Overview

Useful For

Diagnosis of inherited peripheral neuropathies associated with known causal genes

Serving as a second-tier test for patients in whom previous targeted gene mutation analyses for specific inherited peripheral neuropathy-related genes were negative

Identifying mutations within genes known to be associated with inherited peripheral neuropathy, allowing for predictive testing of at-risk family members

Genetics Test Information

This ordered service includes the option for one of several peripheral neuropathy related panel tests to be performed. The specific peripheral neuropathy panel requested must be provided in order to perform this test. Testing options include the following:

-Hereditary Motor Neuropathy Panel (23 genes)

-Hereditary Sensory Neuropathy Panel (18 genes)

-Metabolic or Syndromic Neuropathies (74 genes)

-Motor and Sensory Neuropathy Panel (82 genes)

-Peripheral Neuropathy Expanded Panel (193 genes)

-*SEPT9* Gene, Full Gene Analysis (1 gene)

-Spastic Paraplegia Neuropathy Panel (41 genes)

-Custom Gene Panel (https://orders.mayocliniclabs.com/en/tools/gene_panels/)

-Custom Gene Ordering tutorial: https://vimeo.com/299737728/23d56922f1

See Frequently Asked Questions: Custom Gene Ordering Tool in Special Instructions.

See Targeted Genes and Methodology Details for Peripheral Neuropathy Gene Panels in Special Instructions for details regarding the targeted genes for each test.

*Related testing to neuromuscular conditions is available. See NMPAN / Neuromuscular Genetic Panels by Next-Generation Sequencing (NGS) for more information about neuromuscular testing.

Highlights

This test may aid in the diagnosis of inherited peripheral neuropathy

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
_G103	Peripheral Neuropathy Expanded Panel	No, (Bill Only)	No

Test ID	Reporting Name	Available Separately	Always Performed
_G104	Motor and Sensory Neuropathy Panel	No, (Bill Only)	No
_G105	Hereditary Sensory Neuropathy Panel	No, (Bill Only)	No
_G106	Hereditary Motor Neuropathy Panel	No, (Bill Only)	No
_G107	Spastic Paraplegia Neuropathy Panel	No, (Bill Only)	No
_G108	Metabolic or Syndromic Neuropathies	No, (Bill Only)	No
_G132	SEPT9 Gene, Full Gene Analysis	No, (Bill Only)	No
G145	Hereditary Custom Gene Panel Tier 1	No, (Bill Only)	No
G146	Hereditary Custom Gene Panel Tier 2	No, (Bill Only)	No
G151	Custom Gene Panel(CPT 81448) Tier 2	No, (Bill Only)	No
G152	Custom Gene Panel(CPT 81448) Tier 3	No, (Bill Only)	No
G153	Custom Gene Panel(CPT 81448) Tier 4	No, (Bill Only)	No
G154	Custom Gene Panel(CPT 81448) Tier 5	No, (Bill Only)	No

Testing Algorithm

This test includes the option for either one of several predefined panel tests or the option to create a custom gene panel. Pricing for the Custom Gene Panel will be based on the number of genes selected (1, 2-4, 5-14, 15-49, 50-100, and 101-500).

See Hereditary Peripheral Neuropathy Diagnostic Algorithm in Special Instructions.

Special Instructions

- Informed Consent for Genetic Testing
- Hereditary Peripheral Neuropathy Diagnostic Algorithm
- Molecular Genetics: Neurology Patient Information
- Frequently Asked Questions: Custom Gene Ordering Tool
- Informed Consent for Genetic Testing (Spanish)
- Targeted Genes and Methodology Details for Peripheral Neuropathy Gene Panels

Method Name

Custom Sequence Capture and Targeted Next-Generation Sequencing (NGS)/Polymerase Chain Reaction (PCR)/qPCR, Sanger Sequencing/and/or Gene Dosage Analysis by Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Advisory Information

The recommended first-tier test to screen for hereditary motor and sensory neuropathy is PMPDD / *PMP22* Gene, Large Deletion and Duplication Analysis, which assesses for large deletions and duplications of the *PMP22* gene.

