Corporate Medical Policy

Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies AHS – M2072

File Name:	genetic_testing_for_diagnosis_of_inherited_peripheral_neuropathies
Origination:	01/01/2019
Last CAP Review:	07/2021
Next CAP Review:	07/2022
Last Review:	07/2021

Description of Procedure or Service

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, 2020a).

Related Policies
Nerve Fiber Density Testing AHS – M2112
General Genetic Testing, Germline Disorders AHS – M2145
General Genetic Testing, Somatic Disorders AHS – M2146
Celiac Disease Testing AHS – G2043

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for genetic testing for diagnosis of inherited peripheral neuropathies when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies is covered

1. Reimbursement is allowed for genetic counseling for genetic testing for Charcot-Marie-Tooth (CMT) disease and other inherited peripheral neuropathies. Genetic counseling is recommended for genetic testing of CMT disease or other inherited peripheral neuropathies.

2. Genetic Testing for CMT disease is considered medically necessary when the patient displays clinical features of CMT and a definitive diagnosis remains uncertain after history, physical examination, genetic counseling, and completion of conventional diagnostic studies

(i.e. nerve conduction studies and/or electromyography). If results indicate a demyelinating neuropathy, then first test for the most commonly identified CMT subtype, CMT1A (*PMP22* duplication).

3. Genetic testing for CMT is considered medically necessary for prenatal diagnosis of known familial mutation(s) in at-risk pregnancies

4. Peripheral nerve biopsy is considered medically necessary to diagnose CMT when clinical features are significantly suggestive of CMT and the genetic tests are negative.

5. Genetic testing for Hereditary Neuropathy with liability to Pressure Palsies (*PMP22* deletion) is considered medically necessary when the patient displays clinical features of HNPP and a definitive diagnosis remains uncertain after history, physical examination, genetic counseling, and completion of electrophysiologic studies.

6. Genetic testing for Hereditary Motor Neuropathy (HMN) (*BSCL2* gene) is considered medically necessary when the patient displays clinical features of HMN and a definitive diagnosis remains uncertain after history, physical examination, genetic counseling, and completion of electrophysiologic studies.

Note: For all other uncommon hereditary peripheral neuropathy gene testing, refer to policy, General Genetic Testing, Germline Disorders AHS – M2145.

When Genetic Testing for Diagnosis of Inherited Peripheral Neuropathies is not covered

Genetic testing for CMT in asymptomatic individuals is considered investigational.

Additional testing for other genes associated with CMT is considered investigational.

Policy Guidelines

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, 2019; UTD, 2021). 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, 2019).

Charcot-Marie-Tooth (CMT) 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, 2020a).

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 (Bird, 2020; NINDS, 2007). Typical symptoms include the following:

- Weakness of the foot and lower leg muscles, which may result in foot drop and a high-stepped gait with frequent ankle sprains, tripping or falls

- Foot deformities, such as pes cavus and hammertoes
- Distal calf muscle atrophy often occurs, causing the stork leg deformity or inverted champagne bottle appearance
- Weakness and muscle atrophy may occur in the hands, resulting in difficulty with carrying out fine motor skills.
- Sensory loss is gradual and mainly involves proprioception and vibration.
- Spinal deformities like kyphosis and scoliosis can often develop (NINDS, 2007).

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. Although in rare cases, individuals may have respiratory muscle weakness, CMT is not considered a fatal disease and people with most forms of CMT have a normal life expectancy (NINDS, 2007).

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, 2020a).

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. In the X-linked recessive patterns, only males develop the disease, although females who inherit the defective gene can pass the disease onto their sons. In the X-linked dominant pattern, an affected mother can pass on the disorder to both sons and daughters, while an affected father can only pass it onto his daughters. 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, 2020a).

CMT1
CMT1 is a demyelinating peripheral neuropathy characterized by distal muscle weakness and atrophy, sensory loss, and slow nerve conduction velocity (Bird, 2019). 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

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).

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).

The less common CMT1C, CMT1D, and CMT1E, which also have symptoms similar to those found in CMT1A, are caused by mutations in the LITAF, EGR2, and NEFL genes, respectively (NINDS, 2007).

