



# Louisiana

## Genetic Testing for the Diagnosis of inherited Peripheral Neuropathies

**Policy #** 00378

**Original Effective Date:** 08/21/2013

**Current Effective Date:** 04/18/2018

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### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing 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 to be **eligible for coverage**.

Coverage eligibility will be considered in individuals when the following criteria are met:

- Patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype may be considered for initial genetic testing of the most common genetic abnormalities, e.g. PMP22 (CMT1A duplication/ deletion), GJB1, or MFN2. Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features. If these initial tests are negative, then second bullet will be considered.
- Evaluation of rarer genetic causes would be appropriate only if initial testing is negative.

### **When Services Are Considered Investigational**

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers genetic testing for an inherited peripheral motor or sensory neuropathy for all other indications to be **investigational**.\*

Based on review of available data, the Company considers initial testing with comprehensive multigene panels that test most known genes related to hereditary neuropathies to be **investigational**.\*

### **Background/Overview**

Inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is 1 in 2500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.

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Peripheral neuropathies can be subdivided into 2 major categories: primary axonopathies and primary myelinopathies, depending on which portion of the nerve fiber is affected. 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 the 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 the hereditary motor and sensory neuropathies and HNPP.

A genetic etiology of a 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. A family history of at least 3 generations with details on health issues, cause of death, and age at death should be collected.

### 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. 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. In addition, 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.

CMT subtypes are characterized by variants in one 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%-50% of all CMT cases, with 78%-80% of those due to *PMP22* variants). 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, 2016)**

Locus	Gene	Protein Product	Prevalence (if known)
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Locus	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
CMT1D	<i>EGR2</i>	Early growth response protein 2	
CMT1E	<i>PMP22</i>	Peripheral myelin protein 22 (sequence changes)	$\approx$ 1% of CMT1
CMT1F/2E	<i>NEFL</i>	Neurofilament light polypeptide	
<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	
CMT2E/1F	<i>NEFL</i>	Neurofilament light polypeptide	
CMT2F	<i>HSPB1</i>	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
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-bisphosphate	
<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	

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Locus	Gene	Protein Product	Prevalence (if known)
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	

CMT: Charcot-Marie-Tooth.

The clinical features of CMT are briefly summarized.

### CMT Type 1

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 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. 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 3 normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype.

### CMT Type 2

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. 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 (CMTX1) is characterized by a moderate-to-severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females. Sensorineural deafness and central nervous system symptoms also occur in some families. CMTX1 is inherited in an X-linked dominant manner. Molecular

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genetic testing of *GJB1* (*Cx32*), which is available on a clinical basis, detects about 90% of cases of CMTX1.

### **CMT Type 4**

CMT 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, 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/entrapment. HNPP patients 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. The prevalence is estimated at 16 persons per 100,000, although some authors indicate a potential for underdiagnosis of the disease. An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination. 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. 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 a 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. Studies have also reported that the point variant frequency may vary considerably by ethnicity. About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.

### **TREATMENT**

Currently there is no therapy to slow the progression of neuropathy for the inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with in functional activities and physiological adaptations with exercise. 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. Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.

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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. 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. 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. 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. The study 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 and 2 of PXT3003, in a meta-analysis.

### **MOLECULAR GENETIC TESTING**

Multiple laboratories offer individual mutation testing for genes involved in hereditary sensory and motor neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation sequencing (NGS) followed by deletion/duplication analysis (ie, with array comparative genomic hybridization [CGH]) 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 point variants, in addition to or followed by deletion/duplication analysis for the detection of large deletions or duplications.

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 NGS and exon array CGH. The genes tested include: *AARS*, *BSC12*, *DNM2*, *DYNC1H1*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *HSPB8*, *LMNA*, *LRSAM1*, *MED25*, *MFN2*, *MPZ*, *NEFL*, *PRPS1*, *RAB7A*, and *TRPV4*.<sup>22</sup> InterGenetics (Athens, Greece) offers an NGS panel for neuropathy that includes 42 genes involved in CMT, along with other hereditary neuropathies. Fulgent Clinical Diagnostics Lab offers a broader NGS panel for CMT that includes 48 genes associated with CMT and other neuropathies and myopathies.

