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Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies

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Line(s) of Business: HMO; PPO; QUEST Integration; Medicare; FEP	**Precertification:** Refer to the GTM Utilization Review Matrix

I. Policy Description

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. The inherited peripheral neuropathies can be divided into hereditary motor and sensory neuropathies (such as Charcot-Marie-Tooth disease), hereditary neuropathy with liability to pressure palsies, hereditary sensory and autonomic neuropathies, and other miscellaneous types (e.g., hereditary brachial plexopathy, giant axonal neuropathy). In addition to clinical presentation, nerve conduction studies, and family history, genetic testing can be used to diagnose specific inherited peripheral neuropathies (Kang, 2024c).

When pursuing genetic testing for inherited peripheral neuropathies, genetic counseling is strongly recommended.

II. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

1) For individuals with clinical features of Charcot-Marie-Tooth (CMTA) disease, but for whom a definitive diagnosis cannot be made without genetic testing, genetic testing for *PMP22* deletions/duplication, *GJB1* mutations, **and/or** *MFN2* mutations **MEETS COVERAGE CRITERIA**.

2) For individuals with clinical features of CMT disease who have tested negative for common deleterious variants (*PMP22* deletions/duplication; *GJB1* or *MFN2* mutations), single gene or multi-gene panel testing for CMT disease risk genes **MEETS COVERAGE CRITERIA**.

3) For asymptomatic individuals who have a close blood relative (see Note 1) with a known deleterious mutation in a CMT gene, genetic testing for the known familial mutation **MEETS COVERAGE CRITERIA**.

4) For individuals who are clinically suspected of having hereditary neuropathy with liability to pressure palsies (HNPP), but for whom a definitive diagnosis cannot be made without genetic testing, genetic testing for *PMP22* deletions and duplications **MEETS COVERAGE CRITERIA**.

5) For individuals who are clinically suspected of having hereditary motor neuropathy (HMN), but for whom a definitive diagnosis cannot be made without genetic testing, genetic testing for *BSCL2* mutations **MEETS COVERAGE CRITERIA**.

NOTES:
Note 1: Close blood relatives include 1st-degree relatives (e.g., parents, siblings, and children), 2nd-degree relatives (e.g., grandparents, aunts, uncles, nieces, nephews, grandchildren, and half-siblings), and 3rd-degree relatives (great-grandparents, great-aunts, great-uncles, great-grandchildren, and first cousins).
Note 2: For 2 or more gene tests being run on the same platform, please refer to AHS-R2162 Reimbursement Policy.

III. Table of Terminology

Term	Definition
AAN	American Academy of Neurology
AANEM	American Academy of Neuromuscular and Electrodiagnostic Medicine
AAPM&R	American Academy of Physical Medicine and Rehabilitation
AARS	Alanine-tRNA ligase, cytoplasmic
AIFM1	*Apoptosis-inducing factor 1*
BSCL2	*Seipin lipid droplet biogenesis associated*
DYNC1H1	*Dynein cytoplasmic 1 heavy chain 1*
EFNS	European Federation of Neurological Societies
EGR2	*Early growth response protein 2*
GARS	Glycyl-t-ribonucleic acid synthetase
GDAP1	*Ganglioside-induced differentiation-associated protein-1*
GJB1	Gap junction beta-1 protein (connexin 32)
HMN	Hereditary motor neuropathy
HNPP	Hereditary neuropathy with predisposition to pressure palsy
HSANs	Hereditary sensory and autonomic neuropathies
HSPB1	*Heat-shock protein beta-1*
HSPB8	*Heat-shock protein beta-8*
KIF1B	*Kinesin family member 1B*
LITAF	Lipopolysaccharide induced tumor necrosis factor
LMNA	Lamin A/C
MED25	*Mediator complex subunit 25*
MPZ	Myelin protein P_0
NEFL	Neurofilament light polypeptide

