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, 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 heterogeneous as well as clinically heterogeneous. Mutations in more than 30 genes and more than 44 different genetic loci have been associated with the inherited neuropathies. In addition, different pathogenic variants in a single gene can lead to different inherited neuropathy phenotypes and different inheritance patterns. CMT subtypes are characterized by mutations in one of several myelin genes, which lead to abnormalities in myelin structure, function or upkeep. There are 7 subtypes of CMT, with type 1 and 2 representing the most common hereditary peripheral neuropathies.

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

**CMT Type 1**
Charcot-Marie-Tooth 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 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 (CMT1A-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 mutation and about one third have CMT1A as the result of a de novo mutation.

CMT1A involves duplication of the gene PMP22. PMP22 encodes an integral membrane protein, peripheral membrane protein 22, which is a major component of myelin in the peripheral nervous system. The phenotypes associated with this disease arise because of abnormal PMP22 gene dosage effects. Two normal alleles represent the normal wild-type condition. Four normal alleles (as in the homozygous CMT1A duplication) results in the most severe phenotype whereas 3 normal alleles (as in the heterozygous CMT1A duplication) causes a less severe phenotype. CMT1B (6-10% of all CMT1) is associated with point mutations in 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.

**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. 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. 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. Sensorineuronal 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) detects about 90% of cases of CMTX1, which is available on a clinical basis.

**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.
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It occurs more rarely than the other forms of CMT neuropathy. There are ten 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. 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 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 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. Poor recovery usually involves a history of prolonged pressure on a nerve, but in these cases the remaining symptoms are typically mild.

PMP 22 is the only gene in which mutation is known to cause HNPP. A large deletion occurs in approximately 80% of patients and the remaining 20% of patients have point mutations and small deletions in the 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. Studies have also reported that the point mutation frequency may vary considerably by ethnicity. About 10-15% of mutation 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. 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, taxol, 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. Ascorbic acid has been investigated as a treatment for CMT1A based on animal models, but trials in humans have not demonstrated significant clinical benefit. 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 and sorbitol) in 80 adults with cMT1A. The study demonstrated the safety and tolerability of the drug, but further studies are needed.

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
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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.

Policy

Genetic testing for the diagnosis of inherited peripheral neuropathies is considered investigational. BCBSNC does not provide coverage for investigative 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 mutations associated with hereditary motor and sensory neuropathies in patients with a suspected inherited peripheral neuropathy consists primarily of case-control and genome-wide association studies (GWAS) reporting associations between a number of genes and clinical diagnosis. Relevant outcomes include change in disease status, symptoms, test accuracy, and test validity. 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 (HNLP), 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 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. Therefore, the evidence is insufficient to determine the effects of the technology on health outcomes.
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**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, 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.

**Scientific Background and Reference Sources**


Medical Director review 7/2013


Specialty Matched Consultant Advisory Panel review 8/2014

Medical Director review 8/2014

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Specialty Matched Consultant Advisory Panel review 8/2015
Medical Director review 8/2015


Medical Director review 7/2016

Policy Implementation/Update Information

8/13/13  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)

8/12/14  Description section updated. Added the following codes to the Billing/Coding section: 81403, 81404, 81406, 81479. References updated. No changes to Policy Statements. (mco)


8/30/16  Specialty Matched Consultant Advisory Panel review 7/2016. Medical Director review 7/2016. (jd)

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 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.