

(20489)

<b>Medical Benefit</b>		<b>Effective Date:</b> 01/01/14	<b>Next Review Date:</b> 09/17
<b>Preauthorization</b>	No	<b>Review Dates:</b> 09/13, 09/14, 09/15, 09/16	

***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.*

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>With suspected inherited peripheral neuropathy</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Testing for genes associated with inherited peripheral neuropathies for diagnostic purposes</li> <li>Testing for genes associated with inherited peripheral neuropathies for prognostic purposes</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Clinical management without genetic testing</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Test accuracy</li> <li>Test validity</li> <li>Symptoms</li> <li>Change in disease status</li> </ul>

### 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.<sup>1</sup>

Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary myelinopathies, 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.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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).<sup>5</sup> 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<sup>5</sup>)

Locus Name	Gene	Protein Product	Prevalence (if known)
<b>CMT type 1</b>			
CMT1A	<i>PMP22</i>	Peripheral myelin protein 22	70-80% of CMT1
CMT1B	<i>MPZ</i>	Myelin P0 protein	10-12% of CMT1
CMT1C	<i>LITAF</i>	Lipopolysaccharide-induced tumor necrosis factor- $\alpha$ factor	≈ 1% of CMT1
CMT1D	<i>EGR2</i>	Early growth response protein 2	
CMT1E	<i>PMP22</i>	Peripheral myelin protein 22 (sequence changes)	≈ 1% of CMT1
<b>CMT type 2</b>			
CMT2A1	<i>KIF1B</i>	Kinesin-like protein KIF1B	
CMT2A2	<i>MFN2</i>	Mitofusin-2	20% of CMT2
CMT2B	<i>RAB7A</i>	Ras-related protein Rab-7	
CMT2B1	<i>LMNA</i>	Lamin A/C	
CMT2B2	<i>MED25</i>	Mediator of RNA polymerase II transcription subunit 25	
CMT2C	<i>TRPV4</i>	Transient receptor potential cation channel subfamily V member 4	
CMT2D	<i>GARS</i>	Glycyl-tRNA synthetase	
CMT2E/1F	<i>NEFL</i>	Neurofilament light polypeptide	
CMT2F	<i>HSPB1</i>	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein-1	
CMT2I/2J	<i>MPZ</i>	Myelin P0 protein	
CMT2L	<i>HSPB8</i>	Heat-shock protein beta-8	
CMT2N	<i>AARS</i>	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	<i>DYNC1H1</i>	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	<i>LRSAM1</i>	E3 ubiquitin-protein ligase LRSAM1	
CMT2S	<i>IGHMBP2</i>	DNA-binding protein SMUBP-2	
CMT2T	<i>DNAJB2</i>	DnaJ homolog subfamily B member 2	
CMT2U	<i>MARS</i>	Methionine--tRNA ligase, cytoplasmic	
<b>CMT type 4</b>			
CMT4A	<i>GDAP1</i>	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	<i>MTMR2</i>	Myotubularin-related protein 2	
CMT4B2	<i>SBF2</i>	Myotubularin-related protein 13	
CMT4C	<i>SH3TC2</i>	SH3 domain and tetratricopeptide repeats-containing protein 2	

Locus Name	Gene	Protein Product	Prevalence (if known)
CMT4D	<i>NDRG1</i>	Protein NDRG1	
CMT4E	<i>EGR2</i>	Early growth response protein 2	
CMT4F	<i>PRX</i>	Periaxin	
CMT4H	<i>FGD4</i>	FYVE, RhoGEF and PH domain-containing protein 4	
CMT4J	<i>FIG4</i>	Phosphatidylinositol 3, 5-biphosphate	
<b>X-linked CMT</b>			
CMTX1	<i>GJB1</i>	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX2	<i>Xp22.2</i>	Unknown	
CMTX3	<i>Xq26</i>	Unknown	
CMTX4	<i>AIFM1</i>	Apoptosis-inducing factor 1	
CMTX5	<i>PRPS1</i>	Ribose-phosphate pyrophosphokinase 1	
CMTX6	<i>PKD3</i>	Pyruvate dehydrogenase kinase isoform 3	

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.<sup>6</sup> 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 three normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype.<sup>7</sup> 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.<sup>7</sup>

### 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.<sup>8</sup> 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* (CMT2C), *GARS* (CMT2D), *NEFL* (CMT2E/1F), *HSPB1* (CMT2F), *MPZ* (CMT2I/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, 2J, 2H/K, 2L, 2N, 2O, and 2P.<sup>8</sup> The most common subtype of CMT2 is CMT2A, which accounts for approximately 20% of CMT2 cases and is associated with mutations in the *MFN2* gene.

#### X-Linked CMT

CMT X type 1 (CMTX1) is characterized by a moderate to severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females.<sup>9</sup> 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.<sup>9</sup>

#### 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 *GDAP1* (CMT4A), *MTMR2* (CMT4B1), *SBF2* (CMT4B2), *SBF1* (CMT4B3), *SH3TC2* (CMT4C), *NDRG1* (CMT4D), *EGR2* (CMT4E), *PRX* (CMT4F), *FGD4* (CMT4H), and *FIG4* (CMT4J).