NINDS	National Institute of Neurological Disorders and Stroke
PDK3	*Pyruvate dehydrogenase kinase isoform 3*
PMP22	*Peripheral myelin protein 22*
PRPS1	*Ribose-phosphate pyrophosphokinase 1*
RAB7A	*Member RAS oncogene family*
Sep T9	*Septin 9*
SH3TC2	*SH3 domain and tetratricopeptide*
TRPV4	*Transient receptor potential cation channel subfamily V member 4*
WES/WGS	Whole exome or genome sequencing

IV. Scientific Background

Peripheral neuropathies encompass the set of disorders that primarily lead to peripheral nerve dysfunction. Symptoms typically include weakness of muscles at extremities, spine curvature, and loss of sensation at extremities (Kang, 2024c; UpToDate, 2024). Neuropathies may be caused by a variety of different factors, such as metabolic issues (including Fabry disease, Niemann-Pick disease, et al.) or present as a secondary symptom to another condition (such as Tangier disease) (Kang, 2024c).

Charcot-Marie-Tooth (CMTA) disease, also known as hereditary motor sensory neuropathy, is a group of progressive disorders that affect the peripheral nerves. CMT is caused by a mutation in one of several myelin genes that result in defects in myelin structure, maintenance, or function within peripheral nerves. Charcot-Marie-Tooth disease is one of the most common inherited neurological disorders, affecting approximately 1 in 2,500 people in the United States (Kang, 2024a).

Symptoms

The neuropathy of CMT affects both motor and sensory nerves. Symptoms usually start in childhood and have a gradual progression. The severity of symptoms varies greatly among individuals and even among family members with the disease and gene mutation (Bird, 2023; NINDS, 2007, 2023). Typical symptoms include the following:

- “Weakness or paralysis of the foot and lower leg muscles, which can cause difficulty lifting the foot (foot drop)
- A high-stepped gait with frequent tripping or falling
- Balance problems
- Foot deformities, such as high arches and curled toes (hammertoes)
- Lower legs may take on an "inverted champagne bottle" shape due to the loss of muscle bulk
- Reduced ability to feel heat, cold, and touch
- Weakness and atrophy may occur in the hands, causing difficulty with fine motor skills
- Decreased sense of vibration and position (proprioception)
- Curvature of the spine (scoliosis)
- Hip displacement
- Contractures (chronic shortening of muscles or tendons around joints)
- Muscle cramping

- Nerve pain" (NINDS, 2023)

Pain can range from mild to severe, and some people may need to rely on foot or leg braces or other orthopedic devices to maintain mobility. Some people living with CMT experience tremor, and vision and hearing can also be affected. In rare cases, breathing difficulties may occur if the nerves that control the muscles of the diaphragm are affected (NINDS, 2023).

Causes

CMT is caused by mutations in genes that produce proteins involved in the structure and function of either the peripheral nerve axon or the myelin sheath. Although different proteins are abnormal in different forms of CMT disease, all mutations affect the normal function of the peripheral nerves. There is little correlation between the genotype and phenotype of CMT; it is common to see differing mutations result in various clinical phenotypes all within the same gene (Kang, 2024a).

Pattern of Inheritance

The pattern of inheritance varies with the type of CMT disease. CMT1, most cases of CMT2, and most intermediate forms are inherited in an autosomal dominant pattern. CMT4, a few CMT2 subtypes, and some intermediate forms are inherited in an autosomal recessive pattern. CMTX is inherited in an X-linked pattern. Some cases of CMT disease result from a new mutation and occur in people with no history of the disorder in their family. In rare cases the gene mutation causing CMT disease is a new mutation which occurs spontaneously in the individual's genetic material and has not been passed down through the family (Kang, 2024a).

