Medical Policy

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Title: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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Populations	Interventions	Comparators	Outcomes
Individuals: • With suspected inherited motor and sensory peripheral neuropathy	Interventions of interest are: • Testing for genes associated with inherited peripheral neuropathies	Comparators of interest are: • Clinical management without genetic testing	Relevant outcomes include: • Test validity • Symptoms • Change in disease status

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. These diseases can generally be diagnosed based on clinical presentation, nerve conduction studies, and family history. Genetic testing has been used to diagnose specific inherited peripheral neuropathies.

Objective

The objective of this evidence review is to evaluate whether genetic testing in patients with suspected inherited motor and sensory peripheral neuropathy improves health outcomes.

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

Inherited peripheral neuropathies are divided into the 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 the hereditary motor and sensory neuropathies and HNPP.

A genetic etiology of peripheral neuropathy is typically suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course.[2,] A family history of at least three generations with details on health issues, the cause of death, and age at death should be collected.

Charcot-Marie-Tooth Disease
Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of 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 the inherited neuropathies.[4,] Also, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and inheritance patterns. A 2016 cross-sectional study of 520 children and adolescents with CMT found variability in CMT-related symptoms across the 5 most commonly represented subtypes.[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 seven 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 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	70%-80% of CMT1
CMT1B	*MPZ*	Myelin P0 protein	10%-12% of CMT1
CMT1C	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-α factor	≈1% of CMT1
CMT1D	*EGR2*	Early growth response protein 2	
CMT1E	*PMP22*	Peripheral myelin protein 22 (sequence changes)	≈1% of CMT1
CMT1F/2E	*NEFL*	Neurofilament light polypeptide	
CMT type 2			
CMT2A1	*KIF1B*	Kinesin-like protein KIF1B	
CMT2A2	*MFN2*	Mitofusin-2	20% of CMT2
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	
CMT2E/1F	*NEFL*	Neurofilament light polypeptide	
CMT2F	*HSPB1*	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT2I/2J	*MPZ*	Myelin P0 protein	
CMT2L	*HSPB8*	Heat-shock protein beta-8	
CMT2N	*AARS*	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	*DYNC1H1*	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	*LRSAM1*	E3 ubiquitin-protein ligase LRSAM1	
CMT2S	*IGHMBP2*	DNA-binding protein SMUBP-2	
CMT2T	*DNAJB2*	DnaJ homolog subfamily B member 2	
CMT2U	*MARS*	Methionine–tRNA ligase, cytoplasmic	
CMT type 4			
CMT4A	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	*MTMR2*	Myotubularin-related protein 2	
CMT4B2	*SBF2*	Myotubularin-related protein 13	
CMT4C	*SH3TC2*	SH3 domain and tetratricopeptide repeats-containing protein 2	

Locus	Gene	Protein Product	Prevalence (if known)
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			
CMTX1	*GJB1*	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX2	*Xp22.2*	Unknown	
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 three normal alleles (as in the heterozygous CMT1A duplication) cause a less severe phenotype.[8,]

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.[9,] The subtypes of CMT2 are similar clinically and distinguished only by molecular genetic findings. CMT2B1, CMT2B2, and CMT2H/K are inherited in an autosomal recessive

manner; all other subtypes of CMT2 are inherited in an autosomal dominant manner. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with variants in the *MFN2* gene.

X-Linked CMT

CMT X type 1 is characterized by a moderate-to-severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.[10,] 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.[10,]

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.[11,] The prevalence is estimated at 16 persons per 100000, although some authors have indicated a potential for under diagnosis of the disease.[11,] An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination.[12,] 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.[12,] Poor recovery usually involves a history of prolonged pressure on a nerve, but, in these cases, the remaining symptoms are typically mild.

PMP22 is the only gene for which a variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have single nucleotide variants (SNVs) and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. SNVs in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.[13,] Studies have also reported that the SNV frequency may vary considerably by ethnicity.[14,] About 10% to 15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.[15,]

Treatment

Currently, there is no therapy to slow the progression of neuropathy for the inherited peripheral neuropathies. A 2015 systematic review of exercise therapies for CMT including 9 studies described in 11 articles reported significant improvements with functional activities and physiological adaptations with exercise.[16,] 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.[17,] Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.[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.[18,] 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.[8,18,] 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.[19,] 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.[20,] 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.[21,]

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.

