLOGY<sup>[3]</sup>

The American Academy of Neurology (AAN) published an evidence-based in 2009, tiered approach for the evaluation of distal symmetric polyneuropathy, and for suspected hereditary neuropathies, which concluded that:

- genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (level A classification of recommendations- established as effective, ineffective, or harmful for the given condition in the specified population)
- genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (level C- possibly effective, ineffective, or harmful for the given condition in the specified population)

- 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 in *PMP22*, *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 (level U-data inadequate or conflicting; given current knowledge)

These recommendations were reaffirmed in 2013.

### AMERICAN ACADEMY OF FAMILY PHYSICIANS<sup>[35]</sup>

The American Academy of Family Physicians (AAFP) recommends genetic testing in 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, and vasculitides can be ruled out.<sup>[35]</sup>

## SUMMARY

There is not enough research to show that genetic testing for inherited peripheral neuropathies can change treatment decisions or improve health outcomes in people who might have these diseases. Therefore, genetic testing for inherited peripheral neuropathies, including genetic panel testing, is considered investigational.

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## CODES

Codes	Number	Description
CPT	81324	PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
	81325	;full gene sequencing
	81326	;family variant
	81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)

<b>Codes</b>	<b>Number</b>	<b>Description</b>
	81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81448	Hereditary peripheral neuropathies (eg, Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (eg, BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)
	81479	Unlisted molecular pathology procedure
HCPCS	None	

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