CMT1

Charcot-Marie-Tooth disease type 1 (CMT1) is a demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and are usually slowly progressive and often associated with *pes cavus* foot deformity and bilateral foot drop (Bird, 2023). The six subtypes of CMT1 shown in Table 1 are clinically indistinguishable and are designated solely on molecular findings (Saporta et al., 2011)

Table 1: Molecular Genetics of CMT1 (Saporta et al., 2011)

Locus Name	Proportion of CMT1 (excluding CMTX)	Gene	Protein Product
CMT1A	70%-80%	*PMP22*	Peripheral myelin protein 22
CMT1B	10%-12%	*MPZ*	Myelin protein P_0
CMT1C	~1%	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-alpha factor
CMT1D	Unknown	*EGR2*	Early growth response protein 2
CMT1E	~1%	*PMP22*	Peripheral myelin protein 22 (sequence changes)
CMT1F/2E	Unknown	*NEFL*	Neurofilament light polypeptide

Charcot-Marie-Tooth disease type 1A (CMT1A) is an autosomal dominant disease that results from a duplication of the gene on chromosome 17 that carries the instructions for producing the peripheral myelin protein-22 (PMP-22). Overexpression of this gene causes the structure and function of the myelin sheath to be abnormal. A different neuropathy distinct from CMT1A called hereditary neuropathy with predisposition to pressure palsy (HNPP) is caused by a deletion of one of the PMP-22 genes. In this case, abnormally low levels of the PMP-22 gene result in episodic, recurrent demyelinating neuropathy (NINDS, 2007, 2023).

Charcot-Marie-Tooth disease type 1B (CMT1B) is an autosomal dominant disease caused by mutations in the gene that carries the instructions for manufacturing the myelin protein zero (P0), which is another critical component of the myelin sheath. Most of these mutations are point mutations. As a result of abnormalities in P0, CMT1B produces symptoms similar to those found in CMT1A (NINDS, 2007, 2023).

Other less common causes genetic causes of CMT1 result from mutations within *LITAF, EGR2, PMP22*, and *NEFL* genes, respectively (NINDS, 2023).

CMT2

Charcot-Marie-Tooth disease type 2 (CMT2) is an axonal (non-demyelinating) peripheral neuropathy characterized by distal muscle weakness and atrophy. Axonal peripheral neuropathy shows extensive clinical overlap with CMT1 (Bird, 2023). In general, individuals with CMT2 tend to be less disabled and have less sensory loss than individuals with CMT1 (Bird, 2023). It is less common than CMT1. CMT2A, the most common axonal form of CMT, is caused by mutations in Mitofusin 2, a protein associated with mitochondrial fusion. Symptoms are similar to those seen in CMT1, but people with CMT2 often have less disability and sensory loss than individuals with CMT1. Additionally, symptoms for CMT2 may have vocal cord or phrenic nerve involvement, causing speech or respiratory problems (NINDS, 2023).

Table 2: Molecular Genetics of CMT2 (Anthony Antonellis, 2018; Bird, 2023; Peter De Jonghe, 2011; Schindler, 2014; Züchner, 2013)

Locus	Proportion of CMT	Gene / Chromosome Locus	Protein Product
CMT2A1	Unknown	*KIF1B*	Kinesin-like protein KIF1B
CMT2A2[1]	20%	*MFN2*	Mitofusin-2
CMT2B	Unknown	*RAB7*A	Ras-related protein Rab-7
CMT2B1	Unknown	*LMNA*	Lamin A/C
CMT2B2	Unknown	*MED25*	Mediator of RNA polymerase II transcription subunit 25
CMT2C[2]	Unknown	*TRPV4*	Transient receptor potential cation channel subfamily V member 4
CMT2D[3]	3%	*GARS*	Glycyl-tRNA synthetase
CMT2E/1F[4]	4%	*NEFL*	Neurofilament light polypeptide
CMT2F	Unknown	*HSPB1*	Heat-shock protein beta-1
CMT2G	Unknown	12q12-q13	Unknown

CMT2H/2K	5%	*GDAP1*	Ganglioside-induced differentiation-associated protein-1
CMT2I/2J	Unknown	*MPZ*	Myelin protein P_0
CMT2L	Unknown	*HSPB8*	Heat-shock protein beta-8
CMT2N	Unknown	*AARS*	Alanine--tRNA ligase, cytoplasmic
CMT2O	Unknown	*DYNC1H1*	Cytoplasmic dynein 1 heavy chain 1
CMT2P	Unknown	*LRSAM1*	E3 ubiquitin-protein ligase LRSAM1
CMT2S	Unknown	*IGHMBP2*	DNA-binding protein SMUBP-2
CMT2T	Unknown	*DNAJB2*	DnaJ homolog subfamily B member 2
CMT2U	Unknown	*MARS*	Methionine--tRNA ligase, cytoplasmic