#### *Hereditary Neuropathy with Liability to Pressure Palsies*

The largest proportion of CMT1 cases are due to mutations in *PMP22*. In HNPP (also called tomaculous neuropathy), inadequate production of *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.<sup>10</sup> The prevalence is estimated at 16 persons per 100,000, although some authors indicate a potential for underdiagnosis of the disease.<sup>10</sup> An estimated 50% of carriers are asymptomatic and do not display abnormal neurologic findings on clinical examination.<sup>11</sup> 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.<sup>11</sup> Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases, the remaining symptoms are typically mild.

*PMP22* is the only gene in which 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 *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point mutations in *PMP22* have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome.<sup>12</sup> Studies have also reported that the point mutation frequency may vary considerably by ethnicity.<sup>13</sup> About 10% to 15% of mutation carriers remain clinically asymptomatic, suggesting incomplete penetrance.<sup>14</sup>

#### *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.<sup>15</sup> Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, Taxol, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.<sup>5</sup>

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.<sup>16</sup> 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.<sup>7,16</sup> Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit.<sup>17</sup> 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.<sup>18</sup> 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*.<sup>19</sup> 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.

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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.



1. Burgunder JM, Schols L, Baets J, et al. EFNS guidelines for the molecular diagnosis of neurogenetic disorders: motoneuron, peripheral nerve and muscle disorders. *Eur J Neurol*. Feb 2011; 18(2):207-217. PMID 20500522
2. Alport AR, Sander HW. Clinical approach to peripheral neuropathy: anatomic localization and diagnostic testing. *Continuum (Minneapolis, Minn)*. Feb 2012; 18(1):13-38. PMID 22810068
3. England JD, Gronseth GS, Franklin G, et al. Practice Parameter: evaluation of distal symmetric polyneuropathy: role of laboratory and genetic testing (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. *Neurology*. Jan 13 2009; 72(2):185-192. PMID 19056666
4. Saporta AS, Sottile SL, Miller LJ, et al. Charcot-Marie-Tooth disease subtypes and genetic testing strategies. *Ann Neurol*. Jan 2011; 69(1):22-33. PMID 21280073
5. Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews*. Seattle (WA) 2015 (last revision).
6. Stankiewicz P, Lupski JR. The genomic basis of disease, mechanisms and assays for genomic disorders. *Genome Dyn*. 2006; 1:1-16. PMID 18724050
7. Bird TD. Charcot-Marie-Tooth Neuropathy Type 1. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews*. Seattle (WA); 1993.
8. Bird TD. Charcot-Marie-Tooth Neuropathy Type 2. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews*. Seattle (WA); 1993.
9. Bird TD. Charcot-Marie-Tooth Neuropathy X Type 1. In: Pagon RA, Bird TD, Dolan CR, et al., eds. *GeneReviews*. Seattle (WA) 1993.
10. Meretoja P, Silander K, Kalimo H, et al. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. *Neuromuscul Disord*. Dec 1997; 7(8):529-532. PMID 9447611
11. Celik Y, Kilincer C, Hamamcioglu MK, et al. Hereditary neuropathy with liability to pressure palsies in a Turkish patient (HNPP): a rare cause of entrapment neuropathies in young adults. *Turk Neurosurg*. Jan 2008; 18(1):82-84. PMID 18382985
12. Taioli F, Cabrini I, Cavallaro T, et al. Inherited demyelinating neuropathies with micromutations of peripheral myelin protein 22 gene. *Brain*. Feb 2011; 134(Pt 2):608-617. PMID 21252112
13. Bissar-Tadmouri N, Parman Y, Boutrand L, et al. Mutational analysis and genotype/phenotype correlation in Turkish Charcot-Marie-Tooth Type 1 and HNPP patients. *Clin Genet*. Nov 2000; 58(5):396-402. PMID 11140841
14. Dubourg O, Mouton P, Brice A, et al. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. *Neuromuscul Disord*. Mar 2000; 10(3):206-208. PMID 10734269
15. Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. *Adv Exp Med Biol*. 07-224. PMID 20225028
16. Bird TD. Hereditary neuropathy with liability to pressure palsies. *Gene Reviews* 2005, last update 2014; <http://www.ncbi.nlm.nih.gov/books/NBK1392/>. Accessed June 9, 2015.
17. Lewis RA, McDermott MP, Herrmann DN, et al. High-dosage ascorbic acid treatment in Charcot-Marie-Tooth disease type 1A: results of a randomized, double-masked, controlled trial. *JAMA Neurol*. Aug 2013; 70(8):981-987. PMID 23797954

