Regence

Medical Policy Manual Genetic Testing, Policy No. 66

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Effective: May 1, 2025

Next Review: January 2026
Last Review: March 2025

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

Note: Please see Cross References for individual gene and panel testing for genes not associated with peripheral neuropathies and for reproductive carrier testing.

I. Genetic testing to diagnose an inherited peripheral neuropathy, including targeted panel testing (see Policy Guidelines), may be considered **medically necessary** when both of the following are met:

   A. When an individual has signs and/or symptoms of an inherited peripheral motor or sensory neuropathy; and

   B. One of the following is met:

      i. A definitive clinical diagnosis cannot be made; or

      ii. A genetic diagnosis is needed to inform reproductive planning.

II. Genetic testing to diagnose an inherited peripheral neuropathy is considered **investigational** when Criterion I. is not met, including for non-targeted panels (see Policy Guidelines).

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

POLICY GUIDELINES

PANEL TESTING

Targeted Panels for Inherited Peripheral Neuropathies

Targeted panel testing for peripheral neuropathies includes panels that are specifically designed to diagnose patients suspected of having an inherited peripheral neuropathy, such as Charcot-Marie-Tooth disease. They may include the following genes: *PMP22*, *MFN2*, *MPZ*, *LITAF*, and *GJB1*.

Examples of targeted panels for peripheral neuropathies include, but are not limited to:

- Distal Hereditary Motor Neuropathy Panel (Prevention Genetics)
- Hereditary Neuropathy Panel (GeneDx)
- Invitae Hereditary Sensory and Autonomic Neuropathy Panel (Invitae)
- Invitae Small Fiber Neuropathy Test (Invitae)

Non-targeted Panels

Some commercially available panels are not targeted toward genes that are specifically associated with peripheral neuropathies. They often include testing for a large number of disorders that could be distinguished based on clinical presentation.

Non-targeted panels for neuropathies and related disorders, but are not limited to:

- Comprehensive Neuropathy Panel (Prevention Genetics)
- Comprehensive Neuropathies (NGS Panel and Copy Number Analysis + mtDNA) (MNG Laboratories)
- Invitae Comprehensive Neuropathies Panel (Invitae)

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Evaluating the Utility of Genetic Panels, Genetic Testing, Policy No. 64
3. Reproductive Carrier Screening for Genetic Diseases, Genetic Testing, Policy No. 81

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.[1]

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.[2] 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 were originally described clinically as 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.[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 the inherited neuropathies.[4] 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.[5]

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 (demyelinating) and 2 (axonal or non-demyelinating) 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). CMT type 2 is associated with about 10% to 15% of CMT cases. CMT2A is the most common subtype of CMT2 and about 20% of CMT2A is 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, 2022[6])

Locus Name	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-α factor	
CMT1D	*EGR2*	Early growth response protein 2	
CMT1E	*PMP22*	Peripheral myelin protein 22 (sequence changes)	

Locus Name	Gene	Protein Product	Prevalence (if known)
CMT1F/2E	*NEFL*	Neurofilament light peptide	
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	
CMT2H	*GDAP1*	Ganglioside-induced differentiation-associated protein-1	
CMT2I/J	*MPZ*	Myelin P0 protein	
CMT2L	*HSPB8*	Heat-shock protein beta-8	
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			
CMTX1	*GJB1*	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX3	*Xq26*	Unknown	
CMTX4	*AIFM1*	Apoptosis-inducing factor 1	
CMTX5	*PRPS1*	Ribose-phosphate pyrophosphokinase 1	
CMTX6	*PDK3*	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.[7] 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.[8]

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.[8] 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.[9] 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.[9]

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.[10] The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for under diagnosis of the disease.[10] An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination.[11] 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.[11] 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.[12] Studies have also reported that the point variant frequency may vary considerably by ethnicity.[13] About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.[14]

TREATMENT

Currently there is no effective treatment to prevent or slow the progression of peripheral neuropathy and therapy for the inherited peripheral neuropathies is based on symptoms. 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.[15] 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.[16] Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.[17]

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.[18] 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.[8, 18] Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit.[19] 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.[20] 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.[21]

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[22] 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).[23] 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.[3] 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.