CMT3

Dejerine-Sottas disease (CMT3), is a severe demyelinating neuropathy that begins in infancy. Infants have severe muscle atrophy, weakness, and sensory problems. This rare disorder can be caused by mutations in multiple genes, including *PMP22, MPZ,* and *EGR2*, and can be inherited either dominantly or recessively (NINDS, 2023).

CMT4

Charcot-Marie-Tooth disease type 4 (CMT4) comprises several different subtypes of autosomal recessive demyelinating motor and sensory axonal neuropathies. Each neuropathy subtype is caused by a different genetic mutation, may affect a particular ethnic population, and produces distinct physiologic or clinical characteristics. Affected individuals have the typical CMT phenotype of distal muscle weakness and atrophy associated with sensory loss and, frequently, pes cavus foot deformity. Several genes have been identified as causing CMT4, including *GDAP1* (CMT4A), *MTMR13* (CMT4B1), *MTMR2* (CMT4B2), *SH3TC2* (CMT4C), *NDG1* (CMT4D), *EGR2* (CMT4E), *PRX* (CMT4F), *FDG4* (CMT4H), and *FIG4* (CMT4J) (Kang, 2024a; NINDS, 2007, 2023).

Table 3: Molecular Genetics of CMT4 (Bird, 2017; Delague, 2013; Hamid Azzedine, 2015; Li, 2013)

Locus Name	Proportion of CMT4	Gene	Protein Product
CMT4A[1]	Unknown	*GDAP1*	Ganglioside-induced differentiation-associated protein 1
CMT4B1		*MTMR2*	Myotubularin-related protein 2
CMT4B2		*SBF2*	Myotubularin-related protein 13
CMT4C[2]		*SH3TC2*	SH3 domain and tetratricopeptide repeats-containing protein 2
CMT4D		*NDRG1*	Protein NDRG1
CMT4E		*EGR2*	Early growth response protein 2
CMT4F		*PRX*	Periaxin
CMT4H[3]		*FGD4*	FYVE, RhoGEF and PH domain-containing protein 4
CMT4J[4]		*FIG4*	Phosphatidylinositol 3, 5 biphosphate

CMTX

CMTX is caused by a point mutation in the connexin-32 gene on the X chromosome. The connexin-32 protein is expressed in Schwann cells, which wrap around nerve axons and make up a single segment of the myelin sheath (NINDS, 2007, 2023). CMTX type 1 is characterized by a moderate to severe motor and sensory neuropathy. Hearing loss and central nervous system symptoms may also occur in certain affected families (Abrams, 2020).

Table 4: Molecular Genetics of CMTX (Bird, 2023; Kim, 2013)

Disease Name	Proportion of X-Linked CMT	Gene / Chromosome Locus	Protein Product
CMTX1[1]	90%	*GJB1*	Gap junction beta-1 protein (connexin 32)
CMTX2[2]	Unknown	Xp22.2	
CMTX3[1]			Not applicable
CMTX4[1]		*AIFM1*	Apoptosis-inducing factor 1
CMTX5[2]		*PRPS1*	Ribose-phosphate pyrophosphokinase 1
CMTX6[1]		*PDK3*	Pyruvate dehydrogenase kinase isoform 3

Hereditary Brachial Plexopathy (Hereditary Neuralgic Amyotrophy)

This condition is primarily characterized by painful injuries to the brachial plexus nerves as well as episodic weakness of the shoulder and arm. Other symptoms such as winging of the scapula, short stature, neck folds, small face, and hypotelorism may be present. Nerve conduction velocity is typically normal, and the histopathology of this condition is non-specific. The *septin 9 gene* (*SEPT9*) on chromosome 17 has been associated with this condition (Bromberg, 2023).

