Medical Policy

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Title: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Description/Background

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.[1]

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

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

A genetic etiology of 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.[2] A family history of at least 3 generations with details on health issues, cause of death, and age at death should be collected.

Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure.[3] CMT disease is genetically and clinically heterogeneous. Variants in more than 30 genes and more than 44 different genetic loci have been associated with inherited neuropathies.[4] Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different 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.[5]

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).[6] 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	of CMT1
CMT1B	*MPZ*	Myelin P0 protein	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	*MED25*	Mediator of RNA polymerase II transcription subunit 25	
CMT2C	*TRPV4*	Transient receptor potential cation channel subfamily V member 4	
CMT2D	*GARS*	Glycyl-tRNA synthetase	
CMT2F	*HSPB1*	Heat-shock protein beta-1	
CMT2G		E3 ubiquitin-protein ligase LRSAM1	

CMT2H/2K	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT2I/2J	*MPZ*	Myelin P0 protein	
CMT2L	*HSPB8*	Heat-shock protein beta-8	
CMT2M	*DNM2*	Dynamin 2	
CMT2N	*AARS*	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	*MARS*	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	
X-linked CMT			
CMTX3	*Xq26*	Unknown	
CMTX4	*AIFM1*	Apoptosis-inducing factor 1	
CMTX5	*PRPS1*	Ribose-phosphate pyrophosphokinase 1	
CMTX6	*PDK3*	Pyruvate dehydrogenase kinase isoform 3	

Adapted from Bird (2016).[6,]
CMT: Charcot-Marie-Tooth.
The clinical features of CMT are briefly summarized.

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.[7] Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) result in the most severe phenotype, whereas 3 normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.[6]

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.[6] The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

X-Linked CMT

CMT X type 1 (CMTX1) is characterized by a moderate-to-severe motor and sensory neuropathy in affected male and mild to no symptoms in carrier females.[8] Sensorineural deafness and central nervous system symptoms also occur in some families. CMT X type 1 is inherited in an X-linked dominant manner. Molecular genetic testing of *GJB1* (*Cx32*), which is available on a clinical basis, detects about 90% of cases of CMT X type 1.

CMT Type 4

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

Hereditary Neuropathy With Liability to Pressure Palsies

The largest proportion of CMT1 cases are due to variants in *PMP22*. In HNPP (also called tomaculous neuropathy), inadequate production of *PMP22* causes nerves to be more susceptible to trauma or minor compression or entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some have reported presentation as early as birth or as late as the seventh decade of life.[9] The prevalence is estimated at 16 persons per 100,000, although some authors have indicated a potential for underdiagnosis of the disease.[9] An estimated 50% of carriers are asymptomatic and do not display abnormal

neurologic findings on clinical examination.[10] 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.[10] 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.[11] Studies have also reported that SNV frequency may vary considerably by ethnicity.[12] About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.[13]

TREATMENT

Currently there is no therapy to slow the progression of neuropathy for inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with functional activities and physiological adaptations with exercise.[14] Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.[15] Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended for patients with CMT.[6]

Supportive treatment for HNPP can include transient bracing (eg, wrist splint or ankle-foot orthosis) which may become permanent in some cases of foot drop.[16] Prevention of HNPP manifestations can be accomplished by wearing protective padding (eg, elbow or knee pads) to prevent trauma to nerves during activity. Some have reported that vincristine should also be avoided in HNPP patients.[6,16] 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.[17] 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.[18] The trial demonstrated the safety and tolerability of the drug. Mandel et al (2015) included this randomized controlled trial and 3 other trials (1 of ascorbic acid, 2 of PXT3003) in a meta-analysis.[19]

MOLECULAR GENETIC TESTING

Multiple laboratories offer individual variant testing for genes involved in hereditary sensory and motor neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation sequencing followed by deletion/duplication analysis (ie, with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in *MFN2,* whole gene or select 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).[20] The clinical sensitivity (ie, the proportion of positive tests if the disease is present) for the detection of deletions/duplications or mutations to PMP22 was about 50% and 1%, respectively, for single nucleotide variants. The clinical specificity (ie, the proportion of negative tests if the disease is not present) was nearly 100%.

