Protocol

Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies

(20489)

Medical Benefit		**Effective Date**: 01/01/18	**Next Review Date**: 09/18
Preauthorization	No	**Review Dates**: 09/13, 09/14, 09/15, 09/16, 09/17	

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: • With suspected inherited motor and sensory peripheral neuropathy	Interventions of interest are: • Testing for genes associated with inherited peripheral neuropathies	Comparators of interest are: • Clinical management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Symptoms • Change in disease status

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

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.

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.

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.

Testing Strategy

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

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

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background

Inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is one in 2500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.[1]

Peripheral neuropathies can be subdivided into two major categories: primary axonopathies and primary 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 neuro-

pathies but typically have other predominating symptoms. This protocol 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 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.[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 five 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 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 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.

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	

Locus	Gene	Protein Product	Prevalence (if known)
CMT2T	DNAJB2	DnaJ homolotg subfamily B member 2	
CMT2U	MARS	Methionine-RNA 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 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 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 three 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 nine 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 (e.g., vincristine, paclitaxel, cisplatin, isoniazid, nitrofurantoin) is recommended in CMT patients.[6]

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

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.**

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

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