Uchôa Cavalcanti (2021) reported on results from genetic testing of 503 patients (94 families and 192 unrelated individuals) who underwent testing in a Brazilian neuromuscular outpatient clinic from 2015 to 2020.[24] The diagnosis of CMT was established based on the presence of slowly progressive, motor and sensory neuropathy, independent of any family history. Patients were assessed utilizing clinical and neurophysiological data along with targeted gene panel sequencing. Among the 503 patients, a genetic diagnosis was reported in 394 patients (77 families and 120 unrelated individuals). The following confirmed genetic diagnoses were identified: demyelinating CMT (n=317), intermediate CMT (n=34), and axonal CMT (n=43). The genetic diagnosis rate in probands was 68.9% (197/286). The most common causative genes were *PMP22* duplication *GJB1*, *MFN2*, *GDAP1*, *MPZ*, *PMP22* point mutation, *NEFL*, *SBF2*, and *SH3TC2*.

Volodarsky (2021) reported the results of genetic testing, including comprehensive sequencing and copy number analysis of 34 genes, in a cohort of 2,517 Canadian patients.[25] A molecular diagnosis was made in 440 (17.5%) patients, and the diagnostic yield was greater for females (21%) than males (15%). Six genes constituted 80% of the overall results.

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.[4] 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.[26] 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.[27] 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.[28] 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.[29] 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.[30] 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.[31] 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.[32] 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.[33] 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.

Chao (2023) evaluated the clinical manifestations and genetic findings of 21 people from 9 families with *NEFL*-associated CMT in Taiwan.[34] The families had six different *NEFL* variants which represented almost 2% of CMT in Taiwan. All variants were heterozygous, and autosomal dominant inheritance was confirmed in four families. About 70% of the patients were characterized as having intermediate CMT based on ulnar nerve conduction velocities (MNCV). The phenotypes exhibited wide variability including a wide range of forearm MNCV of between 25 and 45m/s. The age at onset ranged from age 1-year to 40 years, and severity of symptoms varied. Delayed walking (after age 15 months) was experienced by 19% of patients.

Morel (2022) compared the genetic and clinical features of 7 French patients with *HINT1*-associated CMT to previous reports of *HINT1*-positive patients.[35] Homozygous *HINT1* variants are a rare cause of recessive axonal CMT that has been reported in many Eastern and Western European countries, as well as Asia, Africa, and South America. The 7 French patients were similar in presentation in terms of age of onset (mean age 7 years vs. 9 years in published reports) dysmorphologies (e.g., foot abnormalities in 6/7 French patients vs. 85% of published reports) and neuromuscular/sensory findings (all French patients had nerve conduction studies that found sensory-motor or distal motor neuropathy) to previously reported *HINT1* cohorts. However, unlike previous reports, 6 of the 7 French patients exhibited neurodevelopmental or psychiatric disorders, including intellectual disability, dyslexia, depression, attention deficit hyperactivity disorder, anxiety, and obsessive-compulsive disorder. Further study is needed to know whether the *HINT1* neuropathy phenotype is associated with developmental and/or psychiatric disorders.

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.[36] 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 ≥ 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.[37] Choi (2007) reported on genotype-phenotype correlations between *MFN2* variants and CMT2A symptoms in 160 families with CMT2A, 36 of which had *MFN2* variants.[38] Among patients with *MFM2* 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.[39] 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%).

WHOLE GENOME SEQUENCING

Record (2024) reported the use of whole genome sequencing to diagnose CMT.[40] Among the 1515 patients with a clinical diagnosis of CMT or a related disorder who were referred to a single inherited neuropathy center, the genetic diagnostic yield was 76.9%. The most common diagnosis was CMT1 (41.0%), followed by CMT2 (19.4%), intermediate CMT (13.5%); 4.8% of patients had HNPP. The most common genetic diagnoses were PMP22 duplication *GJB1*, *PMP22* deletion, and *MFN2*.