CMT2

CMT2 is an axonal (non-demyelinating) peripheral neuropathy characterized by distal muscle weakness and atrophy. Nerve conduction velocities are usually within the normal range; however, occasionally they fall in the low-normal or mildly abnormal range (Bird, 2019). In general, individuals with CMT2 tend to be less disabled and have less sensory loss than individuals with CMT1 (Bird, 2019). 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. CMT2A has also been linked to mutations in the gene that codes for the kinesin family member 1B-beta protein, but this has not been replicated in other cases. Other less common forms of CMT2 are associated with various genes:

CMT2B (associated with RAB7), CMT2D (GARS). CMT2E (NEFL), CMT2H (HSP27), and CMT2l (HSP22) (NINDS, 2007).

Table 2: Molecular Genetics of CMT2 (Bird, 2019)

Locus	**Proportion of CMT**	**Gene / Chromosome Locus**	**Protein Product**
CMT2A1	Unknown	*KIF1B*	Kinesin-like protein KIF1B
CMT2A2	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	Unknown	*TRPV4*	Transient receptor potential cation channel subfamily V member 4

CMT2D	3%	*GARS*	Glycyl-tRNA synthetase
CMT2E/1F	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

(Züchner, 2013). 2. (Schindler, 2014). 3. (Anthony Antonellis, 2018). 4. (Peter De Jonghe, 2011)

CMT3

CMT3 or Dejerine-Sottas disease 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 a specific point mutation in the P0 gene or a point mutation in the PMP-22 gene (NINDS, 2007).

CMT4

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, 2019; NINDS, 2007).

Table 3: Molecular Genetics of CMT4 (Bird, 2019)

Locus Name	**Proportion of CMT4**	**Gene**	**Protein Product**
CMT4A		*GDAP1*	Ganglioside-induced differentiation-associated protein 1
CMT4B1		*MTMR2*	Myotubularin-related protein 2
CMT4B2		*SBF2*	Myotubularin-related protein 13

CMT4C	Unknown	*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

(Bird, 2017) 2. (Hamid Azzedine, 2015) 3. (Delague, 2013) 4. (Li, 2013)

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). CMTX type 1 is characterized by a moderate to severe motor and sensory neuropathy although symptoms tend to be less severe in women. Hearing loss and central nervous system symptoms may also occur in certain affected families (Abrams, 2020).

Table 4: Molecular Genetics of CMTX

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

(Bird, 2016); (Kim, 2013)

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, 2021).

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 other axonal dysfunction. This diagnosis is confirmed by testing of the *GAN* gene (Kang, 2019).

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, 2021):

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, 2021).

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, 2020a, 2020b).

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; Kang, 2020a). 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, 2020a). 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, 2018; Invitae, 2020). Other pane's include ones by Athena Diagnostics (23 genes) (Athena_Diagnostics, 2021), Claritas Genomics (*PMP22* gene) (Claritas_Genomics, 2021), MNG Laboratories (139 genes) (MNG_Laboratories, 2021), and Prevention Genetics (44 genes) (Prevention_Genetics, 2021).