### **FDA or Other Governmental Regulatory Approval**

#### **U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) 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 LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

#### **Centers for Medicare and Medicaid Services (CMS)**

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

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### **Rationale/Source**

#### **INHERITED PERIPHERAL NEUROPATHIES**

##### **Clinical Context and Test Purpose**

The purpose of testing for variants associated with hereditary motor and sensory neuropathies in patients with suspected inherited peripheral neuropathy is to make a diagnosis of an inherited peripheral neuropathy or to inform the prognosis of an inherited peripheral neuropathy.

The question addressed in this evidence review is whether and how the use of genetic testing would improve health outcomes compared with a management strategy without testing.

The following PICOTS were used to select literature to inform this review.

##### ***Patients***

Individuals with suspected inherited peripheral neuropathy will present with sensory, motor, or mixed findings, sometimes with other findings. CMT disease is clinically heterogeneous.

##### ***Interventions***

Testing for variants associated with CMT, by deletion/duplication analysis, usually by multiplex ligation–dependent probe amplification (MLPA), and gene sequencing, usually by NGS.

##### ***Comparators***

A clinical diagnosis of an inherited peripheral neuropathy may be made by a combination of clinical features, family pedigree, and characteristic nerve conduction velocity (NCV)/electromyography studies. However, subtypes of CMT are defined based on their genotype.

##### ***Outcomes***

The general outcomes of interest are test accuracy and validity, symptom, and change in disease status. Beneficial outcomes resulting from a true test include avoiding potentially harmful therapies. Harmful outcomes resulting from a false-positive test include potential unneeded treatments due to misidentified patients.

##### ***Time***

Years.

##### ***Setting***

Outpatient, ordered by a specialist. Genetic counseling is particularly important for CMT given the extreme genetic heterogeneity of the disorder.

Validation of the clinical use of any genetic test focuses on 3 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; and (3) clinical

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utility of the test (ie, 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).

Most published data on analytic and clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the *PMP22* gene in the diagnosis of CMT and HNPP, respectively.

### Analytic Validity

A variety of methods, in addition to fluorescence in-situ hybridization (FISH), can be used for deletion/duplication analysis targeted specifically at *PMP22*, including quantitative polymerase chain reaction (qPCR), MLPA, and chromosomal microarray (CMA), with high agreement between testing methods (see Table 2).

**Table 2. Agreement Between CMT1A and HNPP Genetic Tests**

Reference	Disorders Tested	Test Method	Confirmation Method	Percent Agreement	
				CMT1A	HNPP
Hung et al (2007)	CMT1A; HNPP	CE PCR	RFLP-PCR	100%	100%
Ravise et al (2003)	CMT1A; HNPP	Direct FISH	Southern blot	94%	100%
Hung et al (2008)	CMT1A; HNPP	MLPA	Competitive multiplex PCR	100%	100%
Slater et al (2004)	CMT1A; HNPP	MLPA	FISH	90%	100%
Stangler et al (2009)	CMT1A; HNPP	MLPA	FISH	100%	100%
Hung et al (2008)	CMT1A; HNPP	MLPA	RFLP-PCR	78%	86%
Stangler et al (2009)	CMT1A; HNPP	MLPA	RFLP-PCR <sup>b</sup>	88%	NA
Lin et al (2006)	CMT1A; HNPP	DHPLC	Microsatellite analysis	100%	100%
Aarskog et al (2000)	CMT1A; HNPP	RT-qPCR	Clinical and EMG characteristics	89.6%	100%
Thiel et al (2003)	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%	100%
Chen et al (2008)	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%	100%
Kim et al (2003)	CMT1A; HNPP	RT-qPCR	Microsatellite analysis	100%	100%
Choi et al (2005)	CMT1A; HNPP	RT-qPCR	Repeat PCR	100% <sup>a</sup>	100% <sup>a</sup>

CE: capillary electrophoresis; CMT1A: Charcot-Marie-Tooth type 1A; DHPLC: denaturing high-performance liquid chromatography; EMG: electromyography; FISH: fluorescence in-situ hybridization; HNPP: hereditary neuropathy with liability to pressure palsies; MLPA: multiplex ligation-dependent probe amplification; NA: not applicable; PCR: polymerase chain reaction; q: quantitative; RFLP: restriction fragment length polymorphism; RT: reverse transcriptase.

