Test Definition: NPCZ

NPC1/NPC2 Genes, Full Gene Analysis

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 in cases when an affected individual is not available for testing or disease-causing variants 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

Test ID	Reporting Name	Available Separately	Always Performed
CULFB	Fibroblast Culture for Genetic Test	Yes	No

Testing Algorithm

If a skin biopsy is received, fibroblast culture will be performed at an additional charge.

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) followed by DNA Sequencing/ Multiplex Ligation-Dependent Probe Amplification (MLPA)

NY State Available

Yes

Specimen

Specimen Type

Varies

Ordering Guidance

First-tier testing to screen for Niemann-Pick type C disease is available. Order OXNP / Oxysterols, Plasma.

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.

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

Supplies: Fibroblast Biopsy Transport Media (T115)

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.

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 at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Varies	Varies		

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 variant in the *SMPD1* gene, which encodes the enzyme sphingomyelinase, whereas NPC is caused by variants 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 variants in either the *NPC1* or *NPC2* gene. Most variants are family specific, although there are 2 variants in the *NPC1* gene that are more common than others. The G992W alteration is common in the French Acadian population of Nova Scotia. The I1061T alteration is the most common variant 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 variants.

The recommended first-tier test to screen for NPC is a biochemical test measuring oxysterols (OXNP / Oxysterols, Plasma). 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 variants by molecular testing. Additionally, cholesterol esterification coupled with filipin staining on a fibroblast specimen (NIEM / Niemann-Pick Type C Detection, Fibroblasts) can aid in diagnosis.

Reference Values

An interpretive report will be provided.

Interpretation

All detected alterations are evaluated according to American College of Medical Genetics and Genomics (ACMG) 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 variant that is not identified by this method (eg, promoter alterations, deep intronic alterations). The absence of a variant, 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 variants 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

1. Richards S, 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 May;17(5):405-424

2. NP-C Guidelines Working Group, Wraith JE, Baumgartner MR, et al: Recommendations on the diagnosis and management of Niemann-Pick disease type C. Mol Genet Metab. 2009 Sep-Oct;98(1-2):152-65

3. Park WD, O'Brien JF, Lundquist PA, et al: Identification of 58 novel mutations in Niemann-Pick disease type C: correlation with biochemical phenotype and importance of PTC1-like domains in NPC1. Hum Mutat. 2003 Oct;22(4):313-325

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 variant 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) Performed

Varies

Report Available

14 to 20 days

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

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

88233-Tissue culture, skin or solid tissue biopsy (if appropriate)

88240-Cryopreservation (if appropriate)

LOINC® Information

Test ID	Test Order Name	Order LOINC Value
NPCZ	NPC1/NPC2 Genes, Full Gene Analysis	94211-0

Result ID	Test Result Name	Result LOINC Value
53533	Result Summary	50397-9

Result ID	Test Result Name	Result LOINC Value
53534	Result	82939-0
53535	Interpretation	69047-9
53536	Additional Information	48767-8
53537	Specimen	31208-2
53538	Source	31208-2
53539	Released By	18771-6