



## Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Policy # 00378

Original Effective Date: 08/21/2013

Current Effective Date: 05/08/2023

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### When Services May Be 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**.\*\*

#### Patient Selection Criteria:

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

- Individuals 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.

#### *Note:*

*Genetic testing is only necessary once per lifetime. A multi-gene panel (with 5 or more genes, including rarer genetic causes) can be considered when billed with the appropriate CPT panel code (81448), if there was no previous peripheral neuropathy multi-gene panel testing and no known relevant genetic abnormalities. Multi-gene panel may include PMP22, GJB1, MFN2, and MPZ, SH3TC2, HINT1, HSPB1, NEFL, PRX, IGHMBP2, NDRG1, TTR, EGR2, FIG4, GDAP1, LMNA, LRSAM1, POLG, TRPV4, AARS, BIC2, DHTKD1, FGD4, HK1, INF2, KIF5A, PDK3, REEP1, SBF1, SBF2, SCN9A, SPTLC2.*

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### When Services Are Considered Investigational

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

The use of 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 when patient selection criteria are not met is considered to be **investigational**.\*

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 or repeat testing with comprehensive multigene panels that test most known genes related to hereditary neuropathies to be **investigational**.\*

### Policy Guidelines

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

#### Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping,

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single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.

**Table PG1. Nomenclature to Report on Variants Found in DNA**

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

**Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification**

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

### Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of

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the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

## **Background/Overview**

### **Inherited Peripheral Neuropathies**

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.

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

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

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

### **Charcot-Marie-Tooth Disease**

#### **Hereditary Motor and Sensory Neuropathies**

Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and "stork legs" to a severe polyneuropathy with respiratory failure. CMT disease is genetically and clinically heterogeneous. Variants in more

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than 30 genes and more than 44 different genetic loci have been associated with inherited neuropathies. Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and inheritance patterns. A 2016 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the 5 most commonly represented subtypes.

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

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

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

**Table 1. Molecular Genetics of CMT Variants**

Locus	Gene	Protein Product	Prevalence (if known)
CMT type 1			
CMT1A	<i>PMP22</i>	Peripheral myelin protein 22	50% of CMT1
CMT1B	<i>MPZ</i>	Myelin P0 protein	25% of CMT1
CMT1C	<i>LITAF</i>	Lipopolysaccharide-induced tumor necrosis factor- $\alpha$ factor	
CMT1D	<i>EGR2</i>	Early growth response protein 2	
CMT1E	<i>PMP22</i>	Peripheral myelin protein 22 (sequence changes)	
CMT1F/2E	<i>NEFL</i>	Neurofilament light polypeptide	
CMT1G	<i>PMP2</i>	Peripheral myelin protein 2	

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Locus	Gene	Protein Product	Prevalence (if known)
CMT type 2			
CMT2A1	<i>KIF1B</i>	Kinesin-like protein KIF1B	
CMT2A2A/B	<i>MFN2</i>	Mitofusin-2	
CMT2B	<i>RAB7A</i>	Ras-related protein Rab-7	
CMT2B1	<i>LMNA</i>	Lamin A/C	
CMT2B2	<i>PNKP</i>		
CMT2C	<i>TRPV4</i>	Transient receptor potential cation channel subfamily V member 4	
CMT2D	<i>GARS1</i>	Glycyl-tRNA synthetase	
CMT2F	<i>HSPB1</i>	Heat-shock protein beta-1	
CMT2G	<i>LRSAM1</i>	E3 ubiquitin-protein ligase LRSAM1	
CMT2H/2K	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
CMT2I/ J	<i>MPZ</i>	Myelin P0 protein	
CMT2L	<i>HSPB8</i>	Heat-shock protein beta-8	
CMT2M	<i>DNM2</i>	Dynamin 2	
CMT2N	<i>AARS1</i>	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	<i>DYNC1H1</i>	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	<i>LRSAM1</i>	E3 ubiquitin-protein ligase LRSAM1	
CMT2Q	<i>DHTKD1</i>	Dehydrogenase E1 And Transketolase Domain Containing 1	
CMT2R	<i>TRIM2</i>	Tripartite Motif Containing 2	