<sup>a</sup> RT-qPCR detected 4 of 13 suspected cases of HNPP and 2 of 16 suspected cases of CMT1A not discovered by repeat PCR.

<sup>b</sup> RFLP-PCR had 1 false-negative and 3 false-positive results.

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The analytic performance of several molecular analytic methods was presented in a review by Aretz et al (2010). The reported analytic sensitivity and specificity were given as almost 100% (tests considered included MLPA, qPCR, FISH, direct sequencing). Further evidence is provided by another review (2009) in which segregation studies followed by several prospective cohort studies have also documented that currently available genetic testing results for CMT are unequivocal for diagnosis of established pathogenic variants, providing a specificity of 100% (ie, no false positives) and high sensitivity.

### **Section Summary: Analytic Validity**

Studies comparing different methods of measuring variants in genes associated with CMT1A and HNPP have reported generally high association. Additional review articles have suggested that the analytic sensitivity of other available methods for molecular diagnostics is high.

### **Clinical Validity**

A general estimation of the clinical sensitivity was presented by Aretz et al on hereditary motor and sensory neuropathy and HNPP with a variety of analytic methods (MLPA, multiplex amplicon quantification, qPCR, Southern blot, FISH, pulsed-field gel electrophoresis, denaturing high-performance liquid chromatography, high-resolution melting, restriction analysis, direct sequencing). The clinical sensitivity (ie, proportion of positive tests if the disease is present) for the detection of deletions and duplications to *PMP22* was about 50% and 1% for point mutations. The clinical specificity (ie, proportion of negative tests if the disease is not present) was nearly 100%.

An evidence-based review by England et al (2009) on the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathies concluded that genetic testing is 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. Six studies included in the review showed that when the test for *CMT1A* duplication is restricted to patients with clinically probable CMT1 (ie, autosomal dominant, primary demyelinating polyneuropathy), the yield is 54% to 80%, compared with testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathies, where the yield is only 25% to 59% (average, 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 the 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 et al (2011) reported results from genetic testing of 1024 patients with clinically suspected CMT who were evaluated at a single institution's CMT clinic from 1997 to 2009. 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, neurophysiologic testing, and neurologic examination were typical for CMT1, CMT2, CMTX, or

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CMT4. Seven hundred eighty-seven patients were diagnosed with 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. Most (98.2%) of those with clinically diagnosed CMT1 had a genetic diagnosis, and of all of the patients with a genetic diagnosis, most (80.8%) had clinically diagnosed CMT1. The authors characterized several clinical phenotypes of CMT based on clinical presentation and physiologic testing.

In 2016, Rudnik-Schoneborn et al reported results from genetic testing of 1206 index patients and 124 affected relatives who underwent genetic testing at a single reference laboratory from 2001 to 2012. Patients were referred by neurologic or genetic centers throughout Germany, and were grouped by age at onset (early infantile [ $<2$  years], childhood [2-10 years], juvenile [10-20 years], adult [20-50 years], late adult [ $>50$  years]), and by electroneurographic findings. Molecular genetic methods changed over the course 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* deletion or duplication (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%) variant analysis.

In an earlier study, Gess et al (2013) reported on sequential genetic testing for CMT-related genes from 776 patients at a single center for suspected inherited peripheral neuropathies from 2004 to 2012. 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.

In 2013, Ostern et al reported on a retrospective analysis of cases of CMT diagnostic testing referred to a single reference laboratory in Norway from 2004 to 2010. 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 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.

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In 2012, Murphy et al reported on the yield of sequential testing for CMT-related gene variants from 1607 patients with testing sent to a single center. Of the 916 patients seen in the authors' clinic, 601 (65.6%) had a primary inherited neuropathy, including 425 with CMT and 46 with HNPP. Of the 425 with a clinical diagnosis of CMT, 240 had CMT1 (56.5%), and 115 (27.1%) had CMT2. Of those with CMT, 266 (62.6%) of 425 received a genetic diagnosis, most frequently (92%) with a variant in 1 of 4 genes (*PMP22* duplication, and *GJB1*, *MPZ*, and *MFN2*).

