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
  - 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.
  - Children with NPC exhibit progressive ataxia, vertical supranuclear gaze palsy (VSGP) and dementia.
  - 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 pan-ethnic with a prevalence of 1 in 100,000 live births.\textsuperscript{1} There are a few populations that have a founder effect, including French Acadians of Nova Scotia, Canada originally from Normandy France; individuals of Hispanic descent in the Upper Rio Grande valley of the United States; 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 when the causative mutations in the family are known.

- The NPC-suspicion index assists in the diagnosis of adult patients with NPC, with strong indicators including cognitive and psychiatric symptoms, and the combination of neurological with psychiatric signs is highly suggestive of NPC.\textsuperscript{1,11}

- Once a diagnosis of NPC is suspected clinically, the diagnosis can be confirmed through a combination of biochemical and genetic studies.

- 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**

- **Oxysterols (cholesterol oxidation products)** includes measurement of the oxysterols cholestane-3 3\(\beta\), 5\(\alpha\), 6\(\beta\)-triol (C-triol) and 7-ketocholesterol (7-KC) in blood. Both are sensitive markers for NPC.\textsuperscript{1,12,13}
  - When this testing indicates an individual is affected, the diagnosis must be confirmed by sequence/mutation analysis and if necessary, filipin test.
    - Carrier testing is not reliable through biochemical testing.

- **Filipin biochemical testing for Niemann-Pick type C** involves demonstration of abnormal intracellular cholesterol homeostasis in cultured fibroblasts.\textsuperscript{7,14} 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.

- The filipin test is no longer considered a first line test for the diagnosis of NPC. It is still an extremely useful test for cases in which molecular or biochemical results are not conclusive.
- 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.

- **NPC1 sequence analysis** can identify ~80-90% of mutations in the NPC1 gene.
- **NPC2 sequence analysis** identifies virtually 100% of mutations in the NPC2 gene.
- **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.

Guidelines and evidence

- Consensus-based diagnostic recommendations are available from the International NP-C Disease Registry (2018), an international, collaborative group of disease experts:
  - “Once NPC is suspected clinically, diagnosis can be confirmed by the combination of biochemical and molecular genetic studies. In recent years, several plasma metabolites (cholestane-3β, 5α, 6β-triol, lyso-sphingomyelin isoforms and bile acid metabolites) have emerged as sensitive and specific diagnostic biomarkers for NPC and their study, completed by genetic analyses, should now be considered as the first line laboratory testing. The filipin test, although still very useful, is no longer considered as the primary tool.”
  - “Assessment of biomarkers should be considered as a first-line test to screen for NPC. Three classes of biochemical markers are either currently in use (oxysterols; lyso-SM-509 and lyso-sphingomyelin) or are in development (bile acid derivatives). They can be used alone or in combination to enhance sensitivity and specificity. The diagnosis, however, must in all cases be confirmed by mutation analysis and if necessary, filipin test.”
Any individual in whom the diagnosis of NPC is considered based on their clinical manifestation and/or abnormal biomarker profile should undergo genetic testing for NPC genes to confirm the diagnosis. Referral to a clinical geneticist or genetic counsellor should be considered upon the diagnosis of NPC.

“Filipin test is no longer considered a first line test for the diagnosis of NPC. It still remains an extremely useful diagnostic tool in uncertain cases in which biomarkers and/or molecular analysis present inconclusive results and to assess the pathogenicity of novel genetic variants.”

Regarding genetic testing:

- Mutation analysis of NPC1 and NPC2 genes is mandatory to confirm the diagnosis of NPC. In addition, it is the only reliable method to diagnose NPC carriers within the family and the highly preferred strategy for prenatal diagnosis. This testing will also expedite identification of potentially presymptomatic affected siblings.
- Although genotype/phenotype correlations are difficult to establish, some conclusions can be drawn from current evidence.

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:
  - Niemann-Pick C family mutation identified in biologic relative(s), OR
- Prenatal Testing:
  - 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:
  - Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- Previous Genetic Testing:
  - Biochemical testing performed showing abnormal biomarkers, and
  - No previous genetic testing for Niemann-Pick C, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Hepatosplenomegaly and/or liver failure, or
  - Central hypotonia or low muscle tone characterized by frequent falls and clumsiness, or
  - Ocular motor abnormalities, especially saccadic eye movements (SEM) and vertical supranuclear gaze palsy, or
  - Delayed or arrested speech development with or without cognitive impairment, or
  - Cerebellar ataxia, or
  - Seizures, or
  - Dystonia, or
  - Dysphagia, OR
- Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  - 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:
  - Biochemical testing performed showing abnormal biomarkers, and
  - 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) (1\textsuperscript{st}, 2\textsuperscript{nd}, or 3\textsuperscript{rd} 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