Clinical Validity and Utility

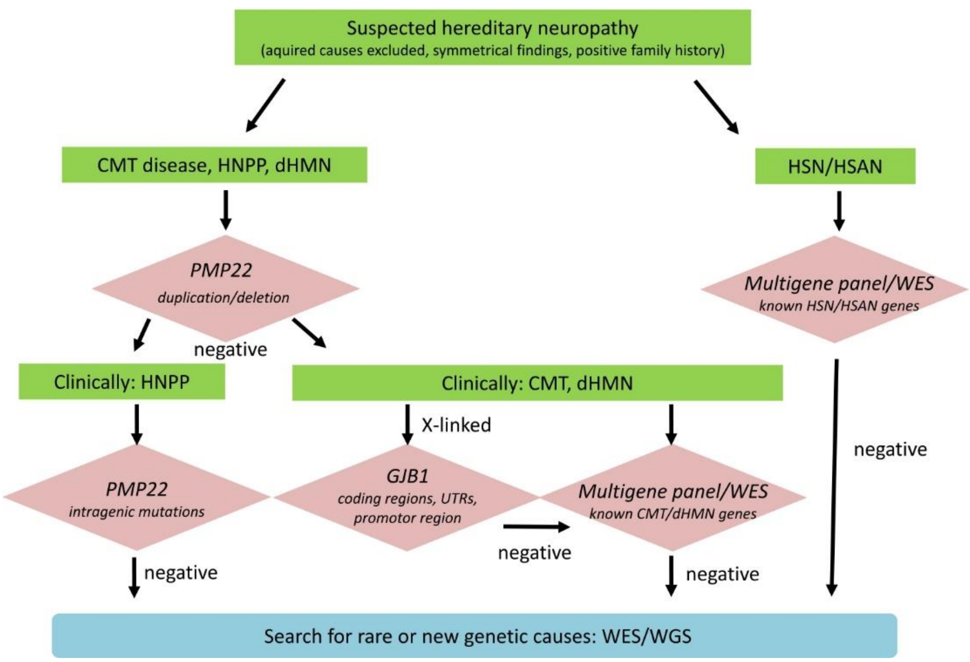
DiVincenzo et al performed an analysis of the genetic landscape of CMT. 14 genes associated with CMT (PMP22, GJB1, MPZ, MFN2, SH3TC2, GDAP1, NEFL, LITAF, GARS, SHPB1, FIG4, EGR2, PRX, and RAB7A) were evaluated out of 3312 individuals. Deletions and duplications in the PMP22 gene consisted of about 78% 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 concluded that these four genes should be screened first before proceeding with further genetic testing (DiVincenzo et al., 2014).

Pareyson (2017) reviewed the current literature on CMT diagnosis stating that data justifies a stepwise 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-Schöneborn and colleagues 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 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, Auer-Grumbach, and Senderek (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)."

Guidelines and Recommendations

AAN, AANEM, and AAPM&R (2009, reaffirmed 2013, reaffirmed 2019)

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). 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).

European Federation of Neurological Societies (EFNS, 2011)

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* (in case no male-to-male transmission is present), *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).

Applicable Federal Regulations

A search on the FDA website for "neuropathy" on April 22, 2021 yielded no results pertaining to genetic testing (FDA, 2021). Additionally, 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). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Reimbursement:

If five or more genes are being tested, use appropriate genetic procedure sequencing panel code.

Applicable service codes: 81324, 81325, 81326, 81403, 81404, 81405, 81406, 81448, 96040, S0265

