# Test Specific Guidelines

# Canavan Disease Genetic Testing

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## Introduction

**Canavan disease testing is addressed by this guideline.**

**Procedures Addressed**

**The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.**

| Procedures addressed by this guideline | Procedure codes |
|---|---|
| ASPA Deletion/Duplication Analysis | 81479 |
| ASPA Known Familial Mutation Analysis | 81403 |
| ASPA Sequencing | 81479 |
| ASPA Targeted Mutation Analysis | 81200 |

## What Is Canavan Disease?

**Definition**

**Canavan disease is a genetic disorder leading to progressive damage to the brain's nerve cells.[1,2]**

**Prevalence**

**Canavan disease is most often found in Ashkenazi Jewish populations.[1,2]**

- **Between 1 in 40 and 1 in 82 people of Ashkenazi Jewish descent are carriers for Canavan disease.[2] Because of this relatively high carrier rate, population based screening in the Ashkenazi Jewish population is available.**
  - **For information on Ashkenazi Jewish carrier screening, please refer to the guideline *Ashkenazi Jewish Carrier Screening,* as this testing is not addressed here.**
- **Between 1 in 6,400 and 1 in 13,500 Ashkenazi Jews have the disease.[1]**

Canavan disease occurs in all ethnic groups, and the prevalence among the general population is significantly lower than that in the Ashkenazi Jewish population.[2]

## Symptoms

Signs and symptoms of Canavan disease usually begin in infancy and include:[1]

- developmental delays including motor skills, learning disabilities, or problems sleeping
- weak muscle tone (hypotonia)
- large head size (macrocephaly)
- abnormal posture
- leukodystrophy on neuroimaging, and
- seizures.

## Cause

Canavan disease is caused by changes, or mutations, in the ASPA gene.[1] ASPA helps make an enzyme called aspartoacylase.[1]

This enzyme is essential to maintain the health of myelin, the nerve cells' protective covering, by breaking down harmful compounds that would otherwise degrade myelin.[1] The most significant of these compounds that breaks down myelin is called N-acetylaspartic acid (NAA).

In the absence of aspartoacylase, the myelin protective covering of the nerve is eventually destroyed. Without this protective covering, nerve cells malfunction and die.[1]

## Inheritance

Canavan disease is an autosomal recessive disorder.

### Autosomal recessive inheritance

In autosomal recessive inheritance, individuals have 2 copies of the gene and an individual typically inherits a gene mutation from both parents. Usually only siblings are at risk for also being affected. Males and females are equally affected. Individuals who inherit only one mutation are called carriers. Carriers do not typically show symptoms of the disease, but have a 50% chance, with each pregnancy, of passing on the mutation to their children. If both parents are carriers of a mutation, the risk for each pregnancy to be affected is 1 in 4, or 25%.

## Diagnosis

Canavan disease is suspected when an individual presents with classic signs and symptoms. Diagnosis is confirmed by biochemical testing, genetic testing, or both.[2] Biochemical tests analyze either NAA levels or aspartoacylase enzyme activity in someone with suspected Canavan disease.

- Affected individuals will have elevated levels of NAA because they cannot break it down; therefore, NAA accumulates in the blood or urine.
- Affected individuals will have severely reduced or nonexistent aspartoacylase enzyme activity.

Molecular genetic testing can be used for confirmation of the diagnosis and to help family planning by identifying individuals at risk of being carriers.[2]

- Targeted mutation analysis is the most common genetic test for Canavan disease. The panel analyzes for up to four of the most common mutations in the ASPA gene linked to Canavan disease, including the Glu285Ala and Tyr231X mutations, which account for 98% of all Ashkenazi Jewish cases.[2,3] The panel also includes the p.Ala305Glu mutation, which accounts for between 30% and 60% of all non-Ashkenazi Jewish cases.[2,3]
- Sequence analysis analyzes for mutations across the entire coding region of the ASPA gene. In addition to the more common mutations found in the Ashkenazi Jewish population, sequencing is also able to find less common mutations found in non-Ashkenazi Jews.[2,3] Sequence analysis has a detection rate of about 99% in all populations.[2]
- Large deletions in the ASPA gene have been reported but are believed to be uncommon.[2] Therefore, deletion/duplication analysis is unlikely to be indicated in most cases.

## Management

Symptomatic infants need supportive care such as ensuring adequate nutrition, addressing infections, and providing protection for their airway. Physical therapy may be helpful in addition to programs to facilitate communication. Antiepileptic medications are used for those with seizures. Hospice care can be a valuable resource as well.[2]

## Survival

Canavan disease does not usually allow survival beyond childhood.[1]

# Test Information

## Introduction

Testing for Canavan disease may include known familial mutation analysis,

targeted mutation analysis, next generation sequencing, and/or deletion/duplication analysis.

### Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

### Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon patient ethnicity, phenotypic presentation, or other case-specific characteristics.

### Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

### Deletion and Duplication Analysis

Analysis for deletions and duplications can be performed using a variety of technical platforms including exon array, Multiplex ligation-dependent probe amplification (MLPA), and NGS data analysis. These assays detect gains and losses too large to be identified through standard sequence analysis, often single or multiple exons or whole genes.

