Gaucher 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 Gaucher Disease

Definition

Gaucher disease is a genetic disease that affects multiple organs and tissues.

- There are several types of Gaucher disease, each with varying signs and symptoms:\cite{1,2}
  - Type 1 is the most common type of Gaucher Disease. Unlike other types, type 1 does not affect the central nervous system (CNS). Symptoms include enlargement of the liver and spleen (hepatosplenomegaly), anemia, low blood platelets, lung disease, and bone abnormalities.
  - Type 2/Type 3. These types are rarer, usually more severe, and affect the brain and CNS. Common symptoms include seizures, hyperextension of the spine, and lockjaw, in addition to the symptoms listed above for type 1. Type 2 is more severe, and affected individuals usually do not survive past childhood. Type 3 affected individuals have more slowly progressing symptoms and can survive into adulthood.
  - Perinatal lethal. The most severe form of Gaucher disease has symptoms that begin during pregnancy or in early infancy, including swelling, dry/scaly skin (ichthyosis), and serious neurological problems. Affected infants usually survive only a few days after birth.
  - Cardiovascular. This type has mainly heart manifestations. Symptoms include the hardening of heart valves, eye abnormalities, bone disease, and enlarged spleen.
• These subtypes are identified through clinical symptoms and do not correlate well with the different mutations that cause Gaucher disease.\textsuperscript{2}

• Gaucher disease is relatively common in Ashkenazi Jewish populations, affecting about 1 in 500 to 1 in 1,000 people.\textsuperscript{1} It is much less common in the general population, affecting about 1 in 50,000 to 1 in 100,000 people.\textsuperscript{1}

• Gaucher disease is caused by changes, or mutations to the GBA gene.\textsuperscript{1-3} The GBA gene makes the enzyme beta-glucosylceramidase, also called acid beta-glucocerebrosidase. This enzyme helps break down fatty substances in cells. Mutations in GBA lead to a buildup of these fatty substances to toxic levels. This buildup damages tissues and organs, leading to symptoms of Gaucher disease.\textsuperscript{1-3}

• Gaucher disease is an autosomal recessive disorder. An affected person inherits two GBA gene mutations -- one from each parent.\textsuperscript{1,2}

  • People who have only one GBA mutation are called carriers. Carriers do not show symptoms of Gaucher disease, but have a 50% chance of passing the mutation on to their children.

  • Two carriers of Gaucher disease have a 25% chance of having a child affected with the disease.

• Clinical findings alone are insufficient for a definitive diagnosis of Gaucher disease.\textsuperscript{2}

• If Gaucher disease is suspected in a symptomatic person, beta-glucosylceramidase enzyme testing should be performed first. People affected with Gaucher disease have 0-15% the normal level of beta-glucosylceramidase compared to healthy individuals. Measuring beta-glucosylceramidase levels is a reliable way to confirm a suspected case of Gaucher disease.\textsuperscript{2,4,5} beta-glucosylceramidase levels within the normal range rule out Gaucher disease.

• Genetic testing can be used to identify the disease-causing mutations in an affected person diagnosed by enzyme analysis.\textsuperscript{1} Identifying the causative GBA mutations can aid in prognostication. Genetic testing is recommended for reproductive purposes when parents of an affected child need to know the mutations for preimplantation genetic diagnosis or prenatal diagnosis. Mutation analysis can also confirm disease-causing mutations when a diagnosis by enzyme analysis is inconclusive.\textsuperscript{1} Enzyme testing is not appropriate to identify unaffected carriers.\textsuperscript{2}

**Test information**

• **GBA Mutation Panel:** Clinically-available testing panels look for four or more of most common mutations in the GBA gene.

  • Four mutations (N370S, L444P, 84GG, IVS2+1) account for about 90% of mutations in the Ashkenazi Jewish population and about 50%-60% of mutations in the non-Ashkenazi Jewish population.\textsuperscript{1}

  • Some laboratories include several other common mutations in their panels.
o Carrier screening by GBA mutation panel for Gaucher 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 Ashkenazi Jewish Carrier Screening for more information.)

- **GBA Sequence Analysis:** This test analyzes the entire coding region of the GBA gene and will find mutations that the GBA mutation panel could not.\(^1\)
  - The detection rate of sequencing is about 99%.
  - This test is indicated in people with Gaucher disease who have one or no mutations identified by mutation panel testing.
  - This test is also indicated for reproductive partners of individuals who have a GBA mutation.