Shipping Instructions

Specimen preferred to arrive within 96 hours of collection**.**

Specimen Required

Patient Preparation: A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Specimen Type: Whole blood

Container/Tube:

Preferred: Lavender top (EDTA) or yellow top (ACD)

Acceptable: Any anticoagulant

Specimen Volume: 3 mL

Collection Instructions:

1. Invert several times to mix blood.

2. Send specimen in original tube.

Additional Information: To ensure minimum volume and concentration of DNA is met, the preferred volume of blood must be submitted. Testing may be canceled if DNA requirements are inadequate.

Forms

1. **New York Clients-Informed consent is required.** Document on the request form or electronic order that a copy is on file. The following documents are available in Special Instructions:

-Informed Consent for Genetic Testing (T576)

-Informed Consent for Genetic Testing-Spanish (T826)

2. Molecular Genetics: Neurology Patient Information in Special Instructions.

3. If not ordering electronically, complete, print, and send a Neurology Specialty Testing Client Test Request (T732) with the specimen.

Specimen Minimum Volume

3 mL

Reject Due To

All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Ambient (preferred)		
	Frozen		
	Refrigerated		

Clinical and Interpretive

Clinical Information

Inherited peripheral neuropathies are a relatively common diverse group of disorders with heterogeneous genetic causes. Due to the considerable overlap in the clinical phenotypes of various neuropathies, it is often difficult to distinguish these specific inherited disorders from sporadic, idiopathic, or acquired forms of neuropathy without genetic testing. Additionally, peripheral neuropathy may be part of an inherited systemic syndromic or metabolic disorder caused by genes in metabolic pathways. Based on the pattern of inheritance and nerve conduction studies, there are 3 major categories of inherited peripheral neuropathies with isolated nerve involvement:

1. Hereditary motor and sensory neuropathy (HMSN), also referred as Charcot Marie Tooth (CMT)

2. Hereditary sensory and autonomic neuropathy (HSAN) or hereditary sensory neuropathy (HSN), if autonomic dysfunction is absent

3. Distal hereditary motor neuropathy (dHMN)

Inherited peripheral neuropathies may also show involvement of the central nervous system (brain or spinal cord), as in hereditary spastic paraplegia (HSP) with neuropathy (complicated form, also referred to as HSMN type 5) or be part of a systemic syndromic or metabolic disorder.

Hereditary Motor and Sensory Neuropathy:

Hereditary motor and sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT) disease, is a major category of inherited peripheral neuropathies and is the most commonly inherited neuromuscular disorder. It is characterized by the motor and/or sensory peripheral nerve involvement. The clinical phenotype is variable, and includes wasting and weakness of the distal limb muscles, skeletal deformities, and hearing loss. HMSN/CMT is classified into 5 groups:

1. HMSN 1, which is a dominantly inherited demyelinating form

2. HMSN 2, a dominantly inherited axonal predominant neuropathy

3. HMSN 3 (also called Dejerine-Sottas disease), which is often inherited dominantly, with onset in infancy or

childhood and is characterized by extremely slow nerve conduction velocities resulting in loss of ambulatory milestones and more generalized neurologic deficit

4. HMSN 4, an autosomal recessive inherited demyelinating form that may also present with extraneural features, including facial dysmorphism and scoliosis, particularly those with HMSN 4C, the most frequent form of HMSN 4

5. HMSN 5, a form associated with spasticity, also known as "complex hereditary spastic paraplegia (HSP)"

Hereditary Motor Neuropathy:

Distal hereditary motor neuropathies (dHMN) are one of the major categories of peripheral inherited neuropathies and are characterized by length-dependent, slowly progressive motor neuropathies with variable nerve conduction velocities. The clinical phenotype is variable, but includes progressive weakness and atrophy of the distal muscles, foot deformities, and decreased reflexes. There is significant phenotypic overlap with hereditary motor sensory neuropathy (HMSN), also known as Charcot-Marie-Tooth (CMT); however, sensory loss is usually absent in dHMN. dHMN are subdivided into 11 subtypes based on inheritance pattern and clinical features and include types 1-7, dHMN plus pyramidal signs, X-linked, congenital distal SMA, and Jerash type.