A number of genetic panel tests for the assessment of peripheral neuropathies are commercially available. For example, GeneDx (Gaithersburg, MD) offers an Axonal CMT panel, which uses next-generation sequencing and exon array comparative genomic hybridization. The genes tested include: *AARS*, *AIFM1*, *BSCL2*, *DNAJB2, DNM2, DYNC1H1, GAN, GARS, GDAP1, GJB1, GNB4, HARS, HINT1, HSPB1, HSPB8, IGHMBP2, INF2, KIF5A, LMNA, LRSAM1, MFN2, MME, MORC2, MPZ, NEFL, PLIKHG5, 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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

Medical Policy Statement

The safety and effectiveness of genetic testing for inherited peripheral neuropathies have been established. It may be considered a useful diagnostic option for patients meeting the specified selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusions:
Genetic testing for an inherited peripheral neuropathy is considered established under the following conditions:

- The diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to clinical signs and symptoms but a definitive diagnosis cannot be made; **AND**

- The following testing strategy is utilized:
  - Initial genetic testing of *PMP22* (duplications or deletions), *GJB1* (Cx32) and *MFN2*.
    - If *PMP22* or *GJB1* or *MFN2* is **positive**, no further testing is indicated
    - If *PMP22, GJB1* and *MFN2* are **negative**, test for the genomic sequence analysis panel that includes at least 5 peripheral neuropathy-related genes (eg, *BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1*)

Exclusions:
- Genetic testing for an inherited peripheral neuropathy is excluded for all other indications

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81324	81325	81326	81403	81404	81405
81406	81448	81479			

Other codes (investigational, not medically necessary, etc.):

NA

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful.

Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.
Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

TESTING FOR GENES ASSOCIATED WITH INHERITED PERIPHERAL NEUROPATHIES

Clinical Context and Test Purpose

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

The question addressed in this evidence review is: Does the use of genetic testing improve health outcomes compared with a management strategy without testing?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with suspected inherited peripheral neuropathy who present with sensory, motor, or mixed findings, and sometimes with other findings. Charcot-Marie-Tooth (CMT) disease is clinically heterogeneous.

Interventions

The relevant intervention of interest is testing for variants associated with CMT, by deletion or duplication analysis, usually by multiplex ligation-dependent probe amplification, and gene sequencing, usually by next-generation sequencing.

Genetic counseling is particularly important for CMT given the extreme genetic heterogeneity of the disorder.

Comparators

The relevant comparator of interest is a clinical diagnosis of an inherited peripheral neuropathy made using a combination of clinical features, family pedigree, and characteristic nerve conduction velocity/electromyography studies. However, subtypes of CMT are defined based on their genotype.

Outcomes

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

Testing can be conducted during diagnostic evaluation, and follow-up should be continued for years after diagnosis.

Study Selection Criteria
For the evaluation of clinical validity, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
England et al (2009) reported on the role of laboratory and genetic tests in the evaluation of distal symmetric polyneuropathies concluded that genetic testing is established as useful for the accurate diagnosis and classification of hereditary polyneuropathies in patients with a cryptogenic polyneuropathy who exhibit a classical hereditary neuropathy phenotype.[3] Six studies included in the review showed that when the test for *CMT1A* duplication is restricted to patients with clinically probable CMT1 (ie, autosomal dominant, primary demyelinating polyneuropathy), the yield is 54% to 80%, compared with testing a cohort of patients suspected of having any variety of hereditary peripheral neuropathies, where the yield is only 25% to 59% (average, 43%).

Sequential Testing
Given the genetic complexity of CMT, many commercial and private laboratories evaluate CMT with a testing algorithm based on patients' presenting characteristics. For the evaluation of the clinical validity of genetic testing for CMT, we included studies that evaluated patients with clinically suspected CMT who were evaluated with a genetic testing algorithm that was described in the study.