CLINICAL UTILITY

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing. The clinical utility of genetic testing for 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 inherited peripheral neuropathies is lacking.

The diagnosis of an inherited peripheral neuropathy can generally be made clinically. However, when the diagnosis cannot be made clinically, a genetic diagnosis may add incremental value. A diagnosis of an inherited peripheral neuropathy is important to direct therapy, regarding early referrals to physical therapy and avoidance of potentially toxic medications. Some specific medications for CMT are under investigation, but their use is not well-established. There are significant differences in prognosis for different forms of CMT, although whether different prognosis leads to choices in therapy that lead to different outcomes is uncertain. In some cases, genetic diagnosis of an inherited peripheral neuropathy may have the potential to avoid other diagnostic tests. There is evidence from observational studies to support 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 and, in turn, to initiate supportive therapies.

PRACTICE GUIDELINE SUMMARY

AMERICAN ACADEMY OF NEUROLOGY[3]

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 2022.

AMERICAN ACADEMY OF FAMILY PHYSICIANS[41]

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 vasculitis can be ruled out.[41]

SUMMARY

There is enough evidence to show that genetic testing may improve overall health outcomes for certain individuals who have signs and/or symptoms of an inherited peripheral neuropathy. This includes individuals for whom a clinical diagnosis cannot be made, and those who require a genetic diagnosis to inform reproductive decision-making. Therefore, genetic testing for inherited peripheral neuropathies may be considered medically necessary when criteria are met.

There is not enough research to show that genetic testing for inherited peripheral neuropathies can change treatment decisions or improve health outcomes for individuals who do not meet the policy criteria, including those who lack signs and symptoms of peripheral neuropathy and those who have already received a clinical diagnosis and do not require molecular testing for reproductive purposes. Therefore, genetic testing for inherited peripheral neuropathies, including genetic panel testing, is considered investigational for these individuals.

REFERENCES

1. Burgunder JM, Schols L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *Eur J Neurol.* 2011;18:207-17. PMID: 20500522
2. Alport AR, Sander HW. Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. *Continuum (Minneap Minn).* 2012;18:13-38. 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.* 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. *Annals of neurology.* 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 neurology.* 2016;73(6):645-51. PMID: 27043305
6. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: MP Adam, DB Everman, GM Mirzaa, et al., eds. GeneReviews(®). Seattle (WA), 2022 (last revision).
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. Bird TD. Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. In: MP Adam, HH Ardinger, RA Pagon, et al., eds. GeneReviews(®). Seattle WA: © 1993-2021, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle, 1993.
9. Bird TD. Charcot-Marie-Tooth Neuropathy X Type 1. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, eds. GeneReviews . Seattle (WA) 1993.
10. Meretoja P, Silander K, Kalimo H, et al. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. *Neuromuscul Disord.* 1997;7:529-32. PMID: 9447611
11. Celik Y, Kilincer C, Hamamcioglu MK, et al. Hereditary neuropathy with liability to pressure palsies in a Turkish patient (HNPP): a rare cause of entrapment neuropathies in young adults. *Turkish neurosurgery.* 2008;18(1):82-4. PMID: 18382985
12. Taioli F, Cabrini I, Cavallaro T, et al. Inherited demyelinating neuropathies with micromutations of peripheral myelin protein 22 gene. *Brain.* 2011;134:608-17. PMID: 21252112
13. 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. *Clinical genetics.* 2000;58(5):396-402. PMID: 11140841
14. Dubourg O, Mouton P, Brice A, et al. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. *Neuromuscul Disord.* 2000;10:206-8. PMID: 10734269
15. Sman AD, Hackett D, Fiatarone Singh M, et al. Systematic review of exercise for Charcot-Marie-Tooth disease. *Journal of the peripheral nervous system : JPNS.* 2015;20(4):347-62. PMID: 26010435
16. Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. *Advances in experimental medicine and biology.* 2009;652:207-24. PMID: 20225028
17. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: RA Pagon, TD Bird, CR Dolan, K Stephens, MP Adam, eds. GeneReviews. Seattle (WA), 2015 (last revision).

