Niemann-Pick Disease Types A and B

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 types A and B

Definition

Niemann-Pick disease is a genetic disorder caused by an inability to process lipids (fats), which results in a toxic buildup of lipids in some organs.  

- Two types of Niemann-Pick disease are caused by a deficiency of the acid sphingomyelinase enzyme:
  - Type A, also called the “neurological” or “neuronopathic” type, causes symptoms beginning in infancy. These include an enlarged liver and spleen (hepatosplenomegaly), psychomotor impairment with neurologic deterioration, interstitial lung disease, and eventually a classic cherry-red spot of the retina. Affected individuals usually do not survive beyond childhood.
  - Type B, also called the “non-neurological” or “non-neuronopathic” type, causes some symptoms similar to type A, but symptoms are usually milder and begin later. Additional symptoms include hyperlipidemia (high fat levels in blood) and thrombocytopenia (low platelets). Affected individuals can survive to adulthood.
  - The SMPD1 gene encodes the acid sphingomyelinase (ASM) enzyme. Gene mutations in the SMPD1 gene lead to reduced or absent sphingomyelinase enzyme activity, causing the symptoms of Niemann-Pick disease.
• Niemann-Pick disease is suspected when a patient presents with hepatosplenomegaly, interstitial lung disease, and depending on the subtype, neurological symptoms in infancy or abnormal blood findings. However, a diagnosis cannot be made clinically.

• When Niemann-Pick disease is suspected, acid sphingomyelinase enzyme activity testing should be performed first. People with Niemann-Pick disease type A or B usually have less than 10% of normal ASM activity compared to healthy individuals. Measuring ASM enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts is a reliable way to confirm a suspected case of Niemann-Pick disease. However, false-negative and inconclusive results are possible. In such cases, genetic testing may be useful to resolve a diagnosis.

• About 1 in 250,000 people have Niemann-Pick disease. Type A is more common in persons of Ashkenazi Jewish descent than in the general population. In the Ashkenazi Jewish population, the frequency of Niemann-Pick disease is 1 in 40,000.

• Niemann-Pick disease is an autosomal recessive disorder. An affected individual must inherit SMPD1 gene mutations from both parents. Individuals who inherit only one mutation are called carriers. Carriers do not show symptoms of Niemann-Pick disease, but have a 50% chance of passing on the mutation to their children. Two carriers of Niemann-Pick disease have a 25% chance of having a child with the disorder. Prenatal diagnosis for at-risk pregnancies can be performed by molecular genetic testing (if the mutations in both parents are known).

• Individuals at increased risk to have a child with Niemann-Pick disease should routinely be offered carrier screening. This includes those with:
  - Ashkenazi Jewish ancestry (1 in 90 carrier risk)
  - A family history of Niemann-Pick disease (regardless of ethnicity)
  - A partner who is a known carrier of Niemann-Pick disease (or affected with the milder type)

Test information

• **SMPD1 Mutation Analysis** tests for four of the most common SMPD1 gene mutations.
  - Three mutations - R496L, L302P, fsP330 - account for 97% of all cases of Niemann-Pick disease type A in Ashkenazi Jewish people.
o The fourth mutation - deltaR608 - is a common cause of Niemann-Pick disease type B in people of North African descent.³

o Carrier screening by SMPD1 mutation panel for Niemann-Pick disease is widely available as part of an “Ashkenazi Jewish Panel” that includes several other genetic disease that are more common in this population. (See Ashkenazi Jewish Carrier Screening.)

- **SMPD1 Sequencing** analyzes the entire coding region of the SMPD1 is available to detect less common mutations that cannot be detected on a common mutation analysis panel. SMPD1 sequencing detects more than 95% of all SMPD1 mutations.³

- **SMPD1 Deletion/Duplication Analysis** is available to detect large gene rearrangements that cannot be detected by sequencing. However, the frequency of such mutations is unknown.³

- **SMPD1 Known Familial Mutation Testing** can be performed for at-risk relatives when the familial mutation is known and is not one of the common mutations.³

### Guidelines and evidence

- Professional guidelines generally support Niemann-Pick disease carrier screening for those at increased risk.⁴,⁵

- Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2009) address carrier screening and prenatal diagnosis for Niemann-Pick disease:
  
  o “Individuals with a positive family history of one of these disorders [including Niemann-Pick disease] should be offered carrier screening for the specific disorder and may benefit from genetic counseling.”

  o Carrier screening for Ashkenazi Jewish people is routinely recommended for some disorders (i.e., Tay-Sachs, Canavan, cystic fibrosis, familial dysautonomia). However, for testing of a group of other disorders more common in this population (including Niemann-Pick disease), ACOG simply states: “Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders.”

  o “If it is determined that this individual [an Ashkenazi Jewish descent partner] is a carrier, the other partner should be offered screening.”

  o “When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis.”

