Policy Statement

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

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

Policy Guidelines

This policy addresses the hereditary motor and sensory peripheral neuropathies, of which peripheral neuropathy is the primary clinical manifestation. A number of other hereditary disorders may have neuropathy as an associated finding but typically have other central nervous system and occasional other systemic findings. Examples include Refsum disease, various lysosomal storage diseases, and mitochondrial disorders.

Testing Strategy

Testing for PMP22 deletions or duplications will detect 40% to 50% of hereditary motor and sensory neuropathies and up to 70% in patients with a family history testing for PMP22 deletions or duplications is the recommended first step in patients for whom testing will be obtained.

For individuals for whom PMP22 deletions or duplications testing is negative, a variety of genes are potential candidates, and some investigators have previously outlined a tiered testing strategy (Bird et al, 2016). However, given that multiple genes are tested in each tier, and that obtaining multiple tests may be necessary, a panel directed toward hereditary motor and sensory neuropathies would be reasonable.

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.

Coding

The following CPT code is specific CPT coding for genetic testing for PMP22 deletions and duplications, full sequencing, and familial variant testing:

- **81324**: PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
- **81325**: PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
- **81326**: PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant

CPT Tier 2 code 81403 (MOLECULAR PATHOLOGY PROCEDURE LEVEL 4) includes the following test mentioned above:
• **GJB1** (gap junction protein, beta 1) (e.g., Charcot-Marie-Tooth X-linked), full gene sequence

CPT tier 2 code 81404 (MOLECULAR PATHOLOGY PROCEDURE LEVEL 5) includes the following tests mentioned above:
- **EGR2** (early growth response 2) (e.g., Charcot-Marie-Tooth), full gene sequence
- **HSPB1** (heat shock 27kDa protein 1) (e.g., Charcot-Marie-Tooth disease), full gene sequence
- **LITAF** (lipopolysaccharide-induced TNF factor) (e.g., Charcot-Marie-Tooth), full gene sequence

CPT tier 2 code 81405 (MOLECULAR PATHOLOGY PROCEDURE LEVEL 6) includes the following tests mentioned above:
- **GDAP1** (ganglioside-induced differentiation-associated protein 1) (e.g., Charcot-Marie-Tooth disease), full gene sequence
- **MPZ** (myelin protein zero) (e.g., Charcot-Marie-Tooth), full gene sequence
- **NEFL** (neurofilament, light polypeptide) (e.g., Charcot-Marie-Tooth), full gene sequence
- **PRX** (periaxin) (e.g., Charcot-Marie-Tooth disease), full gene sequence
- **RAB7A** (RAB7A, member RAS oncogene family) (e.g., Charcot-Marie-Tooth disease), full gene sequence

CPT tier 2 code 81406 (MOLECULAR PATHOLOGY PROCEDURE LEVEL 7) includes the following tests mentioned above:
- **FIG4** (FIG4 homolog, SAC1 lipid phosphatase domain containing [S. cerevisiae]) (e.g., Charcot-Marie-Tooth disease), full gene sequence
- **GARS** (glycyl-tRNA synthetase) (e.g., Charcot-Marie-Tooth disease), full gene sequence
- **LMNA** (lamin A/C) (e.g., 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) (e.g., Charcot-Marie-Tooth disease), full gene sequence.
- **SH3TC2** (SH3 domain and tetratricopeptide repeats 2) (e.g., Charcot-Marie-Tooth disease), full gene sequence.

Effective January 1, 2018, the following CPT code is specific to a panel to test for hereditary peripheral neuropathies like Charcot-Marie Tooth:
- **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)

For the other genes listed in this evidence review, there is no specific CPT listing of the test and the unlisted molecular pathology code 81479 would be reported.

**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.

**Related Policies**

- N/A
 Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

 Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Genetic testing for the diagnosis of inherited peripheral neuropathies is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the 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.

 Rationale

 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. The further anatomic classification includes fiber type (e.g., motor vs sensory, large vs small) and gross distribution of the nerves affected (e.g., symmetry, length-dependency).

Inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies (HNPP), and other miscellaneous, rare types (e.g., hereditary brachial plexopathy, hereditary sensory, autonomic neuropathies). Other hereditary metabolic disorders, such as Friedreich ataxia, Refsum disease, and Krabbe disease, may be associated with motor and/or sensory neuropathies but typically have other predominating symptoms. This 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 a very slowly progressive clinical course.2 A family history of at least 3 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 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 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 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 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>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Protein Product</th>
<th>Prevalence (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1A</td>
<td>PMP22</td>
<td>Peripheral myelin protein 22</td>
<td>70%-80% of CMT1</td>
</tr>
<tr>
<td>CMT1B</td>
<td>MPZ</td>
<td>Myelin P0 protein</td>
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<td>LITAF</td>
<td>Lipopolysaccharide-induced tumor necrosis factor-α</td>
<td>≈1% of CMT1</td>
</tr>
<tr>
<td>CMT1D</td>
<td>EGFR</td>
<td>Early growth response protein 2</td>
<td></td>
</tr>
<tr>
<td>CMT1E</td>
<td>PMP22</td>
<td>Peripheral myelin protein 22 (sequence changes)</td>
<td>≈1% of CMT1</td>
</tr>
<tr>
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<td>NEFL</td>
<td>Neurofilament light polypeptide</td>
<td></td>
</tr>
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<td>CMT2A1</td>
<td>KIF1B</td>
<td>Kinesin-like protein KIF1B</td>
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<td>CMT2A2</td>
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<td>Mitofusin-2</td>
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<td>Lamin A/C</td>
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<tr>
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<td>member 4</td>
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<td>Glycyl-tRNA synthetase</td>
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<td>Neurofilament light polypeptide</td>
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<td>CMT2I/2J</td>
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<td>E3 ubiquitin-protein ligase LRSAM1</td>
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<td>DNA-binding protein SMUBP-2</td>
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<td>Ganglioside-induced differentiation-associated protein 1</td>
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<td>MTRM2</td>
<td>Myotubulin-related protein 2</td>
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<td>SBF2</td>
<td>Myotubulin-related protein 13</td>
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<td>CMT4C</td>
<td>SH3TC2</td>
<td>SH3 domain and tetratricopeptide repeats-containing protein 2</td>
<td></td>
</tr>
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<td>CMT4D</td>
<td>NDRG1</td>
<td>Protein NDRG1</td>
<td></td>
</tr>
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<td>EGFR</td>
<td>Early growth response protein 2</td>
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<td>PRX</td>
<td>Perilaxin</td>
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</tr>
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<td>FG D4</td>
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<td>CMT4J</td>
<td>FIG4</td>
<td>Phosphatidylinositol 3, 5-biphosphate</td>
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</tr>
</tbody>
</table>

X-linked CMT
Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

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<table>
<thead>
<tr>
<th>Locus</th>
<th>Gene</th>
<th>Protein Product</th>
<th>Prevalence (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMTX1</td>
<td>GJB1</td>
<td>Gap junction beta-1 protein (connexin 32)</td>
<td>90% of X-linked CMT</td>
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<td>CMTX2</td>
<td>Xp22.2</td>
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<tr>
<td>CMTX3</td>
<td>Xq26</td>
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</tr>
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<td>CMTX4</td>
<td>AIFM1</td>
<td>Apoptosis-inducing factor 1</td>
<td></td>
</tr>
<tr>
<td>CMTX5</td>
<td>PRPS1</td>
<td>Ribose-phosphate pyrophosphokinase 1</td>
<td></td>
</tr>
<tr>
<td>CMTX6</td>
<td>PDK3</td>
<td>Pyruvate dehydrogenase kinase isoform 3</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Bird (2016).6

CMT: Charcot-Marie-Tooth.

The clinical features of CMT are briefly summarized:

CMT Type 1
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 (CMT1A-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.8

CMT Type 2
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
CMTX type 1 (CMTX1) 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. CMTX1 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 CMTX1.10

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 100,000, although some authors have indicated a potential for underdiagnosis of the disease.11 An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination. HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode.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 (e.g., vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.6

Supportive treatment for HNPP can include transient bracing (e.g., wrist splint or ankle-foot orthosis), which may become permanent in some cases of foot drop.18 Prevention of HNPP manifestations can be accomplished by wearing protective padding (e.g., elbow or knee pads) to prevent trauma to nerves during activity. Some have reported that vincristine should also be avoided in HNPP patients.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 (i.e., with array comparative genomic hybridization) to detect large deletions or duplications. For the detection of variants in MFN2, whole gene or select exome sequence analysis is typically used to identify SNVs, in addition to or followed by deletion or duplication analysis for the detection of large deletions or duplications.
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.

**Literature Review**
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 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.

**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 accuracy and validity, symptom, 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 for 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 3 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 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 response to therapy. To simplify terms, we use prognostic to refer to both predicting a future condition or to predicting a 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 (i.e., 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 (i.e., 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. Six studies included in the review showed that when the test for CMT1A duplication is restricted to patients with clinically probable CMT1 (i.e., 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. 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.

