Overview

Useful For

Establishing a diagnosis of a neuromuscular disorder associated with known causal genes

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

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

Genetics Test Information

This test includes the option of performing 1 of several neuromuscular disease-related panels. Options include the following:

Myopathies:

-Myopathy Expanded Panel (141 genes)

-Muscular Dystrophy Panel (77 genes)

-Congenital Myopathy Panel (36 genes)

-Metabolic Myopathy Panel (41 genes)

-Myofibrillar Myopathy Panel (12 genes)

-Distal Myopathy Panel (27 genes)

-Emery-Dreifuss Panel (5 genes)

-Rhabdomyolysis and Myopathy Panel (31 genes)

Distal Myopathy + Peripheral Neuropathy:

-Distal Weakness Expanded Panel (217 genes)

(See below for additional peripheral neuropathy testing options available)

Motor Neuron Disease:

-Motor Neuron Disease Panel (17 genes)

Neuromuscular Junction:

-Congenital Myasthenic Syndromes Panel (25 genes)

Hyperexcitable Muscle Disease:

-Skeletal Muscle Channelopathy Panel (6 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 Neuromuscular Genetic Panels in Special Instructions for details regarding the targeted genes for each test.

Related Testing:

The following focused hereditary peripheral neuropathy tests are separately available:

-PMPDD / *PMP22* Gene, Large Deletion/Duplication Analysis, Varies (1 gene)

-NPPAN / Peripheral Neuropathy Genetic Panels by Next-Generation Sequencing (NGS), Blood

--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)

--Spastic Paraplegia Neuropathy Panel (41 genes)

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

--Custom Gene Panel

Reflex Tests

Test ID	Reporting Name	Available Separately	Always Performed
_G090	Motor Neuron Disease Panel	No, (Bill Only)	No
_G091	Muscular Dystrophy Panel	No, (Bill Only)	No
_G092	Myofibrillar Myopathy Panel	No, (Bill Only)	No
_G093	Congenital Myopathy Panel	No, (Bill Only)	No
_G094	Congenital Myasthenic Syndromes	No, (Bill Only)	No
_G095	Metabolic Myopathy Panel	No, (Bill Only)	No
_G096	Emery-Dreifuss Panel	No, (Bill Only)	No
_G097	Distal Myopathy Panel	No, (Bill Only)	No
_G098	Skeletal Muscle Channelopathy Panel	No, (Bill Only)	No

Test ID	Reporting Name	Available Separately	Always Performed
_G099	Myopathy Expanded Panel	No, (Bill Only)	No
_G100	Distal Weakness Expanded Panel	No, (Bill Only)	No
_G101	Rhabdomyolysis and Myopathy Panel	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
G147	Hereditary Custom Gene Panel Tier 3	No, (Bill Only)	No
G148	Hereditary Custom Gene Panel Tier 4	No, (Bill Only)	No
G149	Hereditary Custom Gene Panel Tier 5	No, (Bill Only)	No

Testing Algorithm

This test includes the option for either 1 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, 2-14, 15-49, 50-100, and 101-500).

The following algorithms are available in Special Instructions:

-Inherited Motor Neuron Disease Testing Algorithm

-Neuromuscular Myopathy Testing Algorithm

Special Instructions

- Informed Consent for Genetic Testing
- Molecular Genetics: Neurology Patient Information
- Targeted Genes and Methodology Details for Neuromuscular Genetic Panels
- Inherited Motor Neuron Disease Testing Algorithm
- Frequently Asked Questions: Custom Gene Ordering Tool
- Neuromuscular Myopathy Testing Algorithm
- Custom Gene Panel Ordering
- Informed Consent for Genetic Testing (Spanish)

Method Name

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

NY State Available

Yes

Specimen

Specimen Type

Varies

Shipping Instructions

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

Necessary Information

The specific neuromuscular panel requested must be provided in order to perform this test.

