MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR THE DIAGNOSIS OF INHERITED PERIPHERAL NEUROPATHIES
POLICY NUMBER	MP 2.355

Clinical benefit	☐ Minimize safety risk or concern. ☐ Minimize harmful or ineffective interventions. ☐ Assure appropriate level of care. ☐ Assure appropriate duration of service for interventions. ☒ Assure that recommended medical prerequisites have been met. ☐ Assure appropriate site of treatment or service.
Effective Date:	5/1/2025

I. POLICY

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

Genetic testing for an inherited peripheral neuropathy or sensory neuropathy is considered **investigational** for all other indications. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

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, 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	Diseased-Associated.Variant	Disease-associated change in the DNA sequence.
	Variant	Change in 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 of 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 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.

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

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FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

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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.

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 (e.g., motor vs sensory, large vs small) and gross distribution of the nerves affected (e.g., 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 (e.g., 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 medical policy 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.

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.

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Variants in more than 30 genes and more than 44 different genetic loci have been associated with the 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 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

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

Locus	Gene	Protein Product	Prevalence (if known)
CMT2G	LRSAM1	E3 ubiquitin-protein ligase LRSAM1	
CMT2H/2K	GDAP1	Ganglioside-induced differentiation-associated protein 1	
CMT2I/ J	MPZ	Myelin P0 protein	
CMT2L	HSPB8	Heat-shock protein beta-8	
CMT2M	DNM2	Dynamin 2	
CMT2N	AARS1	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	DYNC1H1	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	LRSAM1	E3 ubiquitin-protein ligase LRSAM1	
CMT2Q	DHTKD1	Dehydrogenase E1 And Transketolase Domain Containing 1	
CMT2R	TRIM2	Tripartite Motif Containing 2	
CMT2S	IGHMBP2	DNA-binding protein SMUBP-2	
CMT2T	MME	Membrane Metalloendopeptidase	
CMT2U	MARS1	Methionine-tRNA ligase, cytoplasmic	
CMT2V	NAGLU	N-Acetyl-Alpha-Glucosaminidase	
CMT2W	HARS1	Histidyl-TRNA Synthetase 1	
CMT2X	SPG11	Spastic paraplegia 11	
CMT2Y	VCP	Valosin Containing Protein	
CMT2Z	MORC2	Microrchidia Family CW-Type Zinc Finger 2	
CMT type 4			
CMT4A	GDAP1	Ganglioside-induced differentiation-associated protein 1	
CMT4B1		MTMR2	Myotubularin-related protein 2
CMT4B2	SBF2	Myotubularin-related protein 13	
CMT4B3	SBF1	SET Binding Factor 1	
CMT4C	SH3TC2	SH3 domain and tetratricopeptide repeats-containing protein 2	
CMT4D	NDRG1	Protein NDRG1	
CMT4E	EGR2	Early growth response protein 2	
CMT4F	PRX	Periaxin	
CMT4H	FGD4	FYVE, RhoGEF, and PH domain-containing protein 4	
CMT4J	FIG4	Phosphatidylinositol 3, 5-biphosphate	

Locus	Gene	Protein Product	Prevalence (if known)
X-linked CMT			
CMTX3	Xq26	Unknown	
CMTX4	AIFM1	Apoptosis-inducing factor 1	
CMTX5	PRPS1	Ribose-phosphate pyrophosphokinase 1	

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 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
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
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. 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 indicate a potential for under diagnosis 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 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 the 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 (e.g., vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in patients with CMT.

Supportive treatment for HNPP can include transient bracing (e.g., 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 (e.g., 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 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 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 followed by deletion/duplication analysis (i.e., with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in *MFN2,* whole gene or select exome sequence analysis is typically used to identify SNVs, in addition to or followed by deletion or duplication analysis for the detection of large deletions or duplications.

Aretz et al (2010) reported a general estimation of the clinical sensitivity of CMT variant testing for hereditary motor and sensory neuropathy and HNPP using a variety of analytic methods (multiplex ligation-dependent probe amplification, multiplex amplicon quantification, quantitative polymerase chain reaction, Southern blot, fluorescence in-situ hybridization, pulsed-field gel electrophoresis, denaturing high-performance liquid chromatography, high-resolution melting, restriction analysis, direct sequencing). The clinical sensitivity (i.e., 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 (i.e., the proportion of negative tests if the disease is not present) was nearly 100%.

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

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of CLIA. Laboratories that offer laboratory-developed tests must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

IV. RATIONALE

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SUMMARY OF EVIDENCE

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

V. DEFINITIONS

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NA

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations are based on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross' medical policies are developed to assist in administering a member's benefits. These medical policies do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If

there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary for genetic testing for the diagnosis of peripheral neuropathies:

Procedure Codes							
81324	81325	81326	81403	81404	81405	81406	81448
81479							

ICD-10-CM Diagnosis Code	Description
G60.0	Hereditary motor and sensory neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified
Z31.430	Encounter of female for testing for genetic disease carrier status for procreative management
Z31.440	Encounter of male for testing for genetic disease carrier status for procreative management

IX. REFERENCES

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X. POLICY HISTORY

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MP 2.355	**03/23/2020 Consensus Review.** Policy statement unchanged. References, Policy Guidelines, and coding updated. Background reviewed.
	02/02/2021 Consensus Review. Policy statement unchanged. References updated; coding reviewed.
	02/22/2022 Consensus Review. Policy statement unchanged. References updated; coding reviewed.
	02/09/2023 Consensus Review. No change to policy statement. Policy Guidelines and Background updated. References added.
	04/26/2024 Consensus Review. No change to policy statement. References updated. Coding reviewed, no changes.
	1/14/2025 Consensus Review. No changes to policy statement. Coding reviewed, no changes.

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