- Consensus guidelines from the American College of Medical Genetics (2008) recommend routine carrier screening for a group of disorders that includes Niemann-Pick when at least one member of the couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.⁵
No evidence-based US diagnostic testing guidelines have been identified.

A 2015 expert-authored review recommends the following testing strategy for diagnosis of an affected person:

- The diagnosis of ASM deficiency is established by detection of either biallelic pathogenic variants in SMPD1 on molecular genetic testing or residual ASM enzyme activity that is less than 10% of controls (in peripheral blood lymphocytes or cultured skin fibroblasts).

- Molecular testing approaches include single-gene testing and use of a multi-gene panel.

- For individuals from populations in which common SMPD1 pathogenic variants occur (e.g., individuals of Ashkenazi Jewish background with a severe neurodegenerative form of the disease suggestive of NPD-A, individuals of North African descent with NPD-B, or individuals from Chile, Saudi Arabia, and Turkey):
  - Perform targeted analysis for pathogenic variants.
  - If targeted analysis does not identify both pathogenic variants in individuals from these populations, sequence analysis of SMPD1 is appropriate.

- For individuals who are not in the populations discussed above:
  - Perform sequence analysis.
  - "If no or only one pathogenic variant is identified, consider gene-targeted deletion/duplication analysis."

Criteria

Niemann Pick Type A or B 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 A or B, AND
- Diagnostic and Predisposition Testing:
  - Niemann Pick A or B family mutation identified in biologic relative(s), OR
- Prenatal Testing:
  - Niemann Pick A or B mutation identified in both biologic parents, AND
• Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Niemann Pick A or B Targeted Mutation Analysis**

• 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 No previous genetic testing for Niemann Pick A or B

• Diagnostic Testing for Symptomatic Individuals:
  
  o Measurement of acid sphingomyelinase (ASM) enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts (in symptomatic individuals) with negative or equivocal result where suspicion of clinical diagnosis remains high, and
  
  o Hepatosplenomegaly, and/or
  
  o Evidence of interstitial lung disease on chest radiograph, and/or
  
  o Developmental Delay, and/or
  
  o Cherry Red Maculae, and/or
  
  o Hyperlipidemia, and/or
  
  o Thrombocytopenia, OR

• Predisposition/Carrier Testing for Presymptomatic/Asymptomatic Individuals:
  
  o Biologic relative(s) (1st degree) diagnosed with Niemann Pick A or B clinically, and no family mutation identified, or
  
  o Ashkenazi Jewish ancestry and intention to reproduce, AND

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

**Niemann Pick A or B 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 If Ashkenazi Jewish, common mutations have been tested and resulted negative

• Diagnostic Testing for Symptomatic Individuals:
• Measurement of acid sphingomyelinase (ASM) enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts (in symptomatic individuals) with negative or equivocal result where suspicion of clinical diagnosis remains high, and
  o Hepatosplenomegaly, and/or
  o Evidence of interstitial lung disease on chest radiograph, and/or
  o Developmental Delay, and/or
  o Cherry Red Maculae, and/or
  o Hyperlipidemia, and/or
  o Thrombocytopenia, OR

• Predisposition Testing for Presymptomatic/Asymptomatic Individuals:
  o Biologic relative(s) (1st degree) diagnosed with Niemann Pick A or B clinically, and no family mutation identified, and
  o If Ashkenazi Jewish, common mutations have been tested and resulted negative, AND

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

Niemann Pick A or B Deletion/Duplication Analysis

• 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 No previous large rearrangement testing, and
  o Previous SMPD1 sequencing performed and no mutations found, and
  o No known familial mutation, AND

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

References


