This Protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following Protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals: • With suspected inherited peripheral neuropathy</td>
<td>Interventions of interest are: • Testing for genes associated with inherited peripheral neuropathies for diagnostic purposes • Testing for genes associated with inherited peripheral neuropathies for prognostic purposes</td>
<td>Comparators of interest are: • Clinical management without genetic testing</td>
<td>Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status</td>
</tr>
</tbody>
</table>

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.

Summary of Evidence

The evidence for testing for mutations associated with hereditary motor and sensory neuropathies in individuals with a suspected inherited peripheral neuropathy includes case-control and genome-wide association studies reporting associations between a number of genes and clinical diagnosis. Relevant outcomes are test accuracy, test validity, symptoms, and change in disease status. The analytic validity of mutation testing for these diseases is high. For the evaluation of hereditary motor and sensory peripheral neuropathies (Charcot-Marie-Tooth [CMT] types 1, 2, and 4, and X-linked CMT) and for hereditary neuropathy with liability to pressure palsies (HNPP), clinical specificity is reported to be high. The clinical sensitivity has been more variable but tends to be higher for CMT1. 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 studies were identified that evaluate health outcomes for patients managed with genetic testing. Direct evidence for improved health outcomes with the use of genetic testing for hereditary motor and sensory peripheral neuropathies and HNPP is limited. The changes in clinical
management that would occur as a result of testing are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Policy**

Genetic testing is considered *investigational* to confirm a clinical diagnosis of an inherited peripheral neuropathy.

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

**Policy Guidelines**

This Protocol 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.

**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.

**Background**

The inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is estimated at roughly one 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 myelopathies, depending on which portion of the nerve fiber is affected. 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).

The inherited peripheral neuropathies are divided into the hereditary motor and sensory neuropathies, hereditary neuropathy with liability to pressure palsies, 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 Protocol will focus on the hereditary motor and sensory neuropathies and hereditary neuropathy with liability to pressure palsies (HNPP).

A genetic etiology of a peripheral neuropathy is generally 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, cause of death, and age at death should be collected.
Hereditary Motor and Sensory Neuropathies

Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurologic findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure. CMT disease is genetically heterogeneous, as well as clinically heterogeneous. Mutations in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies. In addition, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different inheritance patterns. CMT subtypes are characterized by mutations 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 mutations). CMT type 2 is associated with about 10% to 15% of CMT cases, with 20% of those due to MFN2 mutations.

A summary of the molecular genetics of CMT is outlined in Table 1.

Table 1: Molecular Genetics of CMT Variants (adapted from Bird et al, 2015)
**Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies**

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Gene</th>
<th>Protein Product</th>
<th>Prevalence (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT4D</td>
<td>NDRG1</td>
<td>Protein NDRG1</td>
<td></td>
</tr>
<tr>
<td>CMT4E</td>
<td>EGR2</td>
<td>Early growth response protein 2</td>
<td></td>
</tr>
<tr>
<td>CMT4F</td>
<td>PRX</td>
<td>Periaxin</td>
<td></td>
</tr>
<tr>
<td>CMT4H</td>
<td>FGD4</td>
<td>FYVE, RhoGEF and PH domain-containing protein 4</td>
<td></td>
</tr>
<tr>
<td>CMT4J</td>
<td>FIG4</td>
<td>Phosphatidylinositol 3, 5-biphosphate</td>
<td></td>
</tr>
<tr>
<td>X-linked CMT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMTX1</td>
<td>GJB1</td>
<td>Gap junction beta-1 protein (connexin 32)</td>
<td>90% of X-linked CMT</td>
</tr>
<tr>
<td>CMTX2</td>
<td>Xp22.2</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>CMTX3</td>
<td>Xq26</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<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 pyrophosphokinate 1</td>
<td></td>
</tr>
<tr>
<td>CMTX6</td>
<td>PDK3</td>
<td>Pyruvate dehydrogenase kinase isoform 3</td>
<td></td>
</tr>
</tbody>
</table>

CMT: Charcot-Marie-Tooth.

**CMT Type 1**

CMT type 1 (CMT1) is a 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 age five 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 mutation and about one third have CMT1A as the result of a de novo mutation.

CMT1A involves duplication of the gene PMP22. *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. Six normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype, whereas three normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype. CMT1B (6-10% of all CMT1) is associated with point mutations in MPZ, CMT1C (1%-2% of all CMT1) is associated with mutations in LITAF, and CMT1D (< 2% of all CMT1) is associated with mutations in EGR2. CMT1E (< 5% of all CMT1) is associated with point mutations in PMP22. CMT2E/1F (< 5% of all CMT1) is associated with mutations in NEFL. Molecular genetic testing is clinically available for all of these genes.