Specimen Required

Specimen Type: Whole blood

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.

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

See Specimen Required

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 neuromuscular disorders are a diverse group of diseases with heterogeneous genetic causes that affect the peripheral nervous system. The age of onset for these disorders ranges from in utero to old age. Based on the pattern of inheritance; clinical presentation; nerve conductions including, electromyography (EMG) pattern, and muscle and nerve biopsy findings; inherited neuromuscular disorders can be divided into major categories. These categories include muscular dystrophies, congenital muscular dystrophies, congenital myopathies, distal myopathies, ion channel hyperexcitable muscle diseases, metabolic myopathies, congenital myasthenic syndromes, hereditary motor and sensory neuropathies, hereditary motor neuropathies, motor neuron disorders, hereditary spastic paraplegias, and hereditary sensory neuropathies. Due to the considerable overlap in the clinical phenotypes of various neuromuscular disorders, it is often difficult to distinguish these specific inherited disorders from acquired forms without genetic testing. Additionally, even though most myopathies present with proximal shoulder and girdle weaknesses, some forms may present with distal weakness and, thereby, mimic neuropathies. Therefore, genetic testing can be extremely helpful in making the diagnosis. This is especially true for some genetic forms where neurophysiology may be ambiguous, as both neuropathy and myopathy exist simultaneously.

Motor Neuron Disease (MND):

MND selectively affect the motor neurons with degeneration. MND include 1) primary lateral sclerosis (PLS), 2) primary muscular atrophy (PMA), and 3) amyotrophic lateral sclerosis (ALS). In PLS and PMA, the motor neuron degeneration is limited to the upper motor neuron and lower motor neuron, respectively. The clinical phenotype of PLS can include gradual progressive leg weakness and spasticity and spastic bulbar weakness. In ALS, the most frequent form of MND, degeneration involves both upper and lower motor neurons and results in progressive muscle weakness, paralysis, and death from respiratory failure, usually within 3 to 5 years of disease onset.

Muscular Dystrophy:

Muscular dystrophies are characterized by skeletal muscle wasting.The muscular dystrophies can be subdivided into the dystrophinopathies, Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophies, distal myopathies, and congenital muscular dystrophies. A clinical diagnosis is typically based on distribution and severity of muscular involvement, mode of inheritance, and other associated symptoms.

The dystrophinopathies include Duchenne muscular dystrophy and Becker muscular dystrophy. These 2 forms are inherited in an X-linked manner and typically present with variable degrees of a limb-girdle pattern of weakness and can develop dilated cardiomyopathy. Limb-girdle muscular dystrophy is characterized by weakness and wasting predominately of the hips, shoulders, and proximal extremity muscles. Congenital muscular dystrophies are

progressive early-onset muscle disorders that often have brain and other organ involvement. They are characterized by hypotonia, delayed motor development, and progressive weakness.

Emery-Dreifuss Muscular Dystrophy:

Emery-Dreifuss muscular dystrophy is characterized by the triad of joint contractures, slowly progressive muscle weakness and wasting, and cardiac involvement. Joint contractures usually being in early childhood and predominate in the elbows, ankles, and postcervical muscles. Age of onset, progression, and severity of disease demonstrate inter- and intrafamilial variability.

Distal Myopathy:

Distal myopathies are characterized by distal weakness and atrophy that starts in the muscles of the hands or feet and lack of cranial involvement or sensory loss.Distal myopathies are classified based on clinical features, inheritance pattern, and histopathological findings, such as the presence of rimmed vacuoles. Categories of distal myopathies include late adult-onset autosomal dominant forms, adult-onset autosomal dominant forms, early-onset autosomal dominant forms, early-onset autosomal recessive forms, and early adult-onset autosomal recessive forms. Additionally, inclusion body myositis presents with distal muscle weakness and may be in the differential with the distal myopathies.