Saporta et al (2011) reported results from genetic testing of 1024 patients with clinically suspected CMT who were evaluated at a single institution's CMT clinic from 1997 to 2009.[4] Patients who were included were considered to have CMT if they had a sensorimotor peripheral neuropathy and a family history of a similar condition. Patients without a family history of neuropathy were considered to have CMT if their medical history, neurophysiological testing, and neurologic examination were typical for CMT1, CMT2, CMTX, or CMT4. Seven hundred eighty-seven patients were diagnosed with CMT; of those, 527 (67%) had a specific genetic diagnosis as a result of their visit. Genetic testing decisions were left up to the treating clinician, and the authors noted that decisions about which genes to test changed during the study. Most (98.2%) of those with clinically diagnosed CMT1 had a genetic diagnosis, and of all of the patients with a genetic diagnosis, most (80.8%) had a clinically diagnosed CMT1. The authors characterized several clinical phenotypes of CMT based on clinical presentation and physiologic testing.

Rudnik-Schoneborn et al (2016) reported on results from genetic testing of 1206 index patients and 124 affected relatives who underwent genetic testing at a single reference laboratory from 2001 to 2012.[22] Patients were referred by neurologic or genetic centers throughout Germany,

and were grouped by age at onset (early infantile [<2 years], childhood [2-10 years], juvenile [10-20 years], adult [20-50 years], late adult [>50 years]), and by electroneurographic findings. Molecular genetic methods changed over the course of the study, and testing was tiered by patient features and family history. Of the 674 index patients with a demyelinating CMT phenotype on nerve conduction studies, 343 (51%) had a genetic diagnosis; of the 340 index patients with an axonal CMT phenotype, 45 (13%) had a genetic diagnosis; and of the 192 with hereditary neuropathy with liability to pressure palsies, 67 (35%) had a genetic diagnosis. The most common genetic diagnoses differed by nerve conduction phenotype: of the 429 patients genetically identified with demyelinating CMT (index and secondary), 89.3% were detected with *PMP22* deletion or duplication (74.8%), *GJB1/Cx32* (8.9%), or *MPZ/P0* (5.6%) variant analysis. In contrast, of the 57 patients genetically identified with axonal CMT (index and secondary), 84.3% were detected with *GJB1/Cx32* (42.1%), *MFN2* (33.3%), or *MPZ/P0* (8.8%) variant analysis.

In an earlier study, Gess et al (2013) reported on sequential genetic testing for CMT-related genes from 776 patients at a single center for suspected inherited peripheral neuropathies from 2004 to 2012.[23] Most patients (n=624) were treated in the same center. The test strategy varied based on electrophysiologic data and family history. The testing yield was 66% (233/355) in patients with CMT1, 35% (53/151) in patients with CMT2, and 64% (53/83) in patients with HNPP. Duplications on chromosome 17 were the most common variants in CMT1 (77%), followed by *GJB1* (13%) and *MPZ* (8%) variants among those with positive genetic tests. For CMT2 patients, *GJB2* (30%) and *MFN2* (23%) variants were most common among those with positive genetic tests.

Ostern et al (2013) reported on a retrospective analysis of cases of CMT diagnostic testing referred to a single reference laboratory in Norway from 2004 to 2010.[24] Genetic testing was stratified based on clinical information supplied on patient requisition forms based on age of onset of symptoms, prior testing, results from motor nerve conduction velocity, and patterns of inheritance. The study sample included 435 index cases of a total of 549 CMT cases tested (other tests were for at risk family members or other reasons.) Patients were grouped based on whether they had symptoms of polyneuropathy, classical CMT, with or without additional symptoms or changes in imaging, or had atypical features or the physician suspected an alternative diagnosis. Among the cases tested, 72 (16.6%) were found to be variant-positive, all of whom had symptoms of CMT. Most (69/72 [95.8%]) of the positive molecular genetic findings were *PMP22* region duplications or sequence variants in *MPZ*, *GJB1*, or *MFN2* genes.