- **GBA known familial mutation testing:** When there is a family history of Gaucher disease, the family mutations should be identified prior to carrier testing in at-risk family members when possible. A mutation panel can be used if the family mutations are included in the panel. If the family mutations are not included in the panel and were identified through sequencing, then GBA known familial mutation testing is necessary.\(^2\)

- **Prenatal or preimplantation genetic diagnosis:** This testing is possible in at-risk pregnancies if the parental mutations are known.

### Guidelines and evidence

- No US evidence-based diagnostic guidelines have been identified.

- A 2015 expert-authored review recommends the following testing strategy for diagnosis of an affected person:\(^2\)
  - "Assay of glucosylceramidase enzyme activity in leukocytes or other nucleated cells is the confirmatory diagnostic test."
  - "Molecular genetic testing and the identification of two disease-causing alleles provide an alternative means of confirming the diagnosis. There is broad heterogeneity in causative variants; in individuals in whom genetic testing identifies a novel GBA variant, biochemical testing to confirm the diagnosis should be considered."
  - "Targeted analysis for pathogenic variants in a proband originally diagnosed by biochemical testing may be considered for genetic counseling purposes, primarily to identify the pathogenic variants and permit carrier detection among at-risk relatives."

- Reviews published in peer-reviewed medical literature support this and offer some considerations for genotyping:
Archives of Internal Medicine (1998): 4

- “The most efficient and reliable method of establishing the diagnosis of Gaucher disease is the assay of β-glucocerebrosidase activity.”
- “Knowledge of the genotype may be helpful in predicting the severity and rate of progression of clinical symptoms in patients. For example, the homozygous N370S allele is usually associated with a generally less severe phenotype, although with wide clinical variability; the heterozygous state for N370S is protective against central nervous system involvement; and the L444P allele in the homozygous state is associated with early neurologic symptoms common in the types 2 and 3 clinical classifications.”

The Brazilian Study Group on Gaucher Disease (2009): 5

- “Definitive diagnosis of [Gaucher disease] requires confirmation by the acid β-glucosidase enzyme assay in leukocytes or fibroblasts.”
- “N370S homozygotes generally present with a less severe phenotype, whereas L444P and D409H homozygosity confers neurologic involvement. Despite these general genotype-phenotype correlations, disease severity, and clinical outcomes cannot be predicted on the basis of genotype.”

- Professional guidelines generally support Gaucher disease carrier screening for those at increased risk. 6,7
- Consensus guidelines from the American College of Obstetricians and Gynecologists (ACOG, 2009) address carrier screening and prenatal diagnosis for Gaucher disease: 6
  - “Individuals with a positive family history of one of these disorders [including Gaucher disease] should be offered carrier screening for the specific disorder and may benefit from genetic counseling.”
  - 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 Gaucher disease), ACOG simply states: “Individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for other disorders.”
  - “If it is determined that this individual [an Ashkenazi Jewish descent partner] is a carrier, the other partner should be offered screening.”
  - “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 Gaucher disease when at least one member of the couple is Ashkenazi Jewish and that couple is pregnant or planning pregnancy.”
Criteria
Carrier Testing

GBA 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 GBA, AND

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

- Prenatal Testing for At-Risk Pregnancies:
  - GBA mutation(s) identified in both biologic parents.

GBA Targeted Mutation Analysis for Ashkenazi Mutations (Four 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 GBA genetic testing, including Ashkenazi Jewish screening panels containing targeted mutation analysis for Gaucher disease, AND

- Carrier Screening:
  - Ashkenazi Jewish descent, regardless of disease status and results of glucosylceramidase assay, and
  - Intention to reproduce

Diagnostic and Expanded Carrier Testing

GBA Sequencing

- 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 GBA full sequencing analysis, and
• If Ashkenazi Jewish, testing for 4 common mutations is negative, AND

- Diagnostic Testing for Symptomatic Individuals:
  - Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, and
  - Characteristic bone changes including osteopenia, focal lytic or sclerotic bone lesions or osteonecrosis, or
  - Hepatosplenomegaly and hematologic changes including anemia or thrombocytopenia, or
  - Primary neurologic disease which could include one or more of the following: cognitive impairment, bulbar signs, pyramidal signs, oculomotor apraxia, or seizures (progressive myoclonic epilepsy), OR

- Diagnostic Testing for Asymptomatic Carriers:
  - One mutation detected by targeted mutation analysis, and
  - Glucosylceramidase enzyme activity in peripheral blood leukocytes is 0-15% of normal activity, OR

- Testing for Individuals with Family History or Partners of Carriers:
  - 1st, 2nd, or 3rd degree biologic relative with Gaucher disease clinical diagnosis, family mutation unknown and testing unavailable, or
  - Partner is monoallelic or biallelic for GBA mutation, and has the potential and intention to reproduce with this partner.

References


