MEDICAL POLICY

POLICY TITLE	GENETIC TESTING FOR THE DIAGNOSIS OF INHERITED PERIPHERAL NEUROPATHIES
POLICY NUMBER	MP 2.355

Original Issue Date (Created):	**6/1/2018**
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Effective Date:	**11/1/2018**

I. POLICY

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

Genetic testing for an inherited peripheral neuropathy or sensory neuropathy is considered **investigational** for all other indications. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

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.

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.

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II. PRODUCT VARIATIONS

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This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

FEP PPO - Refer to FEP Medical Policy Manual MP-2.04.89 Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies. The FEP Medical Policy manual can be found at:https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

III. DESCRIPTION/BACKGROUND

TOP

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

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. 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 medical policy focuses on the hereditary motor and sensory neuropathies and HNPP.

A genetic etiology of a peripheral neuropathy is typically suggested by generalized polyneuropathy, family history, lack of positive sensory symptoms, early age of onset, symmetry, associated skeletal abnormalities, and very slowly progressive clinical course.[2] A family history of at least 3 generations with details on health issues, cause of death, and age at death should be collected.

Charcot-Marie-Tooth Disease

Hereditary Motor and Sensory Neuropathies

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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] In addition, 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 about 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. *(See table, next page)*

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Table 1: Molecular Genetics of CMT Variants (adapted from Bird, 2016[6])

Locus	Gene	Protein Product	Prevalence (if known)
CMT type 1			
CMT1A	*PMP22*	Peripheral myelin protein 22	70%-80% of CMT1
CMT1B	*MPZ*	Myelin P0 protein	10%-12% of CMT1
CMT1C	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-α factor	≈1% of CMT1
CMT1D	*EGR2*	Early growth response protein 2	
CMT1E	*PMP22*	Peripheral myelin protein 22 (sequence changes)	≈1% of CMT1
CMT1F/2E	*NEFL*	Neurofilament light polypeptide	
CMT type 2			
CMT2A1	*KIF1B*	Kinesin-like protein KIF1B	
CMT2A2	*MFN2*	Mitofusin-2	20% of CMT2
CMT2B	*RAB7A*	Ras-related protein Rab-7	
CMT2B1	*LMNA*	Lamin A/C	
CMT2B2	*MED25*	Mediator of RNA polymerase II transcription subunit 25	
CMT2C	*TRPV4*	Transient receptor potential cation channel subfamily V member 4	
CMT2D	*GARS*	Glycyl-tRNA synthetase	
CMT2E/1F	*NEFL*	Neurofilament light polypeptide	
CMT2F	*HSPB1*	Heat-shock protein beta-1	
CMT2G	12q12-q13	Unknown	
CMT2H/2K	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT2I/2J	*MPZ*	Myelin P0 protein	
CMT2L	*HSPB8*	Heat-shock protein beta-8	
CMT2N	*AARS*	Alanyl-tRNA synthetase, cytoplasmic	
CMT2O	*DYNC1H1*	Cytoplasmic dynein 1 heavy chain 1	
CMT2P	*LRSAM1*	E3 ubiquitin-protein ligase LRSAM1	
CMT2S	*IGHMBP2*	DNA-binding protein SMUBP-2	
CMT2T	*DNAJB2*	DnaJ homolog subfamily B member 2	
CMT2U	*MARS*	Methionine–tRNA ligase, cytoplasmic	
CMT type 4			
CMT4A	*GDAP1*	Ganglioside-induced differentiation-associated protein 1	
CMT4B1	*MTMR2*	Myotubularin-related protein 2	
CMT4B2	*SBF2*	Myotubularin-related protein 13	
CMT4C	*SH3TC2*	SH3 domain and tetratricopeptide repeats-containing protein 2	
CMT4D	*NDRG1*	Protein NDRG1	
CMT4E	*EGR2*	Early growth response protein 2	
CMT4F	*PRX*	Periaxin	
CMT4H	*FGD4*	FYVE, RhoGEF and PH domain-containing protein 4	
CMT4J	*FIG4*	Phosphatidylinositol 3, 5-biphosphate	
X-linked CMT			
CMTX1	*GJB1*	Gap junction beta-1 protein (connexin 32)	90% of X-linked CMT
CMTX2	*Xp22.2*	Unknown	
CMTX3	*Xq26*	Unknown	
CMTX4	*AIFM1*	Apoptosis-inducing factor 1	
CMTX5	*PRPS1*	Ribose-phosphate pyrophosphokinase 1	
CMTX6	*PDK3*	Pyruvate dehydrogenase kinase isoform 3	