Murphy et al (2012) reported on the yield of sequential testing for CMT-related gene variants from 1607 patients with testing sent to a single center.[25] Of the 916 patients seen in the authors' clinic, 601 (65.6%) had a primary inherited neuropathy, including 425 with CMT and 46 with HNPP. Of the 425 with a clinical diagnosis of CMT, 240 had CMT1 (56.5%), and 115 (27.1%) had CMT2. Of those with CMT, 266 (62.6%) of 425 received a genetic diagnosis, most frequently (92%) with a variant in 1 of 4 genes (*PMP22* duplication, and *GJB1*, *MPZ*, and *MFN2*).

Uchôa Cavalcanti (2021) reported on results from genetic testing of 503 patients (94 families and 192 unrelated individuals) who underwent testing in a Brazilian neuromuscular outpatient clinic from 2015 to 2020.[26] The diagnosis of CMT was established based on the presence of slowly progressive, motor and sensory neuropathy, independent of any family history. Patients were assessed utilizing clinical and neurophysiological data along with targeted gene panel sequencing. Among the 503 patients, a genetic diagnosis was reported in 394 patients (77

families and 120 unrelated individuals). The following confirmed genetic diagnoses were identified: demyelinating CMT (n=317), intermediate CMT (n=34), and axonal CMT (n=43). The genetic diagnosis rate in probands was 68.9% (197/286). The most common causative genes were PMP22 duplication GJB1, MFN2, GDAP1, MPZ, PMP22 point mutation, NEFL, SBF2, and SH3TC2.

In addition to sequential testing algorithms, some studies were reported on the yield of multigene testing panels, most often using next-generation sequencing methods. Studies with populations of suspected inherited motor or sensory neuropathy that reported on next-generation sequencing panel test results are summarized in Table 2.

Table 2. Summary of Genetic Panel Tests in Charcot-Marie-Tooth

Study	N	Population	Test	Diagnostic Yield (NGS Panel)	VUS (NGS Panel)
Antoniadi et al (2015)[27]	448	Suspected inherited peripheral neuropathy, with supportive NCV, some with negative testing for *PMP2*	56-gene NGS panel	137 (31%) patients (31 genes)	NR
DiVincenzo et al (2014)[28]	17,377; 503 with NGS	Suspected peripheral neuropathy, referred to a central laboratory	14-gene NGS panel and *PMP22* del/dup by MLPA	95 (18.9%) patients (8 genes)	38 (7.5%) patients (11 genes)
Volodarsky et al (2021)[29]	2517	Suspected diagnosis of CMT, referred to a molecular genetics laboratory	34-gene NGS panel	440 (17.5%) patients; 6 genes constituted 80% of the overall results	NR

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

Genotype-Phenotype Correlations

There is significant clinical variability within and across subtypes of CMT. Therefore, some studies have evaluated genotype-phenotype correlations within CMT cases. For example, Sanmaneechai et al (2015) characterized genotype-phenotype correlations in patients with CMT1B regarding *MPZ* variants in a cohort of 103 patients from 71 families.[30] Patients underwent standardized clinical assessments and clinical electrophysiology. There were 47 different *MPZ* variants and 3 characteristic ages of onset: infantile (age range, 0to 5 years), childhood (age range, 6to 20 years), and adult (age range, ≥21 years). Specific variants clustered by age group, with only 2 variants found in more than 1 age group.

Karadima et al (2015) investigated the association between *PMP22* variants and clinical phenotype in 100 Greek patients referred for genetic testing for HNPP.[31] In the 92 index cases, the frequency of *PMP22* deletions was 47.8% and the frequency of *PMP22* micro-variants was 2.2%. Variant-negative patients were more likely to have an atypical phenotype (41%), absent family history (96%), and nerve conduction study findings not fulfilling HNPP criteria (80.5%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive

correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing. The clinical utility of genetic testing for hereditary peripheral neuropathies depends on how the results can be used to improve patient management. Published data for the clinical utility of genetic testing for inherited peripheral neuropathies is lacking.

