Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathy

**Description of Procedure or Service**

The inherited peripheral neuropathies are a clinically and genetically heterogeneous group of disorders. The estimated prevalence in aggregate is estimated at roughly 1 in 2,500 persons, making inherited peripheral neuropathies the most common inherited neuromuscular disease.

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 (e.g. motor versus sensory, large versus 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 (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 policy will focus on the hereditary motor and sensory neuropathies and hereditary neuropathy with liability to pressure palsies.

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. 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 neurological findings to the classic picture with pes cavus and “stork legs” to a severe polyneuropathy with respiratory failure. 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. In addition, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different 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.

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.
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Most cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. The majority of cases are CMT type 1 (approximately 40-50% of all CMT cases, with 78-80% of those due to PMP22 variants). CMT type 2 is associated with about 10-15% of CMT cases, with 20% of those due to MFN2 variants.

CMT Type 1
Charcot-Marie-Tooth 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 individuals usually become symptomatic between age 5 and 25 years, and lifespan is not shortened. Less than 5% of individuals 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 70-80% 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 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.

CMT Type 2
Charcot-Marie-Tooth 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. 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 mutations in the MFN2 gene.

X-linked CMT
Charcot-Marie-Tooth X type 1 (CMTX1) is characterized by a moderate to severe motor and sensory neuropathy in affected males and mild to no symptoms in carrier females. Sensorineural deafness and central nervous system symptoms also occur in some families. CMTX1 is inherited in an X-linked dominant manner. Molecular genetic testing of GJB1 (Cx32), which is available on a clinical basis, detects about 90% of cases of CMTX1.

CMT Type 4
Charcot-Marie-Tooth 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 authors report presentation as early as birth or as late as the seventh decade of life. The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for underdiagnosis of the disease. An estimated 50% of carriers...
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are asymptomatic and do not display abnormal neurological findings on clinical examination. HNPP is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop and episodes of numbness, muscular weakness, atrophy, and palsy due to minor compression or trauma to the peripheral nerves. The disease is benign with complete recovery occurring within a period of days to months in most cases, although an estimated 15% of patients have residual weakness following an episode. Poor recovery usually involves a history of prolonged pressure on a nerve, but, in these cases the remaining symptoms are typically mild.

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 single nucleotide variants (SNVs) and small deletions in the PMP22 gene. One normal allele (due to a 17p11.2 deletion) results in HNPP and a mild phenotype. SNVs in PMP22 have been associated with a variable spectrum of HNPP phenotypes ranging from mild symptoms to representing a more severe, CMT1-like syndrome. Studies have also reported that the SNV frequency may vary considerably by ethnicity. About 10-15% of variant carriers remain clinically asymptomatic, suggesting incomplete penetrance.

Treatment
Currently there is no effective therapy to slow the progression of neuropathy for the inherited peripheral neuropathies. 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. Supportive treatment, if necessary, is generally provided by a multidisciplinary team including neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists. Treatment choices are limited to physical therapy, use of orthotics, surgical treatment for skeletal or soft tissue abnormalities, and drug treatment for pain. Avoidance of obesity and drugs that are associated with nerve damage, such as vincristine, paclitaxel, cisplatin, isoniazid, and nitrofurantoin, is recommended in CMT patients.

Supportive treatment for HNPP can include transient bracing (e.g., a wrist splint or ankle-foot orthosis), which may become permanent in some cases of foot drop. Prevention of HNPP manifestations can be accomplished by wearing protective padding (e.g., elbow or knee pads) to prevent trauma to nerves during activity. Some authors reported that vincristine should also be avoided in HNPP patients. 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. Attarian and colleagues (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 and sorbitol) in 80 adults with CMT1A. The trial demonstrated the safety and tolerability of the drug. Mandel and colleagues (2015) included this randomized controlled trial and 3 other trials, 1 of ascorbic acid and 2 of PXT3003, in a meta-analysis.

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). 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.

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.
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Genetic testing for the diagnosis of inherited peripheral neuropathies is considered investigational. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies is covered

Not Applicable

When Genetic Testing for the Diagnosis of Peripheral Neuropathies is not covered

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

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

Policy Guidelines

The evidence for testing for genes associated with inherited peripheral neuropathies for individuals with suspected inherited motor and sensory peripheral neuropathy, includes case-control and genome-wide association studies (GWAS). Relevant outcomes include change in disease status, symptoms, test accuracy, and test validity. 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), 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. The changes in clinical management that would occur as a result of testing are not well-defined. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 81324, 81325, 81326, 81403, 81404, 81406, 81448, 81479

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.
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Scientific Background and Reference Sources


Medical Director review 7/2013


Specialty Matched Consultant Advisory Panel review 8/2014

Specialty Matched Consultant Advisory Panel review 8/2015


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Medical Director review 2/2017

Specialty Matched Consultant Advisory Panel review 7/2017

Medical Director review 7/2017


Medical Director review 1/2018

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>8/13/13</td>
<td>New policy implemented. Genetic testing to confirm a clinical diagnosis of an inherited peripheral neuropathy is considered investigational. Genetic testing for an inherited peripheral neuropathy is considered investigational for all indications. Medical Director review 7/2013. Notification given August 13, 2013 for effective date October 15, 2013. (mco)</td>
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<tr>
<td>8/12/14</td>
<td>Description section updated. Added the following codes to the Billing/Coding section: 81403, 81404, 81406, 81479. References updated. No changes to Policy Statements. (mco)</td>
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<tr>
<td>8/30/16</td>
<td>Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)</td>
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<tr>
<td>2/2017</td>
<td>Description section, Policy Guidelines and references updated. Medical Director review 1/2017. (jd)</td>
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<tr>
<td>12/29/17</td>
<td>Code 81448 added to codes section, effective 1/1/18. (jd)</td>
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<tr>
<td>2/9/18</td>
<td>Minor revision to Description section and Policy Guidelines. Reference updated. Medical Director review 1/2018. (jd)</td>
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*Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and*
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subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.