Title: Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

Professional
Original Effective Date: August 23, 2013
Revision Date(s): August 23, 2013; October 6, 2015
Current Effective Date: August 23, 2013

Institutional
Original Effective Date: August 23, 2013
Revision Date(s): August 23, 2013; October 6, 2015
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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.

Background
The inherited peripheral neuropathies are a clinically and genetically heterogeneous
group of disorders. The estimated prevalence in aggregate is estimated at roughly 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 upon which portion of the nerve
fiber is affected. Further anatomic classification includes fiber type (eg, motor versus
sensory, large versus small), and gross distribution of the nerves affected (eg, symmetry,
length-dependency).

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 (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
policy 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 3 generations with details on health issues, cause of death,
and age at death should be collected.
Hereditary Motor and Sensory Neuropathies
Most inherited polyneuropathies were originally described clinically as variants of Charcot-Marie-Tooth (CMT) disease. The clinical phenotype of CMT is highly variable, ranging from minimal neurological 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 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 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)

<table>
<thead>
<tr>
<th>Locus Name</th>
<th>Gene</th>
<th>Protein Product</th>
<th>Prevalence (if known)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT type 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<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>
<td>10-12% of CMT1</td>
</tr>
<tr>
<td>CMT1C</td>
<td>LITAF</td>
<td>Lipopolysaccharide-induced tumor necrosis factor-α factor</td>
<td>≈1% of CMT1</td>
</tr>
<tr>
<td>CMT1D</td>
<td>EGR2</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>
<td>CMT type 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMT2A1</td>
<td>KIF1B</td>
<td>Kinesin-like protein KIF1B</td>
<td></td>
</tr>
<tr>
<td>CMT2A2</td>
<td>MFN2</td>
<td>Mitofusin-2</td>
<td>20% of CMT2</td>
</tr>
<tr>
<td>CMT2B</td>
<td>RAB7A</td>
<td>Ras-related protein Rab-7</td>
<td></td>
</tr>
<tr>
<td>CMT2B1</td>
<td>LMNA</td>
<td>Lamin A/C</td>
<td></td>
</tr>
<tr>
<td>CMT2B2</td>
<td>MED25</td>
<td>mediator of RNA polymerase II transcription subunit 25</td>
<td></td>
</tr>
<tr>
<td>CMT2C</td>
<td>TRPV4</td>
<td>Transient receptor potential cation channel subfamily V member 4</td>
<td></td>
</tr>
<tr>
<td>CMT2D</td>
<td>GARS</td>
<td>Glycyl-tRNA synthetase</td>
<td></td>
</tr>
<tr>
<td>CMT2E/1F</td>
<td>NEFL</td>
<td>Neurofilament light polypeptide</td>
<td></td>
</tr>
<tr>
<td>CMT2F</td>
<td>HSPB1</td>
<td>Heat-shock protein beta-1</td>
<td></td>
</tr>
<tr>
<td>CMT2G</td>
<td>12q12-q13</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>CMT2H/2K</td>
<td>GDAP1</td>
<td>Ganglioside-induced differentiation-associated protein-1</td>
<td></td>
</tr>
<tr>
<td>CMT2J/2J</td>
<td>MPZ</td>
<td>Myelin P0 protein</td>
<td></td>
</tr>
<tr>
<td>CMT2L</td>
<td>HSPB8</td>
<td>Heat-shock protein beta-8</td>
<td></td>
</tr>
<tr>
<td>CMT2N</td>
<td>AARS</td>
<td>Alanyl-tRNA synthetase, cytoplasmic</td>
<td></td>
</tr>
<tr>
<td>CMT2O</td>
<td>DYNC1H1</td>
<td>Cytoplasmic dynein 1 heavy chain 1</td>
<td></td>
</tr>
</tbody>
</table>

Contains Public Information
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 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 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. Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype whereas 3 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 \textit{MPZ}, CMT1C (1-2\% of all CMT1) is associated with mutations in \textit{LITAF}, and CMT1D (<2\% of all CMT1) is associated with mutations in \textit{EGR2}. CMT1E (<5\% of all CMT1) is associated with point mutations in \textit{PMP22}. CMT2E/1F (<5\% of all CMT1) is associated with mutations in \textit{NEFL}. Molecular genetic testing is clinically available for all of these genes.\textsuperscript{7}