18. Attarian S, Vallat JM, Magy L, et al. An exploratory randomised double-blind and placebo-controlled phase 2 study of a combination of baclofen, naltrexone and sorbitol (PXT3003) in patients with Charcot-Marie-Tooth disease type 1A. *Orphanet J Rare Dis.* 2014; 9:199. PMID 25519680
19. GeneDx. Axonal CMT Panel. <http://www.genedx.com/test-catalog/available-tests/axonal-cmt-panel/>. Accessed June 9, 2015.
20. Hung CC, Chien SC, Lin CY, et al. Use of multiplex PCR and CE for gene dosage quantification and its biomedical applications for SMN, PMP22, and alpha-globin genes. *Electrophoresis.* Aug 2007; 28(16):2826-2834. PMID 17640091
21. Ravise N, Dubourg O, Tardieu S, et al. Rapid detection of 17p11.2 rearrangements by FISH without cell culture (direct FISH, DFISH): a prospective study of 130 patients with inherited peripheral neuropathies. *Am J Med Genet A.* Apr 1 2003; 118A (1):43-48. PMID 12605439
22. Hung CC, Lee CN, Lin CY, et al. Identification of deletion and duplication genotypes of the PMP22 gene using PCR-RFLP, competitive multiplex PCR, and multiplex ligation-dependent probe amplification: a comparison. *Electrophoresis.* Feb 2008; 29(3):618-625. PMID 18200636
23. Slater H, Bruno D, Ren H, et al. Improved testing for CMT1A and HNPP using multiplex ligation-dependent probe amplification (MLPA) with rapid DNA preparations: comparison with the interphase FISH method. *Hum Mutat.* Aug 2004; 24(2):164-171. PMID 15241798
24. Stangler Herodez S, Zagradsnik B, Erjavec Skerget A, et al. Molecular diagnosis of PMP22 gene duplications and deletions: comparison of different methods. *J Int Med Res.* Sep-Oct 2009; 37(5):1626-1631. PMID 19930872
25. Lin CY, Su YN, Lee CN, et al. A rapid and reliable detection system for the analysis of PMP22 gene dosage by MP/DHPLC assay. *J Hum Genet.* 2006; 51(3):227-235. PMID 16463004
26. Aarskog NK, Vedeler CA. Real-time quantitative polymerase chain reaction. A new method that detects both the peripheral myelin protein 22 duplication in Charcot-Marie-Tooth type 1A disease and the peripheral myelin protein 22 deletion in hereditary neuropathy with liability to pressure palsies. *Hum Genet.* Nov 2000; 107(5):494-498. PMID 11140948
27. Thiel CT, Kraus C, Rauch A, et al. A new quantitative PCR multiplex assay for rapid analysis of chromosome 17p11.2-12 duplications and deletions leading to HMSN/HNPP. *Eur J Hum Genet.* Feb 2003; 11(2):170-178. PMID 12634865
28. Chen SR, Lin KP, Kuo HC, et al. Comparison of two PCR-based molecular methods in the diagnosis of CMT 1A and HNPP diseases in Chinese. *Clin Neurol Neurosurg.* May 2008; 110(5):466-471. PMID 18353535
29. Kim SW, Lee KS, Jin HS, et al. Rapid detection of duplication/deletion of the PMP22 gene in patients with Charcot-Marie-Tooth disease Type 1A and hereditary neuropathy with liability to pressure palsy by real-time quantitative PCR using SYBR Green I dye. *J Korean Med Sci.* Oct 2003; 18(5):727-732. PMID 14555828
30. Choi BO, Kim J, Lee KL, et al. Rapid diagnosis of CMT1A duplications and HNPP deletions by multiplex micro-satellite PCR. *Mol Cells.* Feb 28 2007; 23(1):39-48. PMID 17464210
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
32. Rudnik-Schoneborn S, Tolle D, Senderek J, et al. Diagnostic algorithms in Charcot-Marie-Tooth neuropathies: experiences from a German genetic laboratory on the basis of 1206 index patients. *Clin Genet.* Apr 8 2015. PMID 25850958



33. DiVincenzo C, Elzinga CD, Medeiros AC, et al. The allelic spectrum of Charcot-Marie-Tooth disease in over 17,000 individuals with neuropathy. *Mol Genet Genomic Med*. Nov 2014; 2(6):522-529. PMID 25614874
34. Hoyer H, Braathen GJ, Busk OL, et al. Genetic diagnosis of Charcot-Marie-Tooth disease in a population by next-generation sequencing. *Biomed Res Int*. 2014; 2014:210401. PMID 25025039
35. Drew AP, Zhu D, Kidambi A, et al. Improved inherited peripheral neuropathy genetic diagnosis by whole-exome sequencing. *Mol Genet Genomic Med*. Mar 2015; 3(2):143-154. PMID 25802885
36. Choi BO, Nakhro K, Park HJ, et al. A cohort study of MFN2 mutations and phenotypic spectrums in Charcot-Marie-Tooth disease 2A patients. *Clin Genet*. Jun 2015; 87(6):594-598. PMID 24863639
37. Karadima G, Koutsis G, Raftopoulou M, et al. Mutational analysis of Greek patients with suspected hereditary neuropathy with liability to pressure palsies (HNPP): a 15-year experience. *J Peripher Nerv Syst*. Jun 25 2015. PMID 26110377
38. Azhary H, Farooq MU, Bhanushali M, et al. Peripheral neuropathy: differential diagnosis and management. *Am Fam Physician*. Apr 1 2010; 81(7):887-892. PMID 20353146
39. NGS Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 04/01/2016.