Scientific Background and Reference Sources

Abrams, C. (2020). GJB1 Disorders: Charcot Marie Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1374/
Anthony Antonellis, P., Lev G Goldfarb, MD, and Kumaraswamy Sivakumar, MD. (2018). GARS-Associated Axonal Neuropathy. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1242/
Athena_Diagnostics. (2021). CMT Advanced Evaluation - Comprehensive.
Bird, T. (2017). GDAP1-Related Hereditary Motor and Sensory Neuropathy. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1539/
Bird, T. (2019). Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1358/
Bird, T. (2020). Charcot-Marie-Tooth (CMT) Hereditary Neuropathy Overview. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1358/
Bromberg, M. (2021). Brachial plexus syndromes. Retrieved from https://www.uptodate.com/contents/brachial-plexus-syndromes?sectionName=Hereditary%20brachial%20plexopathy&search=Hereditary%20Neuropathy%20with%20liability%20to%20Pressure%20Palsies&topicRef=6207&anchor=H18&source=see_link#H18
Burgunder, J. M., Schols, L., Baets, J., Andersen, P., Gasser, T., Szolnoki, Z., . . . Finsterer, J. (2011). EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *Eur J Neurol, 18*(2), 207-217. doi:10.1111/j.1468-1331.2010.03069.x
Claritas_Genomics. (2021). PMP22 Deletion/Duplication. Retrieved from http://www.claritasgenomics.com/test/pmp22-deletionduplication/index.html
CMTA. Genetic Testing. Retrieved from https://www.cmtausa.org/resource-center/treatment-management/genetic-testing/
Cortese, A., Wilcox, J. E., Polke, J. M., Poh, R., Skorupinska, M., Rossor, A. M., . . . Reilly, M. M. (2020). Targeted next-generation sequencing panels in the diagnosis of Charcot-Marie-Tooth disease. *Neurology, 94*(1), e51-e61. doi:10.1212/wnl.0000000000008672
Delague, V. (2013). Charcot-Marie-Tooth Neuropathy Type 4H. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK153601/
DiVincenzo, C., Elzinga, C. D., Medeiros, A. C., Karbassi, I., Jones, J. R., Evans, M. C., . . . Higgins, J. J. (2014). The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. *Mol Genet Genomic Med, 2*(6), 522-529. doi:10.1002/mgg3.106
Eichler, F. (2021). Hereditary sensory and autonomic neuropathies. Retrieved from https://www.uptodate.com/contents/hereditary-sensory-and-autonomic-neuropathies?search=Hereditary%20Neuropathy%20with%20liability%20to%20Pressure%20Palsies&topicRef=6207&source=see_link
England, J. D., Gronseth, G. S., Franklin, G., Carter, G. T., Kinsella, L. J., Cohen, J. A., . . . Sumner, A. J. (2009). Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of laboratory and genetic testing (an evidence-based review). *Neurology, 72*(2), 185. doi:10.1212/01.wnl.0000336370.51010.a1
FDA. (2021). Devices@FDA. Retrieved from https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm
GeneDx. (2018). Hereditary Neuropathy Panel. Retrieved from https://www.genedx.com/test-catalog/available-tests/hereditary-neuropathy-panel/
Hamid Azzedine, E. L., and Mustafa A Salih. (2015). Charcot-Marie-Tooth Neuropathy Type 4C. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1340/
Invitae. (2020). Invitae Comprehensive Neuropathies Panel. Retrieved from https://www.invitae.com/en/physician/tests/03200/#info-panel-assay_information

Kang, P. (2019). Overview of hereditary neuropathies. Retrieved from https://www.uptodate.com/contents/overview-of-hereditary-neuropathies?search=Hereditary%20Neuropathy%20with%20liability%20to%20Pressure%20Palsies&source=search_result&selectedTitle=1~16&usage_type=default&display_rank=1

Kang, P. (2020a). Charcot-Marie-Tooth disease: Genetics, clinical features, and diagnosis. Retrieved from https://www.uptodate.com/contents/charcot-marie-tooth-disease-genetics-clinical-features-and-diagnosis

Kang, P. (2020b). Charcot-Marie-Tooth disease: Management and prognosis. Retrieved from https://www.uptodate.com/contents/charcot-marie-tooth-disease-management-and-prognosis?topicRef=6220&source=see_link

Kim, J.-W., Kim, Hee-Jin. (2013). Charcot-Marie-Tooth Neuropathy X Type 5. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1876/

Li, J. (2013). Charcot-Marie-Tooth Neuropathy Type 4J. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK169431/

MNG_Laboratories. (2021). Charcot-Marie-Tooth Disease, Axonal (NGS Panel and Copy Number Analysis + mtDNA). Retrieved from https://mnglabs.com/tests/NGS345A/charcot-marie-tooth-disease-axonal-ngs-panel-and-copy-number-analysis-mtdna

NINDS. (2007). Charcot-Marie-Tooth Disease Fact Sheet. Retrieved from https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Charcot-Marie-Tooth-Disease-Fact-Sheet#3092_5

Pareyson, D., Saveri, P., & Pisciotta, C. (2017). New developments in Charcot-Marie-Tooth neuropathy and related diseases. *Curr Opin Neurol, 30*(5), 471-480. doi:10.1097/wco.0000000000000474

Peter De Jonghe, M., PhD and Albena K Jordanova, PhD. (2011). Charcot-Marie-Tooth Neuropathy Type 2E/1F. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1187/