Giant Axonal Neuropathy

This condition is characterized by disorganization of cytoskeletal intermediate filaments stemming from a mutated form of gigaxonin. Patients with this disorder often have a signature physical appearance; red and kinked hair, high foreheads, long eyelashes, and pale complexions are all hallmarks of this condition. The central nervous system may be affected as well with cerebellar dysfunction, spasticity, and potentially intellectual disability as possible symptoms. Nerve biopsy may show axonal loss or another axonal dysfunction. This diagnosis is confirmed by testing of the *GAN* gene (Kang, 2024c).

Hereditary Sensory and Autonomic Neuropathies (HSANs)

This subsection of disorders primarily encompasses non-motor neuropathies and are characterized by major loss of myelinated and unmyelinated fibers. These conditions are not as common as hereditary motor neuropathies and primarily present with sensory dysfunction, although motor functions may be affected. There are five main types of HSAN, each caused by different genes. Genes are associated as shown below (Eichler, 2024):

Disease Name (subtype)	Gene(s) or Locus	Examples of symptoms
HSAN1 (A)	*SPTLC1*	Distal sensory loss, distal muscle wasting
HSAN1 (B)	3p24-p22	Axonal neuropathy with distal sensory impairment
HSAN1 (C)	*SPTLC2*	Distal sensory loss, distal muscle wasting
HSAN1 (D)	*ATL1*	Distal sensory loss, distal muscle wasting
HSAN1 (E)	*DNMT1*	Hearing loss, progressive dementia
HSAN1 (F)	*ATL3*	Distal sensory impairment
HSAN2 (A)	*HSN2*	Loss of pain, pressure, touch, and temperature sensation
HSAN2 (B)	*FAM134B*	Loss of pain, pressure, touch, and temperature sensation
HSAN2 (C)	*KIF1A*	Loss of pain, pressure, touch, and temperature sensation
HSAN2 (D)	*SCN9A*	Loss of pain and temperature sensation, hearing loss
HSAN3/Familial Dysautonomia	9q31	Dysautonomic crises, orthostatic hypotension
HSAN4/Congenital Insensitivity to Pain with Anhidrosis	*NTRK1*	Loss of pain sensation, thermoregulatory dysfunction
HSAN5	*NGFB*	Loss of pain and temperature sensation
HSAN6	*DST*	Lack of psychomotor development, respiratory difficulties
HSAN7	*SCN11A*	Inability to experience pain

Other unclassified HSANs exist, such as spastic paraplegia with ulcerations of the hands and feet (associated with *CCT5*) and sensory neuropathy with ichthyosis and anterior chamber syndrome (Eichler, 2024).

Genetic Testing

Charcot-Marie-Tooth disease is usually diagnosed by an extensive history and physical examination. The clinical diagnosis is then confirmed by electrodiagnostic tests like electromyography and nerve conduction velocity tests, and sometimes by nerve biopsy. Genetic testing is available for most types of CMT, and results are usually enough to confirm a diagnosis. Genetic testing can simplify the diagnosis of CMT by avoiding invasive procedures, such as nerve biopsy. In addition, early diagnosis can facilitate early interventions, including physical therapy. However, most therapies are only supportive (occupational, physical) and generally do not rely on the results of specific genetic testing (Kang, 2024a, 2024b). A positive genetic test can confirm diagnosis in most people with CMT. But a negative result does not exclude the disease, as an unidentified gene may be missed by DNA sampling (Charcot-Marie-Tooth News, 2023).

Genetic testing for CMT is complicated by the extensive underlying genetic heterogeneity. The CMT spectrum of disorders can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner. The most commonly identified CMT subtypes are CMT1A (*PMP22* duplication), CMTX1 (*GJB1* mutation), hereditary neuropathy with liability to pressure palsies (*PMP22* deletion), CMT1B (*MPZ* mutation), and CMT2A (*MFN2* mutation). Together, these five subtypes account for 92 percent of genetically defined CMT cases. All other CMT subtypes and associated mutations each account for <1

percent of genetically defined CMT (CMTA, 2023; Kang, 2024a). Genetic screening for relatives of a patient diagnosed with CMT is an option, but risk assessment depends on several factors, including accuracy of the diagnosis, determination of the mode of inheritance for the individual family, and results of molecular genetic testing (Kang, 2024a).