### Panel Testing

In addition to sequential testing algorithms, some studies reported on the yield of multigene testing panels, most often using NGS methods. Studies with populations of suspected inherited motor or sensory neuropathy that reported on NGS panel test results are summarized in Table 3.

**Table 3: Summary of Genetic Panel Tests in Charcot-Marie-Tooth**

Study	N	Population	Test	Diagnostic Yield (NGS Panel)	VUS (NGS Panel)
Antoniadi et al (2015)	448	Suspected inherited peripheral neuropathy, with supportive NCV, some with negative testing for <i>PMP22</i>	56-gene NGS panel	137 (31%) patients (31 genes)	NR
DiVincenzo et al (2014)	17,377,503 with NGS	Suspected peripheral neuropathy, referred to a central laboratory	14-gene NGS panel and <i>PMP22</i> del/dup by MLPA	95 (18.9%) patients (8 genes)	38 (7.5%) patients (11 genes)

del/dup: deletion/duplication; MLPA: multiplex ligation-dependent amplification; NCV: nerve conduction velocity; NGS: next-generation sequencing; NR: not reported; VUS: variant of uncertain significance.

### 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.

In 2015, Sanmaneechai et al 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. Patients underwent standardized clinical assessments and clinical electrophysiology. There were 47 different *MPZ* variants and 3 characteristic ages of onset, infantile (age range, 0-5 years), childhood (age range, 6-20 years), and adult (age range, ≥21 years). Specific variants clustered by age group, with only 2 variants found in more than 1 age group.

For example, Karadima et al (2015) investigated the association between *PMP22* variants and clinical phenotype in 100 Greek patients referred for genetic testing for HNPP. In the 92 index cases, the frequency of *PMP22* deletions was 47.8% and the frequency of *PMP22* micromutations was 2.2%. Mutation-negative

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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%).

### **Section Summary: Clinical Validity**

A relatively large body of literature, primarily from retrospective, single-center reference labs in which patients with suspected CMT have been tested, addressed clinical validity. The yield of testing is reasonably high, particularly when patients are selected based on clinical phenotype.

### **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 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, in terms of 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 potential to avoid other diagnostic tests.

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

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

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American Academy of Neurology guidelines recommend genetic testing that is guided by the clinical phenotype, inheritance pattern (if available), and electrodiagnostic features (demyelinating and axonal). The AAN does not support complete panels of all known CMT genes, but rather recommends a stepwise evaluation method to improve genetic screening efficiency. Therefore, initially small panels of testing based on inheritance pattern or electrodiagnostic features may be appropriate. Comprehensive CMT panels test most known genes related to CMT simultaneously, but this is not usually necessary or cost-effective, or supported by guidelines.

### 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 accuracy and validity, symptoms, and change in disease status. The analytic validity of variant testing for these diseases is high. For the evaluation of hereditary motor and sensory peripheral neuropathies and for HNPP, the yield of genetic testing 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, in order to initiate supportive therapies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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### **Policy History**

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- |            |  |
|------------|--|
| 08/01/2013 | Medical Policy Committee review  |
| 08/21/2013 | Medical Policy Implementation Committee approval. New policy.            |
| 08/07/2014 | Medical Policy Committee review  |
| 08/20/2014 | Medical Policy Implementation Committee approval. No change to coverage. |
| 08/06/2015 | Medical Policy Committee review  |
| 08/19/2015 | Medical Policy Implementation Committee approval. No change to coverage. |
| 08/04/2016 | Medical Policy Committee review  |
| 08/17/2016 | Medical Policy Implementation Committee approval. No change to coverage. |
| 01/01/2017 | Coding update: Removing ICD-9 Diagnosis Codes                            |

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04/06/2017 Medical Policy Committee review  
 04/19/2017 Medical Policy Implementation Committee approval. Coverage eligibility statements rewritten.  
 01/01/2018 Coding update  
 04/05/2018 Medical Policy Committee review  
 04/18/2018 Medical Policy Implementation Committee approval. No change to coverage.  
 Next Scheduled Review Date: 04/2019

### **Coding**

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2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
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