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 (CMT 1A-E) are separated by molecular findings and are often clinically indistinguishable. CMT1A accounts for 70% to 80% of all CMT1, and about two-thirds of probands with CMT1A have inherited the disease-causing variant and about one-third have CMT1A as the result of a de novo variant.

CMT1A involves duplication of the *PMP22* gene. *PMP22* encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal *PMP22* gene dosage effects.[7] Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype, whereas 3 normal alleles (as in the heterozygous CMT1A duplication) causes 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

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.[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 (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, 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/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 indicate 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.[12] HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsies due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode.[12] Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases, the remaining symptoms are typically mild.

PMP22 is the only gene in which a variant is known to cause HNPP. A large deletion occurs in approximately 80% of patients, and the remaining 20% of patients have point variants and small deletions in the *PMP22* gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. Point variants 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 point variant 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 in functional activities and physiological adaptations with exercise.[16] Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain.[17] Avoidance of obesity and drugs associated with nerve damage (eg, vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.[6]

Supportive treatment for HNPP can include transient bracing (eg, wrist splint or ankle-foot orthosis), which may become permanent in some cases of foot drop.[18] Prevention of HNPP manifestations can be accomplished by wearing protective padding (eg, elbow or knee pads) to prevent trauma to nerves during activity. Some have reported that vincristine should also be avoided in HNPP patients.[8,18] Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but a 2013 trial in humans did not demonstrate significant clinical benefit.[19] Attarian et al (2014) reported results of an exploratory phase 2 randomized, double-blind, placebo-controlled trial of PXT3003, a low-dose combination of 3 approved compounds (baclofen, naltrexone, sorbitol) in 80 adults with CMT1A.[20] The study 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 and 2 of PXT3003, in a meta-analysis.[21]

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 variants in *MFN2*, whole gene or select exome sequence analysis is typically used to identify point variants, 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: *AARS*, *BSCL2*, *DNM2*, *DYNC1H1*, *GARS*, *GDAP1*, *GJB1*, *HSPB1*, *HSPB8*, *LMNA*, *LRSAM1*, *MED25*, *MFN2*, *MPZ*, *NEFL*, *PRPS1*, *RAB7A*, and *TRPV4*.[22] 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 Amendments (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 this test.

IV. RATIONALE

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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. The analytic validity of variant testing for these diseases is high. For the evaluation of hereditary motor and sensory peripheral neuropathies and for hereditary neuropathy with liability to pressure palsies (HNPP), the yield of genetic testing 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 HNPP 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, in order to initiate supportive therapies. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

V. DEFINITIONS TOP

NA

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member's individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member's benefit information or contact Capital BlueCross for benefit information.

VII. DISCLAIMER TOP

Capital BlueCross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. Capital BlueCross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary; genetic testing for the diagnosis of peripheral neuropathies:

CPT Codes®							
81324	81325	81326	81403	81404	81405	81406	81479

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ICD-10-CM Diagnosis Code	Description
G60.0	Hereditary motor and sensory neuropathy
G60.8	Other hereditary and idiopathic neuropathies
G60.9	Hereditary and idiopathic neuropathy, unspecified