Proprietary Testing

Numerous genetic panels are available for the assessment of peripheral neuropathies, such as GeneDx's panel (64 genes) and Invitae's panel (83 genes) (GeneDx, 2024; Invitae, 2024). Other pane's include ones by Athena Diagnostics (23 genes) (Athena Diagnostics, 2023), Claritas Genomics (*PMP22* gene) (Claritas Genomics, 2023), MNG Laboratories (139 genes) (MNG Laboratories, 2022), Prevention Genetics (44 genes) (Prevention Genetics, 2023), and Variantyx's Genomic Unity panel (25 genes).

Clinical Utility and Validity

DiVincenzo et al. (2014) performed an analysis of the genetic landscape of CMT. 14 genes associated with CMT (*PMP22, GJB1, MPZ, MFN2, SH3TC2, GDAP1, NEFL, LITAF, GARS, HSPB1, FIG4, EGR2, PRX*, and *RAB7A*) were evaluated out of 3312 individuals. Deletions and duplications in the PMP22 gene consisted of about 78% of positive findings, followed by mutations in the *GJB1* (6.7%), *MPZ* (5.3%), and *MFN2* (4.3%) genes. 71% of the pathogenic mutations found were missense mutations. Overall, 95% of the positive results involved one of four genes (*PMP22, GJB1, MPZ, MFN2*). The authors conclude that these four genes should be screened first before proceeding with further genetic testing (DiVincenzo et al., 2014).

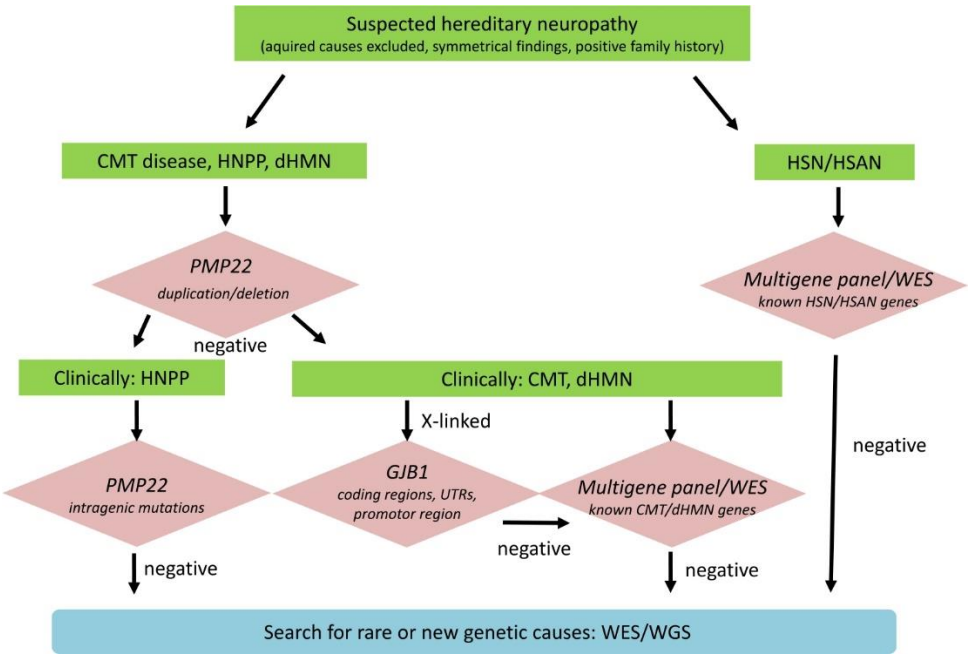
Pareyson et al. (2017) reviewed the current literature on CMT diagnosis stating that data justifies a step-wise algorithm considering a variety of factors, such as phenotype, nerve conduction velocities, and ethnicity. The authors note that NGS is steadily replacing older methods of sequencing in this algorithm. The authors propose evaluating the first few common genes (*PMP22*, *MPZ*, et al) and then considering larger sequencing methods such as NGS. However, due to the growing number of genes associated with CMT, these larger sequencing methods may be considered first-line. Finally, the authors state that due to the growing number of associated genes, newer classifications need to be discussed and validated further (Pareyson et al., 2017).