The diagnosis of an inherited peripheral neuropathy can generally be made clinically. However, when the diagnosis cannot be made clinically, a genetic diagnosis may add incremental value. A diagnosis of an inherited peripheral neuropathy is important to direct therapy, regarding early referrals to physical therapy and avoidance of potentially toxic medications. Some specific medications for CMT are under investigation, but their use is not well-established. There are significant differences in prognosis for different forms of CMT, although whether different prognosis leads to choices in therapy that lead to different outcomes is uncertain. In some cases, genetic diagnosis of an inherited peripheral neuropathy may have potential to avoid other diagnostic tests.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies was identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. There is evidence from observational studies to support 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 and, in turn, to initiate supportive therapies.

Section Summary: Testing for Genes Associated with Inherited Peripheral Neuropathies

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

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 for hereditary neuropathy with liability to pressure palsies (HNPP), the diagnostic testing is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and HNPP was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, in order to initiate supportive therapies. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

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

American Academy of Neurology

In 2009, the American Academy of Neurology (AAN) and 2 other specialty societies published an evidence-based, tiered approach for the evaluation of distal symmetric polyneuropathy and suspected hereditary neuropathies, which concluded the following (Table 3).[3]

Table 3. Recommendations on Distal Symmetric Polyneuropathy and Suspected Hereditary Neuropathies

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

CMT: Charcot-Marie-Tooth; HNPP: hereditary neuropathy with liability to pressure palsies; LOE: level of evidence.
a Grade A: established as effective, ineffective, or harmful for the given condition in the specified population; grade C: possibly effective, ineffective, or harmful for the given condition in the specified population; grade U: data inadequate or conflicting; given current knowledge.

The American Academy of Neurology website indicates the recommendations were reaffirmed on January 26, 2019, and indicated an update is in progress.

American Academy of Family Physicians

In 2020, the American Academy of Family Physicians recommended genetic testing for a patient with suspected peripheral neuropathy, if basic blood tests are negative, electrodiagnostic studies suggest an axonal etiology, and diseases such as diabetes, toxic medications, thyroid disease, vitamin deficiency and vasculitis can be ruled out.[32]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 4.

Table 4. Summary of Key Trials

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

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD) MolDX: Molecular Diagnostic Tests (MDT) L36807
Original effective date: 02/16/2017
Revision effective date: 12/30/2021

CMS National Coverage Policy

Title XVIII of the Social Security Act (SSA) §1862(a)(1)(A), states that no Medicare payment shall be made for items or services that "are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of malformed body member."

Covered Tests

Please refer to the MolDX website www.palmettogba.com/MolDX for covered and excluded tests' specific coding and billing information.

Per the Palmetto GBA MolDx website, accessed 2/1/2023:

> Medicare is a defined benefit program. In order to be considered for Medicare coverage, an item or service must fall within a statutory benefit category. Although IOM 100-2, Ch. 15, Sec 10 identifies “Diagnostic X-Ray tests, laboratory tests, and other diagnostic tests;” as a benefit category; Sec. 1862 (1)(A) Statutory Exclusion “except for items and services that are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member,” must also be applied. In order to be paid under this benefit category, a diagnostic test must be ordered by a physician who is treating the beneficiary and the results used in the management of a beneficiary’s specific medical problem. Although many molecular diagnostic tests may provide valid and useful information, they do not meet this definition.
>
> Does the test fall within a Medicare benefit category?
> Based on the Medicare Benefit requirements, the following test types are examples of services that may not be considered a benefit (statutory excluded) and therefore would be denied as Medicare Excluded tests:

- Tests considered screening in the absence of clinical signs and symptoms of disease that are not specifically identified by the law
- Tests that confirm a diagnosis or known information
- Tests to determine risk for developing a disease or condition
- Tests performed to measure the quality of a process
- Tests without diagnosis specific indications
- Tests identified as investigational by available literature and/or the literature supplied by the developer, and are not a part of a clinical trial
- Tests typically performed on patients less than 65 years of age and outside of the Medicare population
    - Tests performed on patients receiving Medicare benefits less than 65 years will be reviewed on a case-by-case basis

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article Billing and Coding MolDX: Molecular Diagnostic Tests (MDT) (A57772)
Original Effective Date: 11/01/2019
Revision Effective Date: 01/01/2023

Codes 81324, 81325, 81326, 81403, 81404, 81405, 81405, 81406, 81479, and 81448 are listed in the Group 1 Codes.

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article Billing and Coding MolDX: Repeat Germline Testing (A57100)
Original Effective Date: 06/14/2020
Revision Effective Date: 01/01/2022

Codes are identified which may only be covered for one test per lifetime.
Codes 81324, 81325, 81326,81403, 81404, 81405, 81406, and 81448 are listing the Group 1 Codes.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Genetic Testing and Counseling

References

1. Burgunder JM, Schols L, Baets J et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. Eur J Neurol 2011; 18(2): 207-17. PMID 20500522
2. Alport AR, Sander HW. Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. Continuum (Minneap Minn) 2012; 18(1): 13-38. PMID 22810068
3. England JD, Gronseth GS, Franklin G et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. Jan 13 2009; 72(2): 185-92. PMID 19056666
4. Saporta AS, Sottile SL, Miller LJ et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. Ann Neurol. Jan 2011; 69(1): 22-33. PMID 21280073
5. Cornett KM, Menezes MP, Bray P, et al. Phenotypic variability of childhood Charcot-Marie-Tooth disease. JAMA Neurol. Jun 01 2016;73(6):645-651. PMID 27043305
6. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle (WA): University of Washington; 2020.
7. Stankiewicz P, Lupski JR. The genomic basis of disease, mechanisms and assays for genomic disorders. Genome Dyn. 2006;1:1-16. PMID 18724050
8. Abrams CK. GJB1 Disorders: Charcot Marie Tooth Neuropathy (CMT1X) and Central Nervous System Phenotypes. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews. Seattle, WA: University of Washington; 2020.
9. Meretoja P, Silander K, Kalimo H et al. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. Neuromuscul Disord. Dec 1997; 7(8): 529-32. PMID 9447611
10. Celik Y, Kilincer C, Hamamcioglu MK et al. Hereditary neuropathy with liability to pressure palsies in a Turkish patient (HNPP): a rare cause of entrapment neuropathies in young adults. Turk Neurosurg. Jan 2008; 18(1): 82-84. PMID 1832985
11. Taioli F, Cabrini I, Cavallaro T et al. Inherited demyelinating neuropathies with micromutations of peripheral myelin protein 22 gene. Brain. Feb 2011; 134(Pt 2): 608-17. PMID 21252112
12. Bissar-Tadmouri N, Parman Y, Boutrand L et al. Mutational analysis and genotype/phenotype correlation in Turkish Charcot-Marie-Tooth Type 1 and HNPP patients. Clin Genet. Nov 2000; 58(5): 396-402. PMID 11140841
13. Dubourg O, Mouton P, Brice A et al. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord. Mar 2000; 10(3): 206-8. PMID 10734269
14. Sman AD, Hackett D, Fiatarone Singh M, et al. Systematic review of exercise for Charcot-Marie-Tooth disease. J Peripher Nerv Syst. Dec 2015;20(4):347-362. PMID 26010435
15. Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. Adv Exp Med Biol. 2009; 652: 207-24. PMID 20225028
16. Chrestian N. Hereditary neuropathy with liability to pressure palsies. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. Gene Reviews. Seattle, WA: University of Washington; 2020.
17. Lewis RA, McDermott MP, Herrmann DN et al. High-dosage ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A: results of a randomized, double-masked, controlled trial. JAMA Neurol. Aug 2013; 70(8): 981-7. PMID 23797954
18. Attarian S, Vallat JM, Magy L, et al. An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in