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*, *BSCL2*, *DNM2*, *DYNC1H1*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *HSPB8*, *LMNA*, *LRSAM1*, *MED25*, *MFN2*, *MPZ*, *NEFL*, *PRPS1*, *RAB7A*, and *TRPV4*.[22] 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 NGS 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 Act (CLIA). Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

POLICY

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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

B. Genetic testing for an inherited peripheral neuropathy is considered **experimental / investigational** for all other indications.

Policy Guidelines

1. This policy addresses the hereditary motor and sensory peripheral neuropathies, of which peripheral neuropathy is the primary clinical manifestation. A number of other hereditary disorders may have neuropathy as an associated finding but typically have other central nervous system and occasional other systemic findings. Examples include Refsum disease, various lysosomal storage diseases, and mitochondrial disorders.
2. **Genetic Counseling**
   Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

RATIONALE

This evidence review has been updated with searches of the MEDLINE database. The most recent literature update was performed through December 6, 2018 (see Appendix Table 1 for genetic testing categories).

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.

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 whether and how the use of genetic testing would improve health outcomes compared with a management strategy without testing.

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are 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.

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 potentially unneeded treatments due to misidentified patients.

Timing
Years.

Setting
The setting of interest is outpatient, with testing ordered by a specialist. Genetic counseling is particularly important for CMT given the extreme genetic heterogeneity of the disorder.

Simplifying Test Terms
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect the presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops, or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to the response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predict response to therapy.

Most published data on the clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the *PMP22* gene in the diagnosis of CMT and hereditary neuropathy with liability to pressure palsies (HNPP), respectively.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A general estimation of the clinical sensitivity of CMT variant testing was presented by Aretz et al (2010) who assessed 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).[23,] The clinical

sensitivity (ie, the proportion of positive tests if the disease is present) for the detection of deletions and duplications to *PMP22* was about 50% and 1% for single nucleotide variants. The clinical specificity (ie, the proportion of negative tests if the disease is not present) was nearly 100%.

An evidence-based review by England et al (2009) 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, neurophysiologic 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 patients with a genetic diagnosis, most (80.8%) had 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.[24,] 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 HNPP, 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.[25,] 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.[26] 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.[27,] 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*).

Panel Testing

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 have 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)[28,]	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)[29,]	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)

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, 0-5 years), childhood (age range, 6-20 years), and adult (age range, ≥21 years). Specific variants clustered by age group, with only two variants found in more than one 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%).

Section Summary: Clinically Valid

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 yield is reasonably high, particularly when patients are selected based on clinical phenotype.

Clinically Useful

The clinical utility of genetic testing for the 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 the 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 the potential to avoid other diagnostic tests.

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. The relevant outcomes are test validity, symptoms, and change in disease status. For the evaluation of hereditary motor and sensory peripheral neuropathies and hereditary neuropathy with liability to pressure palsies, the diagnostic testing yield is likely to be high, particularly when sequential testing is used based on patient phenotype. However, the clinical utility of genetic testing to confirm a diagnosis in a patient with a clinical diagnosis of an inherited peripheral neuropathy is unknown. No direct evidence for improved outcomes with the use of genetic testing for hereditary motor and sensory peripheral

neuropathies and hereditary neuropathy with liability to pressure palsies was identified. However, a chain of evidence supports the use of genetic testing to establish a diagnosis in cases of suspected inherited motor or sensory neuropathy, when a diagnosis cannot be made by other methods, to initiate supportive therapies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Practice Guidelines and Position Statements

American Academy of Neurology et al

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

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 in 2013 and in November 2017 indicated an update is in progress.

American Academy of Family Physicians

The American Academy of Family Physicians (2010) 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, and vasculitides can be ruled out.[32,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently 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 2019
NCT01193088	Genetics of Charcot Marie Tooth Disease (CMT) - Modifiers of CMT1A, New Causes of CMT	1050	Dec 2019

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

81324 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis

81325 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis

81326 PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant

81403 Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/ deletion variants of 2-5 exons)

81404 Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)

81405 Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81406 Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)

81448 Hereditary peripheral neuropathies (e.g. Charcot-Marie-Tooth, spastic paraplegia), genomic sequence analysis panel, must include sequencing of at least 5 peripheral neuropathy-related genes (e.g., BSCL2, GJB1, MFN2, MPZ, REEP1, SPAST, SPG11, SPTLC1)