Myofibrillar Myopathy:

Myofibrillar myopathies are characterized by slowly progressive weakness involving the proximal and distal muscles.The clinical phenotype can include peripheral neuropathy, cardiomyopathy, muscle stiffness, aching and cramps.While myofibrillar myopathies are typically adult onset disorders, individuals can present anywhere from early childhood through adulthood.

Congenital Myopathy:

Congenital myopathies are characterized by early-onset and specific histopathologic abnormalities on muscle biopsy. The clinical phenotype can include congenital hypotonia, generalized muscle weakness, delayed motor milestones, feeding difficulties, and facial muscle involvement.While congenital myopathies typically occur in childhood, individuals do occasionally present in adulthood.Also, individuals typically have slow progressive weakness, but in some cases the course may be severe.

Congenital Myasthenic Syndrome:

Congenital myasthenic syndromes are characterized by fatigable weakness involving ocular, bulbar, and limb muscles.The severity and disease course is highly variable, but individuals usually present in infancy or early childhood. The clinical phenotype associated with a neonatal onset can include feeding difficulties, poor suck and cry, choking spells, eyelid ptosis, and muscle weakness. The clinical phenotype associated with a later childhood onset can include abnormal muscle fatigue, delayed motor milestones, ptosis, and extraocular muscle weakness.

Metabolic Myopathy:

Metabolic myopathies are a diverse group of inherited biochemical diseases involving limitation of the use of fuels by skeletal muscle to generate energy. These diseases can be categorized as disorders of lipid metabolism, glycogen and glucose metabolism, or mitochondrial myopathies that impair both lipid and glucose metabolism. Biochemical testing in multiple tissue types including blood, urine, and muscle, can help to determine which category of muscle disease is most likely.

Disorders of fatty acid oxidation (FAO) are one category of metabolic myopathies characterized by hypoketotic

hypoglycemia, hepatic dysfunction, skeletal myopathy, dilated and hypertrophic cardiomyopathy, and sudden or unexpected death. Mitochondrial fatty acid beta-oxidation plays an important role in energy production, particularly in skeletal and heart muscle, and in hepatic ketone body formation during periods of fasting. Biochemical testing such as urine organic acids, plasma acylcarnitines, and fatty acids can aid in diagnosis. These test results are influenced by dietary factors and the clinical status of the patient, however, which often leads to incomplete diagnostic information or even false-negative results.

Disorders of glycogen and glucose metabolism are another category of metabolic myopathies primarily affecting muscle and resulting in exercise intolerance, recurrent rhabdomyolysis, and myoglobinuria. Creatine kinase level is typically elevated during a major event. Muscle biopsy is often performed to verify absence of enzyme activity for the specific type of glycogenosis disease.

Polyglucosan body disease involves progressive neurogenic bladder, spasticity and weakness causing gait difficulties from either primary muscle or nerve involvements, sensory loss mainly in the distal lower extremities, and mild cognitive difficulties such as executive dysfunction. Mitochondrial myopathy due to coenzyme Q10 (CoQ10) deficiency is a group of heterogenous diseases. These mitochondrial diseases are characterized by muscle weakness, exercise intolerance, elevated creatine kinase, and abnormal muscle biopsy findings.

Skeletal Muscle Channelopathy:

Nondystrophic myotonias are characterized by muscle stiffness generated by voluntary movement. Other features included transient or prolonged weakness, pain associated with myotonia, and fatigue. The nondystrophic myotonias include myotonia congenita, paramyotonia congenital, and sodium channel myotonia. The periodic paralyses are characterized by episodic attacks of weakness often triggered by diet or rest after exercise. They include hyperkalemic periodic paralysis, hypokalemic periodic paralysis, and Andersen-Tawil syndrome.