Hereditary Sensory and Autonomic Neuropathy:

Hereditary sensory and autonomic neuropathies (HSAN), or hereditary sensory neuropathies (HSN), if autonomic dysfunction is absent, is one of these major categories of inherited peripheral neuropathies. They affect sensory and autonomic nerves and the hallmark feature is the presence of prominent small-fiber involvement. HSAN are subdivided into 5 groups based on age of onset, inheritance pattern, and clinical features:

1. HSAN 1 varieties (HSAN 1A-E) follow an autosomal dominant inheritance pattern with juvenile or adult onset, and severe sensory loss and autonomic dysfunction

2. HSAN 2-5 have an autosomal recessive inheritance pattern and are usually congenital

3. HSAN3, also known as familial dysautonomia or Rilay-Day syndrome, is characterized by prominent autonomic and small-fiber sensory involvement

4. HSAN 4 and 5 are characterized by insensitivity to pain and widespread autonomic disturbance, with HSAN 4 also featuring mental retardation.

Hereditary Spastic Paraplegia:

Hereditary spastic paraplegia (HSP) is characterized by progressive lower extremity weakness and spasticity, and may present with prominent peripheral neuropathy as one of the complicated forms, also known as hereditary motor sensory neuropathy 5 (HMSN 5). The complicated forms are associated with a variety of other neurological systemic abnormalities and usually follow an autosomal recessive inheritance pattern. The uncomplicated or pure form presents with lower limb weakness and spasticity, and is predominantly characterized by an autosomal dominant inheritance pattern.

***SEPT9* Gene, Full Gene Analysis:**

Hereditary neuralgic amyotrophy (HNA) is an autosomal dominant disorder characterized by periods of severe pain involving the brachial plexus followed by muscle atrophy and weakness. These recurrent episodes can also be accompanied by decreased sensation and paresthesias. Individuals with this disease are generally symptom-free between pain attacks, though many experience lingering effects with repeated attacks. The pain episodes are frequently triggered by physical, emotional, or immunological stress. Less commonly, affected individuals can exhibit

non-neurological features including short stature, skin folds, hypotelorism, and cleft palate.

Mutations in the *SEPT9* gene cause the clinical manifestations of HNA. *SEPT9* is currently the only known gene associated with HNA, although approximately 15% of HNA families do not show linkage to this gene.

Given the considerable phenotypic overlap and the broad genetic heterogeneity of inherited peripheral neuropathies a comprehensive diagnostic genetic test is useful to establish the genetic cause in these clinical groups.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance.

Cautions

Clinical Correlations:

Some individuals who have involvement of 1 or more of the genes on the panel may have a mutation that is not identified by the methods performed (eg, large deletions/duplications not targeted, promoter mutations, deep intronic mutations). The absence of a mutation, therefore, does not eliminate the possibility of a hereditary peripheral neuropathy disorder. For predictive testing of asymptomatic individuals, it is important to first document the presence of a gene mutation in an affected family member.

Test results should be interpreted in context of clinical findings, family history, and other laboratory data. Misinterpretation of results may occur if the information provided is inaccurate or incomplete.

Technical Limitations:

In some cases, DNA variants of undetermined significance may be identified.

Due to the limitations of next-generation sequencing, small deletions and insertions may not be detected by this test. If a diagnosis of one of the syndromes on this panel is still suspected, contact a molecular genetic counselor in the Genomics Laboratory at 800-533-1710 for more information regarding follow-up testing options.

Rare polymorphisms exist that could lead to false-negative or false-positive results. If results obtained do not match the clinical findings, additional testing should be considered.

In addition to disease-related probes, the multiplex ligation-dependent probe amplification technique utilizes probes localized to other chromosomal regions as internal controls. In certain circumstances, these control probes may detect other diseases or conditions for which this test was not specifically intended. Results of the control probes are not normally reported. However, in cases where clinically relevant information is identified, the ordering physician will be informed of the result and provided with recommendations for any appropriate follow-up testing.

A previous bone marrow transplant from an allogenic donor will interfere with testing. Call 800-533-1710 for instructions for testing patients who have received a bone marrow transplant.

