Tay-Sachs Disease 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 Tay-Sachs disease

Definition

Tay-Sachs disease is a neurodegenerative genetic disorder.\(^1\) Affected individuals typically present in infancy with progressive weakness, loss of motor skills, decreased attentiveness, and increased startle response between 3-6 months of age. Eventually they develop seizures and blindness, with death in early childhood. There is no cure for Tay-Sachs disease and treatment is supportive.\(^{1,2}\)

- Rare, less severe, Tay-Sachs variants exist that are associated with later onset, and less progressive symptoms, and cause more variable neurological problems. These variants include juvenile, chronic, and adult-onset forms.\(^1\)
- Tay-Sachs disease is caused by mutations in the HEX A gene. HEX A gene mutations lead to reduced activity of the β-hexosaminidase A enzyme, allowing toxic substances to build up in the cells of the brain and spinal cord. Eventually, neurons are destroyed, causing the signs and symptoms of Tay-Sachs disease.\(^1\)
- Before widespread carrier screening, Tay-Sachs disease affected about 1 in 3,600 Ashkenazi Jewish births.\(^1\)
- Tay-Sachs disease is an autosomal recessive disorder. An affected individual must inherit a HEX A gene mutation from both parents.\(^1,2\)
  - Individuals who inherit only one mutation are called carriers. Carriers do not show symptoms of Tay-Sachs disease, but have a 50% chance of passing on the mutation to their children.
  - About 1 in 30 Ashkenazi Jewish individuals are carriers for Tay-Sachs disease.\(^1,3\)
Two carriers of Tay-Sachs disease have a 25% chance of having a child with the disorder.

- Individuals at increased risk to have a child with Tay-Sachs should routinely be offered carrier screening. This includes those with:
  - Ashkenazi Jewish, French Canadian, or Cajun ancestry
  - A family history of Tay-Sachs disease (regardless of ethnicity)
  - A partner who is a known carrier of Tay-Sachs (or affected with a late-onset variant)

- Carrier screening for Tay-Sachs disease is widely available as part of an “Ashkenazi Jewish Panel” that includes several other genetic diseases that are more common in this population (See the Ashkenazi Jewish Carrier Screening).

Test information

- **Hexosaminidase A (HEXA) enzyme analysis** measures the activity of HEXA in the serum or white blood cells. This test is used both for diagnostic testing of symptomatic individuals, and carrier screening.
  - Individuals with classic Tay-Sachs have little to no HEX A enzyme activity in the presence of normal or elevated activity of the beta-hexosaminidase B (HEX B) isoenzyme. HEX A enzyme activity levels correctly diagnose the vast majority of people with all forms of Tay-Sachs disease.
  - Carriers have about 50% of the normal level of HEX A activity. HEX A enzyme analysis detects 97%-98% of carriers, regardless of ethnicity. Enzyme analysis is recommended as the first step for all people being screened.
  - A small percentage of individuals will get a false positive result by enzyme analysis. This means that they have enzyme activity that appears to be in the carrier range, but they are not actually carriers of a disease-causing mutation. These individuals carry a “pseudodeficiency allele.” Inconclusive enzyme analysis results are also possible where enzyme activity is in the overlap range between carrier and normal levels. If HEXA enzyme analysis is abnormal or inconclusive, HEXA mutation analysis may be considered.

- **HEXA mutation panel.** This genetic test looks for the most common HEXA gene mutations (such as +TATC1278, +1 IVS 12, +1 IVS 9, G269, R247W, and R249W), which account for up to 98% of all Ashkenazi Jewish Tay-Sachs mutations. The detection rate of standard HEXA mutation panels is much lower in other ethnicities. Some panels include mutations more common in other at-risk ethnic groups (e.g., a 7.6kb deletion more common in French Canadians). If using mutation panels in non-Ashkenazi Jewish, providers should confirm those mutation panels include any ethnicity-specific mutations.
• **HEXA sequencing** analyzes the entire coding region of the HEXA gene and finds the vast majority of HEXA mutations that cause Tay-Sachs disease. Sequencing is most useful for individuals diagnosed by enzyme analysis, but for whom mutation panels found only one or no disease-causing mutations.¹

• **HEXA known familial mutation analysis:** Once the disease-causing mutations have been identified in an affected family member or known carriers, other at-risk relatives can be tested for just those mutations. Prenatal diagnosis can be performed by mutation analysis if both parental mutations are known.

### Guidelines and evidence

• Professional guidelines support population-based Tay-Sachs carrier screening for those at increased risk. They do not generally recommend a specific testing strategy (enzyme and/or mutation analysis) for Ashkenazi Jewish individuals, but do recommend enzyme analysis as a first-line test for non-Jewish individuals.²,³

• Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2005) recommend: ³
  
  o “Screening for TSD should be offered before pregnancy if both members of a couple are of Ashkenazi Jewish, French–Canadian, or Cajun descent. Those with a family history consistent with TSD also should be offered screening.”
  
  o “When one member of a couple is at high risk (i.e., of Ashkenazi Jewish, French–Canadian, or Cajun descent or has a family history consistent with TSD) but the other partner is not, the high-risk partner should be offered screening…If the high-risk partner is determined to be a carrier, the other partner also should be offered screening. If the woman is already pregnant, it may be necessary to offer screening to both partners simultaneously to ensure that results are obtained promptly and that all options are available to the couple.”
  
  o “Biochemical analysis should be used for individuals in low-risk populations.”

• Consensus guidelines from the American College of Medical Genetics (ACMG, 2008) recommend carrier screening for a group of disorders that includes Tay-Sachs disease when at least one member of the couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.²

• No evidence-based U.S. testing guidelines that address Tay-Sachs diagnostic testing have been identified.

