Niemann-Pick Disease Type C: *NPC1* & *NPC2* Gene Deletion/Duplication

**Test Code:** NE  
**Turnaround time:** 2 weeks  
**CPT Codes:** 81228 x1

### 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 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 majority of *NPC1* and *NPC2* mutations are private missense mutations [4-6]. For questions about testing for NPD-C disease, call EGL Genetics at (470) 378-2200 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 in whom sequence analysis was negative.

### Methodology

DNA isolated from peripheral blood is hybridized to a CGH array to detect deletions and duplications. The targeted CGH array has overlapping probes which cover the entire genomic region. Please note that a “backbone” of probes across the entire genome are included on the array for analytical and quality control purposes. Rarely, off-target copy number variants causative of disease may be identified that may or may not be related to the patient's phenotype. Only known pathogenic off-target copy number variants will be reported. Off-target copy number variants of unknown clinical significance will not be reported.

**Detection**

Detection is limited to duplications and deletions. Array CGH will not detect point mutations or intronic mutations. Results of molecular analysis must be interpreted in the context of the patient's clinical and/or biochemical phenotype.

### Specimen Requirements

Submit only 1 of the following specimen types

- Preferred specimen type: Whole Blood

**Type: Whole Blood**

Specimen Requirements:
In EDTA (purple 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 EGL Genetics, 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.
- 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.