Rudnik-Schoneborn et al. (2016) evaluated the clinical features and genetic results of 1206 CMT patients and 124 affected relatives. Genetic detection rates were 56% in demyelinating CMT and 17% in axonal CMT. "Three genetic defects (*PMP22* duplication/deletion, *GJB1*/*Cx32* or *MPZ*/P0 mutation) were responsible for 89.3% of demyelinating CMT index patients in whom a genetic diagnosis was achieved, and the diagnostic yield of the three main genetic defects in axonal CMT (*GJB1*/*Cx32*, *MFN2*, *MPZ*/P0 mutations) was 84.2%". The authors concluded that "diagnostic algorithms are still useful for cost-efficient mutation detection and for the interpretation of large-scale genetic data made available by next generation sequencing strategies" (Rudnik-Schoneborn et al., 2016).

Vaeth et al. (2019) evaluated the effect of implementing a targeted next-generation sequencing (NGS) approach for identifying CMT. The authors stated that from 1992-2012, a total of 1442 CMT analyses were performed (through Sanger sequencing and other quantitative analyses) and a pathogenic variant was discovered in 21.6% of these cases. From this cohort, 195 samples that did not reach a definitive

diagnosis were sequenced by a custom 63-gene panel. The authors identified a 5.6% increase in diagnostic yield using this targeted NGS approach (Vaeth et al., 2019).

Cortese et al. (2020) investigated the effectiveness of NGS panels in CMT. 220 patients were enrolled in the study and a targeted CMT NGS panel was performed. After NGS sequencing, a molecular diagnosis based on a pathogenic variant was found in 30% of the cases and variants of unknown significance were found in 33% of the cases. 39% of the cases held mutations in *GJB1, MFN2*, and *MPZ* while the others held mutations in *SH3TC2, GDAP1, IGHMBP2, LRSAM1, FDG4,* and *GARS.* Copy number changes were detected in *PMP22, MPZ, MFN2, SH3TC2,* and *FDG4*. The authors conclude that "NGS panels are effective tools in the diagnosis of CMT, leading to genetic confirmation in one-third of cases negative for *PMP22* duplication/deletion, thus highlighting how rarer and previously undiagnosed subtypes represent a relevant part of the genetic landscape of CMT" (Cortese et al., 2020).



Rudnik-Schöneborn et al. (2020) suggested a diagnostic algorithm for genetic testing of suspected hereditary neuropathy. Advanced genetic sequencing allows for comprehensive evaluation of the pathogenic relevance of identified variants. As shown in the chart above, "If *PMP22* copy number analysis is negative, then clinical distinction of HNPP and CMT/dHMN will sort out patients for *PMP22* mutation analysis only and those for broader multigene testing. If a pedigree is compatible with X-linked inheritance, it is recommended to analyze coding and non-coding regions of *GBJ1*. Patients who are tested negative for known neuropathy genes may be included in further whole exome or genome sequencing (WES/WGS) to detect mutations in rare and new genes" (Rudnik-Schöneborn et al., 2020).

Yalcintepe et al. (2021) studied the importance of multiple gene analysis for diagnosis of Charcot Marie Tooth Disease. Fifty-five patients with suspected CMT phenotype were examined using a customized

multigene panel which was compared to the Multiplex Ligand Probe Amplification (MLPA) method. The custom panel identified 13 cases (7.15%) with a pathogenic/likely pathogenic variant. "The affected genes were *MARS1, NDRG1, GJB1, GDAP1, MFN2, PRX, SH3TC2*, and *FGD4*. Six cases (10.9%) had pathogenic variants in *GJB1* and *FGD4* genes, variants of unknown significance (VUS) in *HSPB3, CHRNA1, ARHGEF10,* and *KIF5A* genes. 21 cases (11.55%) had VUS with the genes *HSPB3, KIF1B, SCN11A, CHRNA1, HSPB1, FIG4, ARHGEF10, DHTKD1, SBF1, EGR2, SBF2, IGHMBP2, KIF5A*, and *DNAJB2*." The authors concluded that the NGS customized panel was beneficial, time-saving, and cost-effective in the diagnosis of CMT (Yalcintepe et al., 2021).

