The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary; supporting documentation must be submitted to Utilization Management. 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.

Description
The inherited peripheral neuropathies are the most common inherited neuromuscular disease. Genetic testing has been suggested as a way to diagnose specific inherited peripheral neuropathies.

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 2,500 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 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). This Protocol 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. (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
The majority of inherited polyneuropathies are 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. (3) The majority of cases of CMT are autosomal dominant, although autosomal recessive and X-linked dominant forms exist. The majority of cases are CMT type 1.

Charcot-Marie-Tooth neuropathy 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 individual
usually become symptomatic between age five 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. (4) 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. (5) 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*.

Charcot-Marie-Tooth hereditary neuropathy 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. (6) 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.


Charcot-Marie-Tooth neuropathy 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. (7) 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*) detects about 90% of cases of CMTX1, which is available on a clinical basis. (7)

**Hereditary neuropathy with liability to pressure palsies (HNPP)**

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. (8) The prevalence is estimated at 16 persons per 100,000 although some authors indicate a potential for under diagnosis of the disease. (8) An estimated 50% of carriers are asymptomatic and do not display abnormal neurological findings on clinical examination. (9) 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. (9) 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. (10) Studies have also reported that the point mutation frequency may vary considerably by ethnicity. (11) About 10-15% of mutation carriers remain clinically asymptomatic, suggesting incomplete penetrance. (12)

Treatment

Currently there is no effective therapy 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. (13) Avoidance of obesity and high-risk drugs such as vincristine 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. (14) 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. (5, 14)

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

Related Protocol:

General Approach to Genetic Testing

Corporate Medical Guideline

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.

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.


26. 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 2010; 18(9).