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Locus	Gene	Protein Product	Prevalence (if known)
CMT2S	<i>IGHMBP2</i>	DNA-binding protein SMUBP-2	
CMT2T	<i>MME</i>	Membrane Metalloendopeptidase	
CMT2U	<i>MARS1</i>	Methionine-tRNA ligase, cytoplasmic	
CMT2V	<i>NAGLU</i>	N-Acetyl-Alpha-Glucosaminidase	
CMT2W	<i>HARS1</i>	Histidyl-TRNA Synthetase 1	
CMT2X	<i>SPG11</i>	Spastic paraplegia 11	
CMT2Y	<i>VCP</i>	Valosin Containing Protein	
CMT2Z	<i>MORC2</i>	Microrchidia Family CW-Type Zinc Finger 2	
CMT type 4			
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	
CMT4B3	<i>SBF1</i>	SET Binding Factor 1	
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	

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Locus	Gene	Protein Product	Prevalence (if known)
CMT4J	<i>FIG4</i>	Phosphatidylinositol 3, 5-biphosphate	
X-linked CMT			
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	

Adapted from Bird (2022).  
CMT: Charcot-Marie-Tooth.

### CMT Type 1

CMT1 is an autosomal dominant, demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity. It is usually slowly progressive and often associated with pes cavus foot deformity, bilateral foot drop, and palpably enlarged nerves, especially the ulnar nerve at the olecranon groove and the greater auricular nerve. Affected people usually become symptomatic between ages 5 and 25 years, and 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

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homozygous CMT1A duplication) result in the most severe phenotype, whereas 3 normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.

### **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 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. CMT X type 1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (Cx32), which is available on a clinical basis, detects about 90% of cases of CMT X type 1.

### **CMT Type 4**

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

### **Hereditary Neuropathy with Liability to Pressure Palsies**

The largest proportion of CMT1 cases are due to variants in *PMP22*. In HNPP (also called tomaculous neuropathy), inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression or entrapment. Patients with HNPP rarely present symptoms before the second or third decade of life. However, some have reported presentation as early as birth or as late as the seventh decade of life. The prevalence is estimated at 16 persons per 100,000, although some authors have indicated 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

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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 for which a variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have single nucleotide variants (SNVs) and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. SNVs in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome. Studies have also reported that the SNV 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 inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with functional activities and physiological adaptations with exercise. Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, the use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain. Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended for patients with CMT.

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

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PXT3003, a low-dose combination of 3 approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A. The trial demonstrated the safety and tolerability of the drug. Mandel et al (2015) included this randomized controlled trial and 3 other trials (1 of ascorbic acid, 2 of PXT3003) in a meta-analysis.

### Molecular Genetic Testing

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

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

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

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## **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 must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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

### **Summary of Evidence**

For individuals with suspected inherited motor and sensory peripheral neuropathy who receive testing for genes associated with inherited peripheral neuropathies, the evidence includes case-control and genome-wide association studies. Relevant outcomes are test validity, symptoms, and change in disease status. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies (HNPP), the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and HNPP was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis

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in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

#### **Practice Guidelines and Position Statements**

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

#### **American Academy of Neurology**

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

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

<b>Recommendation</b>	<b>LOE<sup>a</sup></b>
"Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies"	A
"Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype"	C
"Initial genetic testing should be guided by the clinical phenotype, inheritance pattern, and electrodiagnostic features and should focus on the most common abnormalities which are CMT1A duplication/HNPP deletion, Cx32 (GJB1), and MFN2 screening"	
"There is insufficient evidence to determine the usefulness of routine genetic testing in patients with cryptogenic polyneuropathy who do not exhibit a hereditary neuropathy phenotype"	U

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Current Effective Date: 05/08/2023

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

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

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

### American Academy of Family Physicians

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

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

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

### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01193075	Natural History Evaluation of Charcot Marie Tooth Disease (CMT) Type (CMT1B), 2A (CMT2A), 4A (CMT4A), 4C (CMT4C), and Others	5000	December 2022
NCT01193088	Genetics of Charcot Marie Tooth Disease (CMT) - Modifiers of CMT1A, New Causes of CMT	1050	December 2022

NCT: national clinical trial.

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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
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.
04/04/2019	Medical Policy Committee review
04/24/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/02/2020	Medical Policy Committee review
04/08/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/01/2021	Medical Policy Committee review
04/14/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/07/2022	Medical Policy Committee review
04/13/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/06/2023	Medical Policy Committee review
04/12/2023	Medical Policy Implementation Committee approval. Added a note. Repeat testing added to investigational statement.

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Code Type	Code
CPT	81324, 81325, 81326, 81403, 81404, 81405, 81406, 81448, 81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  1. Consultation with technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

**\*\*Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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