• A 2006 comprehensive literature review states that: “The diagnosis of hexosaminidase A deficiency relies upon the demonstration of absent to near-absent beta-hexosaminidase A (HEX A) enzymatic activity.”¹ HEXA mutation analysis can be used in follow-up to resolve inconclusive results or to identify the familial mutations for reproductive purposes.¹

• Professional guidelines generally recommend prenatal testing for Tay-Sachs disease in any of the following situations:¹,⁴
HEX A enzyme activity testing revealed both parents to be carriers of Tay-Sachs disease and pseudodeficiency alleles have been ruled out.

- Disease-causing mutations in HEXA have been identified in both parents.
- One parent is a known carrier and HEX A enzyme activity testing in the other parent was inconclusive.
- The mother is a known carrier and the father is unknown or unavailable for testing.

Guidelines do not generally recommend a specific testing strategy (HEX A enzyme activity and/or mutation analysis). However, the clinical circumstances may deem one strategy more accurate than the other. For instance, mutation analysis is most accurate if both of the parental mutations are known.

- The American College of Obstetricians and Gynecologists (ACOG, 2005) guidelines for Tay-Sachs disease state: “If both partners are determined to be carriers of Tay-Sachs disease, genetic counseling and prenatal diagnosis should be offered.”

- The American College of Obstetricians and Gynecologists (ACOG, 2009) guidelines for Ashkenazi Jewish carrier screening state: “Carrier screening for TSD, Canavan disease, cystic fibrosis, and familial dysautonomia should be offered to Ashkenazi Jewish individuals before conception or during early pregnancy so that a couple has an opportunity to consider prenatal diagnostic testing options. If the woman is already pregnant, it may be necessary to screen both partners simultaneously so that the results are obtained in a timely fashion to ensure that prenatal diagnostic testing is an option… Carrier couples should be informed of the disease manifestations, range of severity, and available treatment options. Prenatal diagnosis by DNA-based testing can be performed on cells obtained by chorionic villus sampling and amniocentesis.”

### Criteria

**HEXA 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 molecular genetic testing of HEXA, AND

- Carrier Screening:
  - Known family mutation in HEXA identified in 1st, 2nd, or 3rd degree biologic relative(s), OR

- Prenatal Testing for At-Risk Pregnancies:
o HEXA mutation identified in both biologic parents, and
o Pseudodeficiency allele mutation has been ruled out, AND

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

HEXA Targeted Mutation Analysis for Common Mutations and Pseudodeficiency Alleles

• 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 This same test has not been performed previously, and
   o No known HEXA mutation in family, AND

• Diagnostic Testing: 6
   o Abnormal or indeterminate HEX A enzymatic activity in serum, white blood cells, or other tissues, and clinical symptoms of TSD, but diagnosis remains uncertain, or
   o Asymptomatic individual with abnormal HEX A enzymatic activity in order to test for a pseudodeficiency allele, or
   o Children under the age of 6 months with
     ▪ Progressive weakness and loss of motor skills, or
     ▪ Decreased attentiveness, or
     ▪ Increased startle response, or
     ▪ Macular cherry red spot, or
     ▪ Seizures, or
     ▪ Blindness, or
   o Young children with
     ▪ Ataxia and incoordination, or
     ▪ Speech, life skills and cognition decline, or
     ▪ Spasticity and seizures, or
     ▪ Loss of vision, sometimes with:
       • Cherry red spot, or
• Optic atrophy, or
• Retinitis pigmentosa, or

  o Adolescent/adult (and SMA type Kugelberg-Welander disease or early onset ALS has been ruled out) with
    ▪ Progressive dystonia, or
    ▪ Spinocerebellar degeneration, or
    ▪ Motor neuron disease, or
    ▪ Cognitive dysfunction, dementia, recurrent psychotic depression or bipolar symptoms, or

  o French Canadian, Cajun, or Old Order Amish descent regardless of symptoms, OR

• Preconception/Prenatal Carrier testing
  o Ashkenazi Jewish descent, and
  o Intention to reproduce, AND

• Carrier testing for Individuals with Family History or Partners of Carriers:
  o 1st, 2nd, or 3rd degree biologic relative with Tay-Sachs clinical diagnosis, family mutation unknown, and affected relative unavailable for testing, or
  o Partner is monoallelic or biallelic for HEXA mutation, and
  o Have the potential and intention to reproduce, AND

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

HEXA 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 No mutations found on targeted mutation analysis, and
  o No previous full sequencing of HEXA, AND

• Diagnostic Testing:\n  o Abnormal or indeterminate HEX A enzymatic activity in serum, white blood cells, or other tissues, and clinical symptoms of TSD, but diagnosis remains uncertain, OR
o Children under the age of 6 months with one or more of the following:
  - Progressive weakness and loss of motor skills,
  - Decreased attentiveness
  - Increased startle response
  - Macular cherry red spot
  - Seizures
  - Blindness, or

o Young children, with one or more of the following:
  - Ataxia and incoordination
  - Speech, life skills and cognition decline
  - Spasticity and seizures
  - Loss of vision, sometimes with:
    - Cherry red spot
    - Optic atrophy
    - Retinitis pigmentosa, or

o Adolescence/adult (and SMA type Kugelberg-Welander disease or early onset ALS has been ruled out), with one or more of the following:
  - Progressive dystonia
  - Spinocerebellar degeneration
  - Motor neuron disease
  - Cognitive dysfunction, dementia, recurrent psychotic depression or bipolar symptoms, and

• Carrier testing for Individuals with Family History or Partners of Carriers:
  o 1st, 2nd, or 3rd degree biologic relative with Tay-Sachs clinical diagnosis, and familial mutation unknown, and affected relative unavailable for testing, or
  o Partner is monoallelic or biallelic for a HEXA mutation, and
  o Have the potential and intention to reproduce, AND

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