18. Chrestian N. Hereditary Neuropathy with Liability to Pressure Palsies. In: MP Adam, HH Ardinger, RA Pagon, et al., eds. GeneReviews(®). Seattle WA: © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle, 1993.
19. 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 neurology.* 2013;70:981-7. PMID: 23797954
20. 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 journal of rare diseases.* 2014;9:199. PMID: 25519680
21. 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 journal of rare diseases.* 2015;10:74. PMID: 26070802
22. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation.* 2016;37(6):564-9. PMID: 26931183
23. 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.* 2010;18. PMID: 20512157
24. Uchôa Cavalcanti EB, Santos SCL, Martins CES, et al. Charcot-Marie-Tooth disease: Genetic profile of patients from a large Brazilian neuromuscular reference center. *Journal of the peripheral nervous system : JPNS.* 2021;26(3):290-97. PMID: 34190362
25. 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.* 2021;58(4):284-88. PMID: 32376792
26. Rudnik-Schoneborn S, Tolle 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. *Clinical genetics.* 2016;89(1):34-43. PMID: 25850958
27. Gess B, Schirmacher A, Boentert M, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. *Neuromuscul Disord.* 2013;23(8):647-51. PMID: 23743332
28. Ostern 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 medical genetics.* 2013;14:94. PMID: 24053775
29. Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. *Journal of neurology, neurosurgery, and psychiatry.* 2012;83(7):706-10. PMID: 22577229
30. Hoyer H, Braathen GJ, Busk OL, et al. Genetic diagnosis of Charcot-Marie-Tooth disease in a population by next-generation sequencing. *BioMed research international.* 2014;2014:210401. PMID: 25025039
31. Frasquet M, Rojas-García R, Argente-Escrig H, et al. Distal hereditary motor neuropathies: Mutation spectrum and genotype-phenotype correlation. *Eur J Neurol.* 2020. PMID: 33369814
32. Drew AP, Zhu D, Kidambi A, et al. Improved inherited peripheral neuropathy genetic diagnosis by whole-exome sequencing. *Molecular genetics & genomic medicine.* 2015;3(2):143-54. PMID: 25802885

33. DiVincenzo C, Elzinga CD, Medeiros AC, et al. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. *Molecular genetics & genomic medicine.* 2014;2(6):522-9. PMID: 25614874
34. Chao HC, Hsiao CT, Lai KL, et al. Clinical and genetic characterization of NEFL-related neuropathy in Taiwan. *J Formos Med Assoc.* 2023;122(2):132-38. PMID: 36031490
35. Morel V, Campana-Salort E, Boyer A, et al. HINT1 neuropathy: Expanding the genotype and phenotype spectrum. *Clinical genetics.* 2022;102(5):379-90. PMID: 35882622
36. 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.* 2015;138(Pt 11):3180-92. PMID: 26310628
37. Bird TD. Charcot-Marie-Tooth Neuropathy Type 2. In: RA Pagon, TD Bird, CR Dolan, K Stephens, MP Adam, eds. GeneReviews. Seattle (WA), 1993.
38. Choi BO, Nakhro K, Park HJ, et al. A cohort study of MFN2 mutations and phenotypic spectrums in Charcot-Marie-Tooth disease 2A patients. *Clinical genetics.* 2015;87(6):594-8. PMID: 24863639
39. 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. *Journal of the peripheral nervous system : JPNS.* 2015;20(2):79-85. PMID: 26110377
40. Record CJ, Pipis M, Skorupinska M, et al. Whole genome sequencing increases the diagnostic rate in Charcot-Marie-Tooth disease. *Brain.* 2024;147(9):3144-56. PMID: 38481354
41. Castelli G, Desai KM, Cantone RE. Peripheral Neuropathy: Evaluation and Differential Diagnosis. *American family physician.* 2020;102(12):732-39. PMID: 33320513

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)
	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)

Codes	Number	Description
	81479	Unlisted molecular pathology procedure
HCPCS	None	

Date of Origin: *January 2014*