Prevention_Genetics. (2021). Charcot-Marie-Tooth (CMT) - Comprehensive Panel. Retrieved from https://www.preventiongenetics.com/testInfo?val=Charcot-Marie-Tooth+%28CMT%29+-+Comprehensive+Panel

Rudnik-Schöneborn, S., Auer-Grumbach, M., & Senderek, J. (2020). Charcot-Marie-Tooth disease and hereditary motor neuropathies – Update 2020. *Medizinische Genetik, 32*(3), 207-219. doi:doi:10.1515/medgen-2020-2038

Rudnik-Schoneborn, S., Tolle, D., Senderek, J., Eggermann, K., Elbracht, M., Kornak, U., . . . Zerres, K. (2016). Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. *Clin Genet, 89*(1), 34-43. doi:10.1111/cge.12594

Saporta, A. S., Sottile, S. L., Miller, L. J., Feely, S. M., Siskind, C. E., & Shy, M. E. (2011). Charcot-Marie-Tooth disease subtypes and genetic testing strategies. *Ann Neurol, 69*(1), 22-33. doi:10.1002/ana.22166

Schindler, A. (2014). TRPV4-Associated Disorders. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK201366/

UTD. (2021). Patient education: Charcot-Marie-Tooth disease (The Basics). Retrieved from https://www.uptodate.com/contents/charcot-marie-tooth-disease-the-basics?search=Hereditary%20Neuropathy%20with%20liability%20to%20Pressure%20Palsies&topicRef=6207&source=see_link

Vaeth, S., Christensen, R., Duno, M., Lildballe, D. L., Thorsen, K., Vissing, J., . . . Jensen, U. B. (2019). Genetic analysis of Charcot-Marie-Tooth disease in Denmark and the implementation of a next generation sequencing platform. *Eur J Med Genet, 62*(1), 1-8. doi:10.1016/j.ejmg.2018.04.003

Züchner, S. (2013). Charcot-Marie-Tooth Neuropathy Type 2A. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK1511/

Specialty Matched Consultant Advisory Panel review 7/2019

Medical Director review 7/2019

Specialty Matched Consultant Advisory Panel review 7/2020

Medical Director review 7/2020

Specialty Matched Consultant Advisory Panel review 7/2021

Medical Director review 7/2021

Policy Implementation/Update Information

1/1/2019 BCBSNC will provide coverage for genetic testing for diagnosis of inherited peripheral neuropathies when it is determined to be medically necessary because criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (jd)

8/13/2019 Specialty Matched Consultant Advisory Panel review 7/2019. Medical Director review 7/2019 (jd)

9/10/2019 Reviewed by Avalon 2nd Quarter 2019 CAB. Related Policies added to Description section. When Covered section revised as follows: Item 1, added "or other inherited peripheral neuropathies"; item 2, added "If results indicate a demyelinating neuropathy, then first test for the most commonly identified CMT subtype, CMT1A (PMP22 duplication.", and removed items a. and b. related to specific values for velocity testing in nerve conduction and specific cascade testing; added item 6 for Genetic testing for Hereditary Motor Neuropathy (HMN) (BSCL2 gene), and added "Note" which refers to policy, General Genetic Testing, Germline Disorders AHS – M2145 for all other uncommon hereditary peripheral neuropathy gene testing. Removed the following statement from the When Not Covered section: "Genetic testing for all other inherited peripheral neuropathies is considered investigational". Code table removed from the Billing/Coding section and reimbursement statement added. Policy guidelines and references updated. Medical Director review. (jd)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. (hb)

7/28/20 Reviewed by Avalon 2nd Quarter 2020 CAB. Policy guidelines and references updated. Specialty Matched Consultant Advisory Panel review 7/2020. Medical Director review 7/2020. (jd)

8/24/21 Reviewed by Avalon 2nd Quarter 2021 CAB. The following statement was added to the When Not Covered section: "Genetic testing for CMT in asymptomatic individuals is considered investigational." Background, policy guidelines, and references updated. Specialty Matched Consultant Advisory Panel review 7/2021. Medical Director review 7/2021. (jd)