**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. Unlike CMT1, peripheral nerves are not enlarged or hypertrophic. 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 15 genes in which mutations are known to cause CMT2 subtypes are KIF1B (CMT2A1), MFN2 (CMT2A2), RAB7A (formerly RAB7) (CMT2B), LMNA (CMT2B1), MED25 (CMT2B2), TRPV4 (CMTC), GARS (CMT2D), NEFL (CMT2E/F), HSPB1 (CMT2F), MPZ (CMT2J/J), GDAP1 (CMT2H/K), HSPB8 (CMT2L), AARS (CMT2N), DYNC1H1 (CMT2O), and LRSAM1 (CMT2P). Molecular genetic testing is clinically available for CMT subtypes 2A1, 2A2, 2B,
2B1, 2B2, 2C, 2D, 2E, 2F, 2I, 2L, 2N, 2O, and 2P. The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with mutations in the \textit{MFN2} gene.

**X-Linked CMT**

CMT X 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. 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 \textit{GJB1} (Cx32), which is available on a clinical basis, detects about 90% of cases of CMTX1.

**CMT Type 4**

CMT type 4 (CMT4) 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. There are 10 genes in which mutations are known to cause CMT4 subtypes, including \textit{GDAP1} (CMT4A), \textit{MTMR2} (CMT4B1), \textit{SBF2} (CMT4B2), \textit{SBF1} (CMT4B3), \textit{SH3TC2} (CMT4C), \textit{NDRG1} (CMT4D), \textit{EGR2} (CMT4E), \textit{PRX} (CMT4F), \textit{FGD4} (CMT4H), and \textit{FIG4} (CMT4J).

**Hereditary Neuropathy with Liability to Pressure Palsies**

The largest proportion of CMT1 cases are due to mutations in \textit{PMP22}. In HNPP (also called tomaculous neuropathy), inadequate production of \textit{PMP22} causes nerves to be more susceptible to trauma or minor compression/entrapment. HNPP patients rarely present symptoms before the second or third decade of life. However, some authors report presentation as early as birth or as late as the seventh decade of life. The prevalence is estimated at 16 persons per 100,000, although some authors indicate a potential for underdiagnosis of the disease. 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. Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases, the remaining symptoms are typically mild.

\textit{PMP22} is the only gene in which mutation is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have point mutations and small deletions in the \textit{PMP22} gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point mutations in \textit{PMP22} have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome. Studies have also reported that the point mutation frequency may vary considerably by ethnicity. About 10% to 15% of mutation carriers remain clinically asymptomatic, suggesting incomplete penetrance.

**Treatment**

Currently there is no effective therapy to slow the progression of neuropathy for the inherited peripheral neuropathies. 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. Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.

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. 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 authors
report that vincristine should also be avoided in HNPP patients. Ascorbic acid has been investigated as a
treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical
benefit. Attarian et al reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled
trial of PXT3003, a low-dose combination of three already approved compounds (baclofen, naltrexone, sorbitol)
in 80 adults with CMT1A. The study demonstrated the safety and tolerability of the drug, but further studies
are needed.

Available Molecular Genetic Testing

Multiple laboratories offer individual mutation testing for genes involved in hereditary sensory and motor
neuropathies, which would typically involve sequencing analysis via Sanger sequencing or next-generation
sequencing (NGS) followed by deletion/duplication analysis (i.e., with array comparative genomic hybridization
[CGH]) to detect large deletions or duplications. For the detection of mutations in MFN2, whole gene or select
exome sequence analysis is typically used to identify point mutations, in addition to or followed by deletion/
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 NGS and exon array CGH. The
genes tested include the following: AARS, BSCL2, DNM2, DYNC1H1, GARS, GDAP1, GJB1, HSPB1, HSPB8, LMNA,
LRSAM1, MED25, MFN2, MPZ, NEFL, PRPS1, RAB7A, and TRPV4. InterGenetics (Athens, Greece) offers an NGS
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.

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are
considered investigational. For explanation of experimental and investigational, please refer to the Technology
Assessment Protocol.

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to
conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced
procedures. Some of this Protocol may not pertain to the patients you provide care to, as it may relate to
products that are not available in your geographic area.

References

We are not responsible for the continuing viability of web site addresses that may be listed in any references
below.


31. 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


39. NGS Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 04/01/2016.