IX. REFERENCES

TOP

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 (Minneap 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. *Cornett KM, Menezes MP, Bray P, et al. Phenotypic variability of childhood Charcot-Marie-Tooth disease. JAMA Neurol. Jun 01 2016;73(6):645-651. PMID 27043305*
6. *Bird TD. Charcot-Marie-Tooth Hereditary Neuropathy Overview. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle (WA): University of Washington; 2015 (last revision).*
7. *Stankiewicz P, Lupski JR. The genomic basis of disease, mechanisms and assays for genomic disorders. Genome Dyn. 2006;1:1-16. PMID 18724050*
8. *Bird TD. Charcot-Marie-Tooth Neuropathy Type 1. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle (WA): University of Washington; 1993.*
9. *Bird TD. Charcot-Marie-Tooth Neuropathy Type 2. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle (WA): University of Washington; 1993.*
10. *Bird TD. Charcot-Marie-Tooth Neuropathy X Type 1. In: Pagon RA, Bird TD, Dolan CR, et al., eds. GeneReviews. Seattle (WA): University of Washington; 1993.*
11. *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*
12. *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*

13. *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*
14. *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*
15. *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*
16. *Sman AD, Hackett D, Fiatarone Singh M, et al. Systematic review of exercise for Charcot-Marie-Tooth disease. J Peripher Nerv Syst. Dec 2015;20(4):347-362. PMID 26010435*
17. *Pareyson D, Marchesi C. Natural history and treatment of peripheral inherited neuropathies. Adv Exp Med Biol. 2009;652:207-224. PMID 20225028*
18. *Bird TD. Hereditary neuropathy with liability to pressure palsies. Gene Reviews. Seattle (WA): University of Washington; 2005, last update 2014.*
19. *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*
20. *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*
21. *Mandel J, Bertrand V, Lehert P, et al. A meta-analysis of randomized double-blind clinical trials in CMT1A to assess the change from baseline in CMTNS and ONLS scales after one year of treatment. Orphanet J Rare Dis. Jun 13 2015;10:74. PMID 26070802*
22. *GeneDx. Axonal CMT Panel. http://www.genedx.com/test-catalog/available-tests/axonal-cmt-panel/. Last accessed June 9, 2015.*
23. *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*
24. *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*
25. *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*

26. *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*
27. *Stangler Herodez S, Zagradisnik 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*
28. *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*
29. *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*
30. *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*
31. *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*
32. *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*
33. *Choi BO, Kim J, Lee KL, et al. Rapid diagnosis of CMT1A duplications and HNPP deletions by multiplex microsatellite PCR. Mol Cells. Feb 28 2007;23(1):39-48. PMID 17464210*
34. *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*
35. *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. Jan 2016;89(1):34-43. PMID 25850958*
36. *Gess B, Schirmacher A, Boentert M, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes in a German neuromuscular center population. Neuromuscul Disord. Aug 2013;23(8):647-651. PMID 23743332*
37. *Ostern R, Fagerheim T, Hjellnes H, et al. Diagnostic laboratory testing for Charcot Marie Tooth disease (CMT): the spectrum of gene defects in Norwegian patients with CMT and its implications for future genetic test strategies. BMC Med Genet. Sep 21 2013;14:94. PMID 24053775*

38. *Murphy SM, Laura M, Fawcett K, et al. Charcot-Marie-Tooth disease: frequency of genetic subtypes and guidelines for genetic testing. J Neurol Neurosurg Psychiatry. Jul 2012;83(7):706-710. PMID 22577229*
39. *Antoniadi T, Buxton C, Dennis G, et al. Application of targeted multi-gene panel testing for the diagnosis of inherited peripheral neuropathy provides a high diagnostic yield with unexpected phenotype-genotype variability. BMC Med Genet. Sep 21 2015;16:84. PMID 26392352*
40. *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*
41. *Sanmaneechai O, Feely S, Scherer SS, et al. Genotype-phenotype characteristics and baseline natural history of heritable neuropathies caused by mutations in the MPZ gene. Brain. Nov 2015;138(Pt 11):3180-3192. PMID 26310628*
42. *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 2015;20(2):79-85. PMID 26110377*
43. *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*
44. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 2.04.89, Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies. January 2018.*

X. POLICY HISTORY

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MP 2.355	**12/1/17** New policy adopted from BCBSA. Genetic testing is considered medically necessary when the diagnosis of an inherited peripheral motor or sensory neuropathy is suspected due to signs and/or symptoms but a definitive diagnosis cannot be made without genetic testing. Coding Completed.
	9/28/18 Consensus review. No change to policy statements. References reviewed. Rationale condensed**.**

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