### Condition Description

Niemann-Pick Disease, Type C (NPD-C) is an autosomal recessive lipid storage disorder caused by a defect in esterification of exogenously derived low-density lipoprotein cholesterol. This impairment in the transport of cholesterol and glycosphingolipids leads to the accumulation of cholesterol in the lysosomes[1,2]. The accumulation of lipids in lysosomes leads to engorged lysosomes, deficiencies in membrane cholesterol, and eventually cell death. NPD-C can present at any stage in life. Infants may present with severe liver disease, organomegaly, pulmonary disease, hypotonia, and developmental delay. Idiopathic neonatal cholestasis is considered a significant indicator of NPD-C. Typical presentation in older children may present with ataxia, vertical and horizontal supranuclear gaze palsy, dementia, dystonia, enlarged liver and spleen, and seizures. As the disease progresses, patients have difficulty coordinating the muscles for eating, walking, and speaking. In the adult onset form of the disease, affected individuals typically present with dementia and psychiatric symptoms. The biochemical diagnosis is made by evaluating LDL-cholesterol esterification in cultured fibroblasts and filipin staining showing accumulation of unesterified cholesterol. Mutations in the NPC1 and NPC2 genes are responsible for NPD-C. Complementation studies indicate that the vast majority of individuals with NPD-C have mutations in the NPC1 gene[3] with ~4% of cases mutations having mutations in the NPC2 gene[4]. Although there is a common NPC1 mutation found in individuals of Mexican descent in the Rio Grande valley and a common NPC2 mutation found in individuals from Nova Scotia, there are over 200 other mutations have been identified in the NPC1 and NPC2 genes. The mutational spectrum of NPC1 and NPC2 mutations are private missense mutations [4-6]. For patients with mutations not identified by full gene sequencing, a separate deletion/duplication assay is available using a targeted CGH array (NE). For questions about testing for NPD-C disease, call the Emory Genetics Laboratory at (404) 778-8409 or (855) 831-7447. For further clinical information about lysosomal storage diseases, including management and treatment, call the Emory Lysosomal Storage Disease Center at (404) 778-8565 or (800) 200-1524.

### References:


### Genes

**NPC1, NPC2**

### Indications

This test is indicated for:

- Confirmation of a clinical diagnosis of Niemann-Pick Disease, Type C
- Prenatal testing for known familial mutations.
- Carrier testing in adults with a family history of Niemann-Pick Disease, Type C.

### Methodology

**Next Generation Sequencing:** In-solution hybridization of all coding exons is performed on the patient's genomic DNA. Although some deep intronic regions may also be analyzed, this assay is not meant to interrogate most promoter regions, deep intronic regions, or other regulatory elements, and does not detect single or multi-exon deletions or duplications. Direct sequencing of the captured regions is performed using next generation sequencing. The patient's gene sequences are then compared to a standard reference sequence. Potentially causative variants and areas of low coverage are Sanger-sequenced. Sequence variations are classified as pathogenic, likely pathogenic, benign, likely benign, or variants of unknown significance. Variants of unknown significance may require further studies of the patient and/or family members.

### Detection

**Clinical Sensitivity:** In a study of 143 unrelated patients with NPC, Park et al. identified mutations in 251 of the 286 alleles assessed, giving a detection rate of 88% [4]. Detection may be lower in variant forms.

**Analytical Sensitivity:** ~99%

**Prevalence:** The estimated prevalence of all lysosomal storage disorders is 2-5 per 100,000. The prevalence of NPD-C is not specifically known, but is likely to be rare and may vary by ethnicity.

### Specimen Requirements

Submit only 1 of the following specimen types
* Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:

In EDTA (purple top) or ACD (yellow top) tube:
- Infants (2 years): 3-5 ml
- Older Children & Adults: 5-10 ml

Specimen Collection and Shipping: Refrigerate until time of shipment. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Type: Saliva**

Specimen Requirements:

Oragene™ Saliva Collection kit (available through EGL) used according to manufacturer instructions.

Specimen Collection and Shipping: Store sample at room temperature. Ship sample within 5 days of collection at room temperature with overnight delivery.

**Special Instructions**

Submit copies of diagnostic biochemical test results with the sample. Sequence analysis is required before deletion/duplication analysis by targeted CGH array. If sequencing is performed outside of Emory Genetics Laboratory, please submit a copy of the sequencing report with the test requisition. Contact the laboratory if further information is needed.

**Related Tests**

- Mucopolysaccharide Screen (Urine GAG) (GA)
- Known Mutation Analysis (KM) is available to test family members.
- Deletion/Duplication Assay is available separately for individuals where mutations are not identified by sequence analysis. Refer to the test requisition or contact the laboratory for more information.
- Prenatal testing is available for known familial mutations only. Please call the Laboratory Genetic Counselor for specific requirements for prenatal testing before collecting a fetal sample.