Evaluation Tools:

Multiple in-silico evaluation tools were used to assist in the interpretation of these results. These tools are updated regularly; therefore, changes to these algorithms may result in different predictions for a given alteration. Additionally,

the predictability of these tools for the determination of pathogenicity clinically is currently not validated.

Unless reported or predicted to cause disease, alterations found deep in the intron or alterations that do not result in an amino acid substitution are not reported. These and common polymorphisms identified for this patient are available upon request.

Reclassification of Variants-Policy:

All detected alterations are evaluated according to American College of Medical Genetics and Genomics recommendations.(1) Variants are classified based on known, predicted, or possible pathogenicity and reported with interpretive comments detailing their potential or known significance. At this time, it is not standard practice for the laboratory to systematically review â€œlikely pathogenicâ€• alterations or â€œvariants of uncertain significanceâ€• that are detected and reported. The laboratory encourages health care providers to contact the laboratory at any time to learn how the status of a particular variant may have changed over time.

Clinical Reference

1. Richards CS, Aziz N, Bale S, et al: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015;17(5):405-424

2. Klein CJ, Duan X, Shy ME: Inherited neuropathies: Clinical overview and update. Muscle Nerve 2013:48(4):604-622

3. Vallat JM, Mathis S, Funalot B: The various Charcot-Marie-Tooth diseases. Curr Opin Neurol. 2013 Oct;26(5):473-80

4. Rossor AM, Kalmar B, Greensmith L, et al: The distal hereditary motor neuropathies. J Neurol Neurosurg Psychiatry 2012:83(1):6-14

5. Rotthier A, Baets J, Timmerman V, et al: Mechanisms of disease in hereditary sensory and autonomic neuropathies. Nat Rev Neurol 2012 Jan:8(2):73-85

6. Finsterer J, Loscher W, Quasthoff S, et al: Hereditary spastic paraplegias with autosomal dominant, recessive, X-linked, or maternal trait of inheritance. J Neurol Sci 2012 Jul:318(1-2):1-18

7. D'Amico A, Bertini E: Metabolic neuropathies and myopathies. Handb Clin Neurol 2013;113:1437-1455

Performance

Method Description

Next-generation sequencing (NGS) and/or Sanger sequencing is performed to test for the presence a mutation in the genes analyzed. See Targeted Genes and Methodology Details for Peripheral Neuropathy Gene Panels in Special Instructions for details regarding the targeted genes for each test.

There may be regions of genes that cannot be effectively amplified and sequenced as a result of technical limitations of the assay, including regions of homology, high guanine-cytosine (GC)-rich content, and repetitive sequences.

Additionally, NGS is used to test for the presence of large deletions and duplications in a subset of genes. See Targeted Genes and Methodology Details for Peripheral Neuropathy Gene Panels in Special Instructions for details regarding the targeted genes analyzed for large deletions and duplications for each test.

Multiplex ligation-dependent probe amplification (MLPA), PCR, and Sanger sequencing is used to confirm alterations detected by NGS when appropriate.(Unpublished Mayo method)

PDF Report

No

Day(s) and Time(s) Test Performed

Performed weekly; Varies

Analytic Time

8 weeks

Maximum Laboratory Time

12 weeks

Specimen Retention Time

Whole Blood: 2 weeks (if available); Extracted DNA: Indefinitely

Performing Laboratory Location

Rochester

Fees and Codes

Fees

- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their Regional Manager. For assistance, contact Customer Service.

Test Classification

This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the U.S. Food and Drug Administration.

CPT Code Information

81448 (if appropriate)

81405 (if appropriate)

81408 (if appropriate)

81407 (if appropriate)

81406 (if appropriate)

81479 (if appropriate)

81325 (if appropriate)

81403 (if appropriate)

81404 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NPPAN	Peripheral Neuropathy Gene Panels	In Process

Result ID	Test Result Name	Result LOINC Value
MG112	Client Provided Sub-Panel	19145-2
MG121	Gene List ID or NA	48018-6
38195	Result Summary	50397-9
38196	Result	38179-8
38197	Interpretation	69047-9
38198	Additional Information	48767-8
113190	Method	49549-9
113191	Disclaimer	62364-5
38199	Specimen	31208-2
38200	Source	31208-2
38201	Released By	18771-6