## Guidelines and Evidence

### Introduction

This section includes relevant guidelines and evidence pertaining to Canavan disease testing.

## American College of Medical Genetics and Genomics

The American College of Medical Genetics and Genomics (ACMG, 2008) supported offering carrier testing for Canavan disease to individuals of Ashkenazi Jewish descent for the two common mutations. It is anticipated that the detection rate will be ~97%. This test should be offered to individuals of reproductive age, preferentially prior to pregnancy, with genetic counseling performed by a geneticist or genetic counselor. ACMG supports the testing of individuals of Ashkenazi Jewish descent, even when their partner is non-Ashkenazi Jewish. In this situation, testing would start with the individual who is Ashkenazi and reflex back to the partner if necessary.[4]

ACMG (2021) released an educational practice resource on carrier screening.[5] This consensus statement asserted that general population carrier screening should be ethnicity and family history agnostic. To accomplish this, screening all individuals in the prenatal/preconception period for autosomal recessive and X-linked conditions with a carrier frequency of >1/200 was suggested. ACMG generated a list of 113 genes, which included the ASPA gene, meeting these criteria.

## American College of Obstetricians and Gynecologists

Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2020) stated:[6]

- "A number of clinically significant, autosomal recessive disease conditions are more prevalent in individuals of Ashkenazi Jewish (Eastern European and Central European) descent…When only one partner is of Ashkenazi Jewish descent, that individual should be offered screening first. If it is determined that this individual is a carrier, the other partner should be offered screening."
- "The American College of Obstetricians and Gynecologists has previously recommended offering carrier screening for four conditions in the Ashkenazi population." Canavan disease is one of the four conditions listed.

## Selected Relevant Publication

A 2018 expert-authored review stated the following regarding molecular genetic testing for diagnostic purposes:[2]

- The targeted mutation panel may be used to confirm a clinical diagnosis, biochemical diagnosis, or both.
- "Targeted analysis for the pathogenic variants p.Glu285Ala, p.Tyr231Ter, and p.Ala305Glu can be performed first in individuals of Ashkenazi Jewish ancestry."
- "Targeted analysis for the pathogenic variant p.Ala305Glu can be performed first in individuals of non-Ashkenazi Jewish ancestry."

- **"Sequence analysis of ASPA detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications."**

## Criteria

### Introduction

**Requests for Canavan Disease testing are reviewed using these criteria.**

**ASPA 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 Genetic Testing:**
  - **No previous genetic testing that would detect the familial mutation, AND**
- **Carrier Screening for Asymptomatic Individuals:**
  - **Known family mutation in ASPA in 1st, 2nd, or 3rd degree biologic relative, OR**
- **Prenatal Testing for At-Risk Pregnancies:**
  - **ASPA mutations identified in both biologic parents, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy**

**ASPA Targeted Mutation Analysis for Common Mutations**

- **Genetic Counseling:**
  - **Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:**
  - **No previous ASPA genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for Canavan disease, AND**
- **Diagnostic Testing or Carrier Screening:**
  - **Ashkenazi Jewish descent, regardless of disease status and N-acetylaspartic acid (NAA) levels, OR**
- **Prenatal Testing for At-Risk Pregnancies:**
  - **ASPA Ashkenazi mutations identified in both biologic parents, AND**

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

**ASPA Sequence Analysis**

- **Genetic Counseling:**
  - **Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND**
- **Previous Genetic Testing:**
  - **No previous ASPA gene sequencing, and**
  - **No known ASPA mutation in family, and**
  - **No mutations or one mutation detected by common mutation panel, AND**
- **Diagnostic Testing for Symptomatic Individuals:**
  - **Increased levels of N-acetylaspartic acid (NAA) in urine, and**
  - **An individual age three to five months of age with a triad of hypotonia, macrocephaly and head lag, or**
  - **Failure to attain independent sitting, walking or speech, OR**
- **Testing for Individuals with Family History or Partners of Carriers:**
  - **1st, 2nd, or 3rd degree biologic relative with Canavan disease clinical diagnosis, family mutation unknown, and testing unavailable, or**
  - **Partner is monoallelic or biallelic for ASPA mutation, and**
    - **Have the potential and intention to reproduce, AND**
- **Rendering laboratory is a qualified provider of service per the Health Plan policy**

## References

**These references are cited in this guideline.**

1. **Canavan Disease. In: Genetics Home References: Your Guide to Understanding Genetic Conditions (database online). A Service of the US National Library of Medicine. Topic last reviewed: 1 Apr 2015. Available at http://ghr.nlm.nih.gov/condition/canavan-disease.**
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3. Elpeleg ON, Shaag A. The spectrum of mutations of the aspartoacylase gene in Canavan disease in non-Jewish patients. *J Inherit Metab Dis.* 1999;22(4):531-4.
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6. ACOG Committee on Genetics. ACOG committee opinion. Number 691. Carrier screening for genetic conditions. *Obstet Gynecol.* 2017; Reaffirmed 2020;129:e41-e55.