81479 Unlisted molecular pathology procedure

- There is specific CPT coding for genetic testing for *PMP22* deletions and duplications, full sequencing, and familial variant testing: 81324, 81325, 81326, 81448.
- CPT Tier 2 code 81403 includes the following test-
  - *GJB1 (gap junction protein, beta 1)* (eg, Charcot-Marie-Tooth X-linked), full gene sequence.
- CPT Tier 2 code 81404 includes the following tests–
  - *EGR2 (early growth response 2)* (eg, Charcot-Marie-Tooth), full gene sequence
  - *HSPB1 (heat shock 27kDa protein 1)* (eg, Charcot-Marie-Tooth disease), full gene sequence
  - *LITAF (lipopolysaccharide-induced TNF factor)* (eg, Charcot-Marie-Tooth), full gene sequence
- CPT Tier 2 code 81405 includes the following tests–
  - *GDAP1 (ganglioside-induced differentiation-associated protein 1)* (eg, Charcot-Marie-Tooth disease), full gene sequence.
  - *MPZ (myelin protein zero)* (eg, Charcot-Marie-Tooth), full gene sequence
  - *NEFL (neurofilament, light polypeptide)* (eg, Charcot-Marie-Tooth), full gene sequence
  - *PRX (periaxin)* (eg, Charcot-Marie-Tooth disease), full gene sequence
  - *RAB7A (RAB7A, member RAS oncogene family)* (eg, Charcot-Marie-Tooth disease), full gene sequence.
- CPT Tier 2 code 81406 includes the following tests–
  - *FIG4 (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae])* (eg, Charcot-Marie-Tooth disease), full gene sequence
  - *GARS (glycyl-tRNA synthetase)* (eg, Charcot-Marie-Tooth disease), full gene sequence
  - *LMNA (lamin A/C)* (eg, Emery-Dreifuss muscular dystrophy [EDMD1, 2 and 3] limb-girdle muscular dystrophy [LGMD] type 1B, dilated cardiomyopathy [CMD1A], familial partial lipodystrophy [FPLD2]), full gene sequence
  - *MFN2 (mitofusin 2)* (eg, Charcot-Marie-Tooth disease), full gene sequence.
  - *SH3TC2 (SH3 domain and tetratricopeptide repeats 2)* (eg, Charcot-Marie-Tooth disease), full gene sequence
- For the other genes listed above, there is no specific CPT listing of the test and the unlisted molecular pathology code 81479 would be reported.

DIAGNOSIS

G60.0	Hereditary motor and sensory neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified

REVISIONS	
08-23-2013	Policy posted to the bcbsks.com web site on 07-24-2013 for an effective date of 08-23-2013.
10-06-2015	Description section added.
	In Policy section: ▪ Policy guidelines added containing clarifying information about the variety of neuropathies and genetic counseling.
	Rationale section updated
	In Coding section: ▪ Added CPT Codes: 81404, 81405, 81406, 81479 ▪ Coding notations updated

REVISIONS	
	References updated
02-15-2018	Policy published 12-29-2017. Policy effective 02-15-2018.
	Description section updated
	In Policy section: ▪ In Item A revised policy position from experimental / investigational to medically necessary to read "Genetic testing is considered medically necessary when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms but a definitive diagnosis cannot be made without genetic testing."
	Rationale section updated
	In Coding section: ▪ Added CPT Code: 81448 (Effective 01-01-2018) ▪ Added ICD-10 Codes: G60.0, G60.8, G60.9 ▪ Coding notations updated
	References updated
04-10-2019	Description section updated
	In Policy section: ▪ Policy Guidelines updated
	Rationale section updated
	In Coding section: ▪ Added CPT Code: 81403
	References updated

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Appendix

Appendix Table 1. Categories of Genetic Testing

Category	Addressed
1. Testing of an affected individual's germline to benefit the individual	
1a. Diagnostic	X
1b. Prognostic	X
1c. Therapeutic	
2. Testing cancer cells from an affected individual to benefit the individual	
2a. Diagnostic	
2b. Prognostic	
2c. Therapeutic	
3. Testing an asymptomatic individual to determine future risk of disease	
4. Testing of an affected individual's germline to benefit family members	
5. Reproductive testing	
5a. Carrier testing: preconception	
5b. Carrier testing: prenatal	
5c. In utero testing: aneuploidy	
5d. In utero testing: mutations	
5e. In utero testing: other	
5f. Preimplantation testing with in vitro fertilization	