Rhabdomyolysis:

Rhabdomyolysis results from the rapid breakdown of skeletal muscle fibers, which lead to leakage of potentially toxic cellular contents into the blood stream. The clinical severity can range from asymptomatic creatine kinase elevation to a life-threatening disease. The clinical features include acute-onset myalgia, transient muscle weakness, and pigmenturia. Genetic causes of rhabdomyolysis include metabolic muscle disorders, mitochondrial disorders, disorders of intramuscular calcium release and excitation-coupling, and muscular dystrophies.

Custom Gene Panel:

Custom gene ordering allows the creation of a custom gene list to tailor testing to a patientâ€™s exact need. After selection of a specific disease state, the custom gene panel can be modified to add or remove genes. Through this option single gene testing can be performed.

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 are a carrier or have a diagnosis of a neuromuscular disorder may have a mutation that is not

identified by the methods performed (eg, large deletions/duplications, promoter mutations, deep intronic mutations, which are not targeted by this assay). The absence of a mutation, therefore, does not eliminate the possibility of a hereditary neuromuscular 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.

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.

Alterations classified as benign (common polymorphisms) and known pseudodeficiency alleles are not reported but are available upon request. Known pseudodeficiency alleles may lead to false-positive biochemical results, do not cause disease, and will only be reported when identified with a reportable alteration in the same gene.

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 "likely pathogenic" alterations or "variants of uncertain significance" 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. Finsterer J, Burgunder JM: Recent progress in the genetics of motor neuron disease. Eur J Med Genet 2014 Feb;57(2-3):103-112

3. Hermans MC, Pinto YM, Merkies IS, et al: Hereditary muscular dystrophies of the heart. Neuromuscul Disord 2010;20(8):479-492

4. Wicklund MP, Kissel JT: The limb-girdle muscular dystrophies. Neurol Clin 2014;32(3):729-749

5. Flanigan KM: The muscular dystrophies. Semin Neurol 2012;32(3):255-263

6. Iannaccone ST, Castro D: Congenital muscular dystrophies and congenital myopathies. Continuum (Minneap Minn). 2013 Dec;19(6 Muscle Disease):1509-1534

7. Olive M, Kley RA, Goldfarb LG: Myofibrillar myopathies: new developments. Curr Opin Neurol 2013;26(5):527-535

8. D'Amico A, Bertini E: Congenital myopathies. Curr Neurol Neurosci Rep 2008;8(1):73-79

9. Engel AG, Shen XM, Selcen D, et al: Congenital myasthenic syndromes: pathogenesis, diagnosis, and treatment. Lancet Neurol 2015;14(4):420-434

10. Sharp LJ, Haller RG: Metabolic and Mitochondrial Myopathies. Neurol Clin 2014;32(3):777-799

11. Emery AE: Emery-Dreifuss muscular dystrophy-a 40 year retrospective. Neuromusc Disord 2000;10(4-5):228-232

12. Udd B: Distal myopathies. Curr Neurosci Rep 2014;14(3):434

13. Burge JA, Hanna MG: Novel insights into the pathomechanisms of skeletal muscle channelopathies. Curr Neurol Neurosci Rep 2012;12(1):62-69

14. Scalco RS, Gardiner AR, Pitceathly RD, et al: Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis 2015;10:51

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 Neuromuscular Genetic 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 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 Neuromuscular Genetic 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 are 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: 3 months

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

81325 (if appropriate)

81403 (if appropriate)

81404 (if appropriate)

81405 (if appropriate)

81406 (if appropriate)

81407 (if appropriate)

81408 (if appropriate)

81443 (if appropriate)

81479 (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NMPAN	Neuromuscular Genetic Panels	In Process

Result ID	Test Result Name	Result LOINC Value
37980	Client Provided Sub-Panel	19145-2
MG119	Gene List ID or NA	48018-6
37981	Result Summary	50397-9
37982	Result	82939-0
37983	Interpretation	69047-9
37984	Additional Information	48767-8
37989	Method	49549-9
37990	Disclaimer	62364-5
37986	Specimen	31208-2
37987	Source	31208-2
37988	Released By	18771-6