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.\textsuperscript{8} 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 \textit{KIF1B} (CMT2A1), \textit{MFN2} (CMT2A2), \textit{RAB7A} (formerly \textit{RAB7}) (CMT2B), \textit{LMNA} (CMT2B1), \textit{MED25} (CMT2B2), \textit{TRPV4} (CMT2C), \textit{GARS} (CMT2D), \textit{NEFL} (CMT2E/1F), \textit{HSPB1} (CMT2F), \textit{MPZ} (CMT2J/J), \textit{GDAP1} (CMT2H/K), \textit{HSPB8} (CMT2L), \textit{AARS} (CMT2N), \textit{DYNC1H1} (CMT2O), and \textit{LRSAM1} (CMT2P). Molecular genetic testing is clinically available for CMT subtypes 2A1, 2A2, 2B, 2B1, 2B2, 2C, 2D, 2E, 2F, 2I, 2J, 2H/K, 2L, 2N, 2O, and 2P.\textsuperscript{8} 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.\textsuperscript{9} 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.\textsuperscript{9}

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{FLG4} (CMT4J).

\textbf{Hereditary Neuropathy With Liability to Pressure Palsies (HNPP)}

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.\textsuperscript{10} The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for underdiagnosis of the disease.\textsuperscript{10} An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination.\textsuperscript{11} 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.\textsuperscript{11} Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases the remaining symptoms are typically mild.

\textit{PMP 22} 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.\textsuperscript{12} Studies have also reported that the point mutation frequency may vary considerably by ethnicity.\textsuperscript{13} About 10% to 15% of mutation carriers remain clinically asymptomatic, suggesting incomplete penetrance.\textsuperscript{14}

\textbf{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.\textsuperscript{15} Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.\textsuperscript{5}

Supportive treatment for HNPP can include transient bracing (eg, a wrist splint or ankle-foot orthosis) which may become permanent in some cases of foot drop.\textsuperscript{16} Prevention of HNPP manifestations can be accomplished by wearing protective padding (eg, elbow or knee pads) to prevent trauma to nerves during activity. Some authors report that vincristine should also be avoided in HNPP patients.\textsuperscript{7,16} Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit.\textsuperscript{17} Attarian et al reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of 3 already approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A.\textsuperscript{18} 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 (ie, 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.
POLICY

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

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

The most recent evidence review is based on a search of the MEDLINE database through June 29, 2015 (see Appendix Table 1 for genetic testing categories).

Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity of the test, which refers to the technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent; (2) clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility of the test (ie, how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

Most of the published data available for analytic and clinical validity of genetic testing for the inherited peripheral neuropathies are for duplications and deletions in the PMP22 gene in the diagnosis of Charcot- Marie-Tooth (CMT) and hereditary neuropathy with liability to pressure palsies (HNPP), respectively.
Analytic Validity

A variety of methods, in addition to fluorescence in-situ hybridization (FISH), can be used for deletion/duplication analysis targeted specifically at PMP22, including quantitative polymerase chain reaction (qPCR), multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA), with high agreement between testing methods (see Table 2).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Disorders Tested</th>
<th>Test Method</th>
<th>Confirmation Method</th>
<th>% Agreement CMT1A; HNPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hung (2007)&lt;sup&gt;20&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>CE PCR</td>
<td>RFLP-PCR</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Ravise (2003)&lt;sup&gt;21&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>dFISH</td>
<td>Southern Blot</td>
<td>94%; 100%</td>
</tr>
<tr>
<td>Hung (2008)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>MLPA</td>
<td>Competitive multiplex PCR</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Slater (2004)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>MLPA</td>
<td>FISH</td>
<td>90%; 100%</td>
</tr>
<tr>
<td>Stangler (2009)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>MLPA</td>
<td>FISH</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Hung (2008)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>MLPA</td>
<td>RFLP-PCR</td>
<td>78%; 86%</td>
</tr>
<tr>
<td>Stangler (2009)&lt;sup&gt;24&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>MLPA</td>
<td>RFLP-PCR&lt;sup&gt;b&lt;/sup&gt;</td>
<td>88%; NA</td>
</tr>
<tr>
<td>Lin (2006)&lt;sup&gt;25&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>DHPLC</td>
<td>Microsatellite analysis</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Aarskog (2000)&lt;sup&gt;26&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>RT-qPCR</td>
<td>Clinical and EMG characteristics</td>
<td>89.6%; 100%</td>
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<tr>
<td>Thiel (2003)&lt;sup&gt;27&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>RT-qPCR</td>
<td>Microsatellite analysis</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Chen (2008)&lt;sup&gt;28&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>RT-qPCR</td>
<td>Microsatellite analysis</td>
<td>100%; 100%</td>
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<tr>
<td>Kim (2003)&lt;sup&gt;29&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>RT-qPCR</td>
<td>Microsatellite analysis</td>
<td>100%; 100%</td>
</tr>
<tr>
<td>Choi (2005)&lt;sup&gt;30&lt;/sup&gt;</td>
<td>CMT1A; HNPP</td>
<td>RT-qPCR</td>
<td>REP-PCR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100%; 100%</td>
</tr>
</tbody>
</table>