In 2016, Rudnik-Schoneborn et al 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. 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 \( \text{PMP22} \) deletion or duplication (74.8%), \( \text{GJB1/Cx32} \) (8.9%), or \( \text{MPZ/P0} \) (5.6%) variant analysis. In contrast, of the 57 patients genetically identified with axonal CMT (index and secondary), 84.3% were detected with \( \text{GJB1/Cx32} \) (42.1%), \( \text{MFN2} \) (33.3%), or \( \text{MPZ/P0} \) (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. 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 \( \text{GJB1} \) (13%) and \( \text{MPZ} \) (8%) variants among those with positive genetic tests. For CMT2 patients, \( \text{GJB2} \) (30%) and \( \text{MFN2} \) (23%) variants were most common among those with positive genetic tests.

In 2013, Ostern et al reported on a retrospective analysis of cases of CMT diagnostic testing referred to a single reference laboratory in Norway from 2004 to 2010. 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 on 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.

In 2012, Murphy et al reported on the yield of sequential testing for CMT-related gene variants from 1607 patients with testing sent to a single center. 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**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Test</th>
<th>Diagnostic Yield (NGS Panel)</th>
<th>VUS (NGS Panel)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antoniadı et al (2015)</td>
<td>448</td>
<td>Suspected inherited peripheral neuropathy, with supportive NCV, some with negative testing for PMP2</td>
<td>56-gene NGS panel</td>
<td>137 (31%) patients (31 genes)</td>
<td>NR</td>
</tr>
<tr>
<td>DiVincenzo et al (2014)</td>
<td>17,377,503 with NGS</td>
<td>Suspected peripheral neuropathy, referred to a central laboratory</td>
<td>14-gene NGS panel and PMP22 del/dup by MLPA</td>
<td>95 (18.9%) patients (8 genes)</td>
<td>38 (7.5%) patients (11 genes)</td>
</tr>
</tbody>
</table>

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, in 2015, Sanmaneechai et al characterized genotype-phenotype correlations in patients with CMT1B regarding MPZ variants in a cohort of 103 patients from 71 families. 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 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. 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 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. Relevant outcomes are test accuracy and 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.

Supplemental Information
Practice Guidelines and Position Statements

American Academy of Neurology et al
In 2009, the American Academy of Neurology 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 (see Table 3).3

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

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies”</td>
<td>A</td>
</tr>
<tr>
<td>“Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype”</td>
<td>C</td>
</tr>
<tr>
<td>“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”</td>
<td></td>
</tr>
<tr>
<td>“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”</td>
<td>U</td>
</tr>
</tbody>
</table>

LOE: level of evidence.

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**

In 2010, 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, and vasculitides can be ruled out.32

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**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**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01193075</td>
<td>Natural History Evaluation of Charcot Marie Tooth Disease (CMT) Type (CMT1B), 2A (CMT2A), 4A (CMT4A), and Others</td>
<td>5000</td>
<td>Dec 2019</td>
</tr>
<tr>
<td>NCT01193088</td>
<td>Genetics of Charcot Marie Tooth Disease (CMT) - Modifiers of CMT1A, New Causes of CMT</td>
<td>1050</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Appendix**

**Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.89**

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td>X</td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td></td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>

**References**


23. 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


**Documentation for Clinical Review**

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history, if applicable
- Reason for procedure/test/device, when applicable
- Pertinent past procedural and surgical history
- Past and present diagnostic testing and results
- Prior conservative treatments, duration, and response
- Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (i.e., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management), when applicable

**Post Service**

- Results/reports of tests performed
- Procedure report(s)
## Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

### MN/IE

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81324</td>
<td></td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis</td>
</tr>
<tr>
<td>81325</td>
<td></td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis</td>
</tr>
<tr>
<td>81326</td>
<td></td>
<td>PMP22 (peripheral myelin protein 22) (e.g., Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant</td>
</tr>
<tr>
<td>81403</td>
<td></td>
<td>Molecular Pathology Procedure Level 4</td>
</tr>
<tr>
<td>81404</td>
<td></td>
<td>Molecular Pathology Procedure Level 5</td>
</tr>
<tr>
<td>81405</td>
<td></td>
<td>Molecular Pathology Procedure Level 6</td>
</tr>
<tr>
<td>81406</td>
<td></td>
<td>Molecular Pathology Procedure Level 7</td>
</tr>
<tr>
<td>81448</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>81479</td>
<td></td>
<td>Unlisted molecular pathology procedure</td>
</tr>
</tbody>
</table>

### HCPCS

None

### ICD-10 Procedure

None

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>03/01/2017</td>
<td>BC BSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.