Niemann-Pick Type C Testing

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

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What is Niemann-Pick Disease type C

Definition

Niemann-Pick Disease, type C (NPC) is a lipid storage condition that can present at any age, though the classic presentation is in mid-to-late childhood. Symptoms fall into one of three categories: visceral, neurological and psychological.¹

• The presentation of clinical symptoms at each stage is different.²,³
  o Infants typically present with hypotonia and developmental delay, with or without lung and liver disease. Liver disease can be severe, resulting in the death of an infant in a few days to a few months.
  o Children with NPC exhibit progressive ataxia, vertical supranuclear gaze palsy (VSGP) and dementia.
  o Adults who develop NPC usually have an onset of progressive cognitive impairment or other psychiatric symptoms.

• There is wide variability with disease progression and survival rate, which can range from just a few days to, in rare circumstances, 60 years. Most individuals survive between 10-25 years.⁴

• Two genes have been associated with NPC: NPC1 and NPC2. The proteins of these genes are thought to work together in the cellular transport of cholesterol and other molecules. Most (90-95%) individuals with NPC have at least one identifiable
gene mutation in NPC1.\textsuperscript{5,6} Only 30 families have been found to have mutations in the NPC2 gene, making mutations in this gene rare (about 4% of NPC cases).\textsuperscript{1,5,7}

- There have been over 200 mutations described that cause NPC.\textsuperscript{8} Genotype-phenotype correlation is difficult to determine as most individuals are compound heterozygotes; however, there has been observation of some alleles being associated with mild or severe disease.\textsuperscript{8-10}

- NPC is thought to have a prevalence of 1 in 120,000 livebirths.\textsuperscript{1} There are a few populations that have a founder effect, including French Acadians of Nova Scotia, Canada originally from Normandy France\textsuperscript{7}; individuals of Hispanic descent in the Upper Rio Grande valley of the United States\textsuperscript{7}; and a Bedouin group in Israel.

- NPC is inherited in an autosomal recessive inheritance pattern. Because NPC is recessive, individuals usually do not have other affected family members. Males and females are equally likely to be affected. When both parents are known carriers, there is a 1/4 (25%) chance for each pregnancy to be affected. Preimplantation and prenatal genetic diagnosis are available for at-risk pregnancies.

- Recently, an NPC suspicion index has been presented as a way to identify individuals with a strong suspicion of NPC, versus those who may need further evaluation and those whose suspicion is low.\textsuperscript{11} This index comprises ranked assessments of visceral, neurological and psychiatric signs and symptoms that are specific to NPC, taking family history into account, to provide an NPC risk prediction score. Patients scoring ≥70 should be referred for immediate testing. Those scoring from 40-69 should be evaluated for further signs and symptoms of a differential diagnosis. Scores below 40 have a low suspicion of NPC.\textsuperscript{1,11}

- Once a diagnosis of NPC is suspected, diagnosis may include biochemical and/or genetic testing.

- Healthcare management after diagnosis includes treatment for current symptoms. This generally includes medications to prevent the onset of seizures, although treatment of liver disease, sleeping dysfunction or other symptoms should be considered as well. There is no definitive therapy available for NPC. Bone marrow transplantation (BMT), liver transplantation or the use of cholesterol lowering drugs did not prevent the progression of neurological disease.

Test information

- **Filipin biochemical testing for Niemann-Pick type C** involves demonstration of abnormal intracellular cholesterol homeostasis in cultured fibroblasts.\textsuperscript{7,12} Fibroblasts are cultured in an LDL-enriched medium, and then fixed and stained with a compound called “filipin”. To perform biochemical testing, filipin interacts with unesterified cholesterol to make specific cholesterol-filled complexes in ~80-85% of cases.
When this testing indicates an individual is affected, sequence/mutation analysis should be considered.

- Carrier testing is not available through biochemical testing, as there is overlap of enzyme activity between carriers and non-carriers.
- The biochemical assay can be used for prenatal diagnosis if both mutations are not known.\(^7\)

- **NPC1 sequence analysis** can identify \(\sim 80\text{-}90\%\) of mutations in the NPC1 gene.\(^{13}\)
- **NPC2 sequence analysis** identifies virtually 100\% of mutations in the NPC2 gene.\(^{13}\)
- **NPC1 and NPC2 deletion/duplication analysis** is available clinically for individuals who test negative on sequence analysis.
- **NPC1 and NPC2 known familial mutations**: Once a disease-causing mutation has been identified, relatives of affected individuals can be tested. Because of the variability of age of onset and presenting symptoms, individuals undergoing carrier testing should be aware that they could be identified as carrying two mutant alleles, and thus affected. Preimplantation or prenatal testing can be performed through mutation analysis on CVS or amniocytes if both parental mutations are known.\(^{13}\)