CE: capillary electrophoresis; CMT: Charcot-Marie-Tooth; d: direct; DHPLC: denaturing high-performance liquid chromatography; EMG: electromyography; FISH: fluorescence in-situ hybridization; HNPP: hereditary neuropathy with liability to pressure palsies; MLPA: multiplex ligation-dependent probe amplification; PCR: polymerase chain reaction; q: quantitative; REP: repeat; RFLP: restriction fragment length polymorphism; RT: reverse transcriptase.

<sup>a</sup> RT-qPCR detected 4 of 13 suspected cases of HNPP and 2 of 16 suspected cases of CMT1A not discovered by REP-PCR.

<sup>b</sup> RFLP-PCR had 1 false-negative and 3 false-positive results.

Analytic performance of several molecular analytic methods was presented in a review by Aretz et al. The reported analytic sensitivity and specificity were given as almost 100% (tests considered included MLPA, qPCR, FISH, direct sequencing). Further evidence is provided by another review in which segregation studies followed by several prospective cohort studies have also documented that currently available genetic testing results for CMT are unequivocal for diagnosis of established pathogenic mutations, providing a specificity of 100% (ie, no false positives) and high sensitivity.<sup>3</sup>

Clinical Validity

The clinical sensitivity of the diagnostic test for CMT and HNPP can be dependent on variable factors such as the age or family history of the patient. A general estimation of the clinical sensitivity was presented in a report by Aretz et al on hereditary motor and sensory neuropathy and HNPP with a variety of analytic methods (MLPA, multiplex amplicon quantification, qPCR, Southern blot, FISH, pulsed-field gel electrophoresis, dHPLC, high-resolution melting, restriction analysis, direct sequencing).<sup>31</sup> The clinical sensitivity (ie, proportion of positive tests if the disease is present) for the detection of deletions and duplications to PMP22 was about 50% and 1% for point mutations. The clinical specificity (ie, proportion of negative tests if the disease is not present) was nearly 100%.

An evidence-based review by England et al 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 (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 neuropathy where the yield is only 25% to 59% (average, 43%).

Saporta et al 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 note that decisions about which genes to test changed over the course of the period included in the study. Most (98.2%) of those with clinically diagnosed CMT1 had a genetic diagnosis, and of all of the patients with a genetic diagnosis, most (80.8%) had clinically diagnosed CMT1. The authors characterize several clinical phenotypes of CMT based on clinical presentation and physiologic testing.

In 2015, Rudnik-Schoneborn et al described clinical features and genetic results from 1206 index patients and 124 affected relatives who underwent testing for CMT neuropathy at a single laboratory over an 11-year period from 2001 to 2012. Patients were categorized on the base of electroneurographic findings, clinical history, and inheritance pattern into CMT1, CMT2, or CMTX, or HNPP. Of the affected patients, 674 had demyelinating CMT, 340 had axonal CMT, and 192 had HNPP; of those, 51%, 13%, and 35% had a genetic diagnosis. Of all patients genetically identified, 89.3% of the 429 patients with demyelinating CMT were detected using PMP22 duplication/deletion analysis (74.8%), GJB1/Cx32 (8.9%), or MPZ/P0 (5.6%) mutation analysis. Of the 57 patients with genetically identified axonal CMT, 84.2% were identified using GJB1/Cx32 (42.1%), MFN2 (33.3%), or MPZ/P0 (8.8%) analysis. For patients with MFN2 and PNP22 mutations, there was a range of clinical severity.

DiVincenzo et al reported the mutation detection rate for 14 hereditary peripheral neuropathy-associated genes in a cohort of 17,880 patients with CMT disease who were referred to a commercial genetic testing laboratory. Test methods included Sanger sequencing assay (n=100,102 assays), next-generation sequencing (NGS) assays (n=2338), and MLPA assays (n=21,990). The genes evaluated include PMP22, GJB1, MPZ, MFN2, SH3TC2, GDAP1, NEFL, LITAF, GARS, HSPB1, FIG4, EGR2, PRX, and RAB7A. Of the patient cohort, 18.5% (n=3312) had a genetic abnormality detected. Among those with a genetic abnormality in a CMT-related gene, 94.9% were positive in 1 of 4 genes (PMP22, GJB1, MPZ, MFN2). Duplications (56.7%) or deletions (21.9%) in the PMP22 gene were the most common finding, followed by GJB1 mutations (6.7%).

