Overview

Useful For
Second-tier test for confirming a biochemical diagnosis of Niemann-Pick type C (NPC)

Carrier testing of individuals with a family history of NPC when an affected individual is not available for testing or disease-causing mutations have not been identified

Genetics Test Information
Testing includes full gene sequencing of the NPC1 and NPC2 genes, including analysis for large deletions and duplications.

Reflex Tests

<table>
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<th>Test ID</th>
<th>Reporting Name</th>
<th>Available Separately</th>
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<tbody>
<tr>
<td>CULFB</td>
<td>Fibroblast Culture for Genetic Test</td>
<td>Yes</td>
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</table>

Testing Algorithm
If skin biopsy is received, fibroblast culture for genetic test will be added and charged separately.

Special Instructions
- Molecular Genetics: Biochemical Disorders Patient Information
- Informed Consent for Genetic Testing
- Informed Consent for Genetic Testing (Spanish)

Method Name
Polymerase Chain Reaction (PCR) Amplification Followed by DNA Sequencing/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 draw.

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.

Submit only 1 of the following specimens:
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.

Specimen Stability Information: Ambient (preferred)/Refrigerated

Specimen Type: Cultured fibroblasts

Container/Tube: T-75 or T-25 flask

Specimen Volume: 1 Full T-75 or 2 full T-25 flasks

Specimen Stability Information: Ambient (preferred)/Refrigerated <24 hours

Specimen Type: Skin biopsy

Container/Tube: Sterile container with any standard cell culture media (eg, minimal essential media, RPMI 1640). The solution should be supplemented with 1% penicillin and streptomycin. Tubes can be supplied upon request (Eagle’s minimum essential medium with 1% penicillin and streptomycin [T115]).

Specimen Volume: 4-mm punch

Specimen Stability Information: Refrigerated (preferred)/Ambient

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: Biochemical Disorders Patient Information (T527) in Special Instructions

3. If not ordering electronically, complete, print, and send an Inborn Errors of Metabolism Test Request (T798) with the specimen.

Specimen Minimum Volume
1 mL
Reject Due To
All specimens will be evaluated by Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

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Clinical and Interpretive

Clinical Information
Niemann-Pick type C (NPC) is an inherited disorder of cholesterol transport that results in an accumulation of unesterified cholesterol and lipids in the lysosomal/endosomal system and in various tissues. Although NPC belongs to a group of lysosomal disorders including Niemann-Pick types A and B, these diseases are metabolically and genetically distinct. Niemann-Pick types A and B are caused by mutations in the SMPD1 gene, which encodes the enzyme sphingomyelinase, whereas NPC is caused by mutations in the NPC1 or NPC2 genes.

The incidence of NPC is approximately 1 in 120,000 to 1 in 150,000 live births. Age of onset is variable and ranges from the perinatal period to adulthood. Clinical presentation is also highly variable. Infants may present with or without liver disease (hepatosplenomegaly) and respiratory failure. Those without liver and pulmonary disease may present with hypotonia and developmental delay. Most individuals are diagnosed during childhood with symptoms including ataxia, vertical supranuclear gaze palsy, dystonia, progressive speech deterioration, and seizures resulting in death by the second or third decade of life. Adult-onset NPC is associated with a slower progression and is characterized by neurologic and psychiatric problems.

NPC is inherited in an autosomal recessive manner, in which affected individuals carry 2 mutations in either the NPC1 or NPC2 gene. Most mutations are family specific, although there are 2 mutations in the NPC1 gene that are more common than others. The G992W mutation is common in the French Acadian population of Nova Scotia. The I1061T mutation is the most common mutation worldwide, and is seen in patients of Hispanic and Western European (United Kingdom and France) descent. Full gene sequencing and analysis for large deletions and duplications of the NPC1 and NPC2 genes detect less common disease-causing mutations.

The recommended first-tier test to screen for NPC is a biochemical test measuring cholesterol esterification coupled with filipin staining on a fibroblast specimen, NIEM / Niemann-Pick Type C Detection, Fibroblasts. Molecular testing provides confirmation of a biochemical diagnosis or a basis for carrier testing of family members. Individuals with abnormal biochemical results are more likely to have 2 identifiable mutations by molecular testing.

Reference Values
An interpretive report will be provided.

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

Cautions
A small percentage of individuals who are carriers or have a diagnosis of, Niemann-Pick type C (NPC) disease may have a mutation that is not identified by this method (eg, promoter mutations, deep intronic alterations). The absence
of a mutation, therefore, does not eliminate the possibility of positive carrier status or the diagnosis of NPC. For carrier testing, it is important to first document the presence of *NPC1* or *NPC2* gene mutations in an affected family member.

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

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.

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

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.

**Clinical Reference**


4. Vanier MT: Niemann-Pick disease type C. Orphanet J Rare Dis 2010 Jun 3;5:16

**Performance**

**Method Description**

Bidirectional sequence analysis is performed to test for the presence of a mutation in all coding regions and intron/exon boundaries of the *NPC1* gene and *NPC2* gene. Gene dosage analysis by multiplex ligation-dependent probe amplification (MLPA) is used to test for the presence of large deletions and duplications within these genes.(Unpublished Mayo method)

**PDF Report**

No

**Day(s) and Time(s) Test Performed**

Performed weekly, Varies

**Analytic Time**

14 days

**Maximum Laboratory Time**

20 days
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
81404-NPC2 (Niemann-Pick disease, type C2 [epididymal secretory protein E1]) (eg, Niemann-Pick disease type C2), full gene sequence

81406-NPC1 (Niemann-Pick disease, type C1) (eg, Niemann-Pick disease), full gene sequence

Fibroblast Culture for Genetic Test
88233-Tissue culture, skin or solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

LOINC® Information

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