patients with Charcot-Marie-Tooth disease type 1A. Orphanet J Rare Dis. Dec 18 2014; 9: 199. PMID 25519680
19. Mandel J, Bertrand V, Lehert P, et al. A meta-analysis of randomized double-blind clinical trials in CMT1A to assess the change from baseline in CMTNS and ONLS scales after one year of treatment. Orphanet J Rare Dis. Jun 13 2015; 10: 74. PMID 26070802
20. Aretz S, Rautenstrauss B, Timmerman V. Clinical utility gene card for: HMSN/HNPP HMSN types 1, 2, 3, 6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA); HNPP. Eur J Hum Genet. Sep 2010; 18(9). PMID 20512157
21. GeneDx. Axonal CMT Panel. https://www.genedx.com/test-catalog/available-tests/axonal-cmt-panel-1/ Accessed 2/1/23.
22. Rudnik-Schoneborn S, Tolle D, Senderek J, et al. Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. Clin Genet. Jan 2016;89(1):34-43. PMID 25850958
23. Gess B, Schirmacher A, Boentert M, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord. Aug 2013; 23(8): 647-651. PMID 23743332
24. Ostern R, Fagerheim T, Hjellnes H, et al. Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies. BMC Med Genet. Sep 21 2013;14:94. PMID 24053775
25. Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry. Jul 2012; 83(7): 706-710. PMID 22577229
26. Uchôa Cavalcanti EB, Santos SCL, Martins CES, et al. Charcot-Marie-Tooth disease: Genetic profile of patients from a large Brazilian neuromuscular reference center. J Peripher Nerv Syst. Sep 2021; 26(3): 290-297. PMID 34190362
27. Antoniadi T, Buxton C, Dennis G, et al. Application of targeted multi-gene panel testing for the diagnosis of inherited peripheral neuropathy provides a high diagnostic yield with unexpected phenotype-genotype variability. BMC Med Genet. Sep 21 2015;16:84. PMID 26392352
28. DiVincenzo C, Elzinga CD, Medeiros AC, et al. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. Mol Genet Genomic Med. Nov 2014; 2(6): 522-529. PMID 25614874
29. Volodarsky M, Kerkhof J, Stuart A, et al. Comprehensive genetic sequence and copy number analysis for Charcot-Marie-Tooth disease in a Canadian cohort of 2517 patients. J Med Genet. Apr 2021; 58(4): 284-288. PMID 32376792
30. Sanmaneechai O, Feely S, Scherer SS, et al. Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain. Nov 2015; 138(Pt 11): 3180-3192. PMID 26310628
31. Karadima G, Koutsis G, Raftopoulou M, et al. Mutational analysis of Greek patients with suspected hereditary neuropathy with liability to pressure palsies (HNPP): a 15-year experience. J Peripher Nerv Syst. Jun 2015; 20(2): 79-85. PMID 26110377
Castelli G, Desai KM, Cantone RE. Peripheral Neuropathy: Evaluation and Differential Diagnosis. Am Fam Physician. Dec 15 2020; 102(12): 732-739. PMID 33320513

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references 3/16/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/20/13	9/10/13	Joint policy established
3/1/15	12/9/14	12/29/14	Routine maintenance. Addition of CPT codes 81404, 81405, 81406 and 81479. Status updated to established when criteria are met.
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance CPT code 81403 added Reference and rationale updated
7/1/18	4/17/18	4/17/18	Routine maintenance; addition of code 81448.
7/1/19	4/16/19		Routine maintenance; inclusions revised with gene testing strategy
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance Ref 26,29 added
7/1/23	4/18/23		Routine maintenance (jf) Vendor managed NA

Next Review Date: 2nd Qtr, 2023

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR THE DIAGNOSIS OF INHERITED PERIPHERAL NEUROPATHIES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered when criteria are met.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.