V. Guidelines and Recommendations

American Academy of Neurology (AAN), the American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R)

The Polyneuropathy Task Force that included 19 physicians with representatives from the American Academy of Neurology (AAN), the American Academy of Neuromuscular and Electrodiagnostic Medicine (AANEM), and the American Academy of Physical Medicine and Rehabilitation (AAPM&R) concluded that "genetic testing is established as useful for the accurate diagnosis and classification of hereditary polyneuropathies (Class I)" (England et al., 2009).

The Task Force stated that "for patients with a cryptogenic polyneuropathy who exhibit a classic hereditary neuropathy phenotype, routine genetic screening may be useful for CMT1A duplication/deletion and *Cx32* mutations in the appropriate phenotype (Class III). Further genetic testing may be considered guided by the clinical question." The Task Force recommended that "genetic testing should be conducted for the accurate diagnosis and classification of hereditary neuropathies (Level A)". The Task force further recommended that "Genetic testing may be considered in patients with a cryptogenic polyneuropathy and classic hereditary neuropathy phenotype (Level 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 [*PMP22]* duplication/HNPP deletion, Cx32 (*GJB1*), and *MFN2* mutation screening. There is insufficient evidence to support or refute the usefulness of routine genetic testing in cryptogenic polyneuropathy patients without a classic hereditary phenotype (Level U)" (England et al., 2009).

These guidelines were reaffirmed on January 22, 2022.

European Federation of Neurological Societies (EFNS)

The EFNS released recommendations on genetic testing for various types of peripheral neuropathies. Regarding CMT, they noted that "Given the rarity of AR CMT in the European population routine diagnostic screening of the many known genes is currently not feasible" but acknowledged that "Currently, molecular genetic testing can be offered for several of the more prevalent CMT genes." EFNS stated that PMP22 duplication should be tested first in patients presenting with CMT1, followed by sequencing of *GJB1*, *MPZ*, and *PMP22*. If a patient presents with CMT2, *MFN2* should be screened first, followed by *MPZ*. If a patient presents with intermediate CMT, *GJB1* and *MPZ* should be screened. EFNS

notes that in patients with hereditary neuropathy with liability to pressure palsies will be investigated for a *PMP22* deletion at the same time as a screening for a *PMP22* duplication (Burgunder et al., 2011).

However, routine diagnostic screenings for hereditary motor neuropathy (HMN) and hereditary sensory-autonomic neuropathy (HSAN) are not feasible due to low mutation frequencies. If screening is performed for these conditions, EFNS recommends *BSCL2* as the first candidate for screening in HMN. NTRK1 may also be screened for in congenital insensitivity to pain with anhidrosis patients (CIPA, a sub-phenotype of HSAN) and *RAB7* may be screened in CMT2B patients. Finally, *SEPT9* may be screened in the context of hereditary neuralgic amyotrophy (HNA) (Burgunder et al., 2011).

VI. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, under Hawaii Administrative Rules (HAR 1700.1-42), generally accepted standards of medical practice and review of medical literature and government approval status.

HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA's determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

Genetic testing is covered for level 1 or 2A recommendations of the National Comprehensive Cancer Network (NCCN and in accordance with Hawaii's Patients' Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4) or for QUEST members, the Hawaii Administrative Rules (HAR 1700.1-42).

VIII. Evidence-based Scientific References

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IX. Policy History

Action Date	Action
June 01, 2023	Policy created
December 03, 2024	Policy approved by Medical Directors
December 20, 2024	Policy approved at UMC
February 01, 2025	Policy effective date following notification period