**Guidelines and evidence**

- Consensus-based diagnostic recommendations are available from the NP-C Guidelines Working Group (2012), an international, collaborative group of disease experts:\(^1\)
  - “Laboratory diagnostic tests for NP-C are complex and can be difficult to interpret due to a variety of methodological factors. Diagnostic testing to confirm NP-C, following screening and differential diagnosis, should therefore be conducted by, or in consultation with, regional or national care centers specializing in the diagnosis of inherited metabolic disorders.”
  - “The demonstration of impaired intracellular cholesterol transport by filipin staining in fibroblasts cultured from patient skin biopsies remains a key diagnostic test for NP-C.”
    - “In 80–85\% of cases, fluorescence microscopic examination of NP-C positive cells typically reveals strongly fluorescent, cholesterol-filled perinuclear vesicles — the ‘classical’ cholesterol storage pattern. Most other cases with a ‘variant biochemical phenotype’ show a less pronounced, more variable cholesterol storage.”
    - “LDL-induced cholesteryl ester formation assays are no longer systematically used as a secondary biochemical test, as they are technically challenging (particularly in variant cases), costly and time-consuming.”
“Biochemical tests cannot be relied upon to identify heterozygote carriers of NP-C in whom filipin test findings may either appear normal or display mild abnormalities, with changes similar to those seen in ‘variant’ cell lines.”

Regarding genetic testing:

- NP-C is caused by autosomal recessive mutations in either of two genes, NPC1 (located to chromosome 18, q11–q12) or NPC2 (located to chromosome 14; q24.3).
- Over 95% of NP-C patients have pathological NPC1 mutations, with approximately 4% of patients expressing disease-causing mutations in NPC2; the remaining patients appear to possess as yet unidentified gene mutations.
- DNA sequencing should ideally be performed in parallel with filipin staining examinations, where possible. Significant advances have been made in genetic sequencing of NPC1 and/or NPC2 gene mutations, but it is not yet possible to replace filipin staining with DNA sequencing as the primary diagnostic method.
- Gene testing should be undertaken in all newly diagnosed patients to:
  - allow safe prenatal diagnosis
  - expedite identification of eventual affected siblings
  - allow detection of carriers in blood relative
  - identify NPC2 patients who may be candidates for hematopoietic stem cell transplantation.

Criteria

Niemann-Pick Disease Type C Known Familial Mutation Analysis

- Genetic Counseling:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Testing:
  - No previous genetic testing for Niemann-Pick C, AND
- Diagnostic and Predisposition Testing:
  - Niemann-Pick C family mutation identified in biologic relative(s), OR
- Carrier Testing:
o Niemann-Pick C family mutation identified in biologic relative(s), OR

• Prenatal Testing:
  o Niemann-Pick C mutation identified in both biologic parents AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Niemann-Pick C Disease Sequencing

• Genetic Counseling:
  o Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o Biochemical testing performed on cultured skin fibroblasts showing abnormal intracellular cholesterol homeostasis, and
  o No previous genetic testing for Niemann-Pick C, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Hepatosplenomegaly and/or liver failure, or
  o Central hypotonia or low muscle tone characterized by frequent falls and clumsiness, or
  o Ocular motor abnormalities, especially saccadic eye movements (SEM) and vertical supranuclear gaze palsy, or
  o Delayed or arrested speech development with or without cognitive impairment, or
  o Cerebellar ataxia, or
  o Seizures, or
  o Dystonia, or
  o Dysphagia, OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Biologic relative(s) (1st, 2nd, or 3rd degree) diagnosed with NPC clinically, and no family mutation identified, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

Niemann-Pick C Disease Deletion/Duplication Analysis

• Genetic Counseling:
• Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

• Previous Genetic Testing:
  o Biochemical testing performed on cultured skin fibroblasts showing abnormal intracellular cholesterol homeostasis, and
  o NPC1 and NPC2 sequencing performed and no mutations or only one mutation identified, AND

• Diagnostic Testing for Symptomatic Individuals:
  o Hepatosplenomegaly and/or liver failure, or
  o Central hypotonia or low muscle tone characterized by frequent falls and clumsiness, or
  o Ocular motor abnormalities, especially saccadic eye movements (SEM) and vertical supranuclear gaze palsy, or
  o Delayed or arrested speech development with or without cognitive impairment, or
  o Cerebellar ataxia, or
  o Seizures, or
  o Dystonia, or
  o Dysphagia, OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Biologic relative(s) (1st, 2nd, or 3rd degree) diagnosed with NPC clinically, and no family mutation identified, AND

• Rendering laboratory is a qualified provider of service per the Health Plan policy.

References