Several studies have evaluated broader panel tests for hereditary peripheral neuropathies. Hoyer et al reported the yield of testing with NGS with a custom panel including 32 CMT genes and 19 other genes associated with inherited neuropathies among 81 families with CMT. Pathogenic or likely pathogenic gene mutations were identified in 37 (46%) of families. Of the 38 families with
CMT1, 55% (21/38) had certain or likely pathogenic genotypes identified (11 copy number variants, 10 point mutations). Of the 33 families with CMT2, 36% (12/33) had certain or likely pathogenic genotypes identified. In 2015, Drew et al reported results of whole exome sequencing for 110 patients with inherited peripheral neuropathies who had previously had negative genetic testing for mutations in common genes associated with peripheral neuropathies. The authors identified 41 missense sequence variants in genes known to be associated with inherited peripheral neuropathies, 9 of which were considered pathogenic, 12 of which were considered novel variants potentially implicated in the disease, and 20 of which were considered polymorphisms.

Few genotype-phenotype correlations for CMT2 are known. Considerable variability of phenotype has been observed within families with CMT2A. Choi et al reported on genotype-phenotype correlations between MFN2 mutations and CMT2A symptoms in 160 families with CMT2A, 36 of which had MFN2 mutations. Among patients with MFN2 mutations, disease severity was correlated with age of onset, but specific associations between genotype and disease severity are not reported.

Genotype-phenotype correlations have also been investigated for other hereditary neuropathies. For example, Karadima et al investigated the association of PMP22 mutations 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 micromutations was 2.2%. Mutation-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%).

**Clinical Utility**
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.

In a discussion of the clinical utility of the molecular diagnostic methods for these neuropathies, Aretz et al suggest that the avoidance of any unnecessary therapy due to an undefined diagnosis, sparing other family members from testing, and avoidance of certain risk factors (eg, obesity or certain occupations and activities) are potential benefits.

The likelihood that genetic testing for this condition will alter patient management is low. Because the diagnosis of an inherited peripheral neuropathy can generally be made clinically and the inherited peripheral neuropathies have no specific therapy, the incremental benefit of a genetic confirmation of these disorders is not known. Ways that genetic testing would change management are not well-defined.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 3.
Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>Ongoing</td>
<td>Ongoing</td>
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<tr>
<td>NCT01193075</td>
<td>Natural History Evaluation of Charcot Marie Tooth Disease (CMT) Type (CMT1B), 2A (CMT2A), 4A (CMT4A), 4C (CMT4C), and Others</td>
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<td>Dec 2016</td>
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<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 2016</td>
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</table>

NCT: national clinical trial.

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.

Practice Guidelines and Position Statements

American Academy of Neurology

The American Academy of Neurology published an evidence-based, tiered approach\(^3\) for the evaluation of distal symmetric polyneuropathy, and for suspected hereditary neuropathies, which concluded that:

- Genetic testing is established as useful for the accurate diagnosis and classification of hereditary neuropathies (level A classification of recommendations – established as effective, ineffective, or harmful for the given condition in the specified population)
- Genetic testing may be considered in patients with cryptogenic polyneuropathy who exhibit a hereditary neuropathy phenotype (level C – possibly effective, ineffective, or harmful for the given condition in the specified population)
- 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 (level U –data inadequate or conflicting; given current knowledge)
American Academy of Family Physicians
The American Academy of Family Physicians recommends genetic testing in 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.\textsuperscript{38}

U.S. Preventive Services Task Force Recommendations
The U.S. Preventive Services Task Force has not addressed genetic testing for inherited peripheral neuropathies.

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

- \textbf{81324} PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; duplication/deletion analysis
- \textbf{81325} PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; full sequence analysis
- \textbf{81326} PMP22 (peripheral myelin protein 22) (eg, Charcot-Marie-Tooth, hereditary neuropathy with liability to pressure palsies) gene analysis; known familial variant
- \textbf{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)
- \textbf{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)
- \textbf{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)
- \textbf{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.
- CPT Tier 2 code 81403 includes the following test mentioned above –
  - \textbf{GJB1 (gap junction protein, beta 1)} (eg, Charcot-Marie-Tooth X-linked), full gene sequence
CPT Tier 2 code 81404 includes the following tests mentioned above –
- 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 mentioned above –
- 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 mentioned above –
- 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**
Experimental / Investigational for all codes related to this medical policy.

**REVISIONS**

<table>
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<td>08-23-2013</td>
<td>Policy posted to the bcbsks.com web site on 07-24-2013 for an effective date of 08-23-2013.</td>
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REFERENCES


31. Arez 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


**Appendix**

**Appendix Table 1. Categories of Genetic Testing**

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