



CIGNA HEALTHCARE COVERAGE POSITION

Subject Genetic Testing for Gaucher Disease

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INSTRUCTIONS FOR USE

Coverage Positions are intended to supplement certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a participant's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Positions are based. For example, a participant's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Position. In the event of a conflict, a participant's benefit plan document **always supercedes** the information in the Coverage Positions. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable group benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Positions and; 4) the specific facts of the particular situation. Coverage Positions relate exclusively to the administration of health benefit plans. Coverage Positions are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2008 CIGNA.

Coverage Position

CIGNA HealthCare covers genetic testing for Gaucher disease (GD) as medically necessary when EITHER of the following criteria is met:

- For carrier testing when there is an affected family member (first- or second-degree relative*) who has an identified GBA mutation or Gaucher disease
- For prenatal testing or preimplantation genetic diagnosis (PGD) when both parents or a prior sibling have an identified GBA mutation or Gaucher disease

*A first-degree relative is defined as a blood relative with whom an individual shares approximately 50% of his/her genes, including the individual's parents, full siblings, and children.

*A second-degree relative is defined as a blood relative with whom an individual shares approximately 25% of his/her genes, including the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces and half siblings.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a physician or a licensed or certified genetic counselor.

CIGNA HealthCare does not cover genetic testing for Gaucher disease in the general population, because such screening is considered not medically necessary or of unproven benefit.

General Background

Gaucher disease (GD) is an autosomal recessive metabolic disorder in which damaging amounts of a fatty substance called glucocerebroside accumulate in the spleen, liver, lungs, bone marrow and, in rare cases, the brain. GD can range from a perinatal lethal disorder to an asymptomatic form. There are three major clinical subtypes (Types 1, 2, and 3) and two other subtypes (perinatal lethal and cardiovascular). Type 1 is the most common and is characterized by clinical or radiographic evidence of bone disease (e.g., osteopenia, sclerotic lesions, and osteonecrosis), hepatosplenomegaly, anemia and thrombocytopenia, lung disease, and the absence of primary central nervous system disease. Types 2 and 3 are characterized by the presence of primary neurologic disease. Individuals with onset before age two years with limited psychomotor development and a rapidly progressive course and often death by age two to four are classified as type 2. Individuals with type 3 GD may have onset before age two, but often have a more slowly progressive course and may live into the third or fourth decade. The perinatal lethal form is associated with skin abnormalities or with edema in the fetal subcutaneous tissue. The cardiovascular form is characterized by calcification of the aortic and mitral valves, mild splenomegaly, corneal opacities, and supranuclear ophthalmoplegia. Cardiopulmonary complications can be found in all the clinical subtypes, but vary in frequency and severity (Pastores, 2005).

Diagnosis/Testing

The diagnosis of GD relies on demonstration of deficient glucosylceramidase enzyme activity in peripheral blood leukocytes or other nucleated cells. Carrier testing by assay of enzyme activity is unreliable due to overlap in enzyme activity between carriers and noncarriers. GBA is the only gene known to be associated with GD. More than 150 GBA gene mutations have been described. Four mutations (N3705, L444P, 84GG, IV52+1) account for approximately 90% of the disease-causing mutations in the Ashkenazi Jewish population. In non-Jewish populations, these four alleles tend to account for about 50–60% of disease-causing alleles. In families in which the disease-causing mutations are known, molecular testing can be used to accurately identify carriers (Pastores, 2005).

GD is inherited in an autosomal recessive manner. Mutation analysis can be used to identify carriers among at-risk family members. Since the carrier frequency for GD in certain populations is high (e.g., one in 18 in individuals of Ashkenazi Jewish heritage) and the N3705/N3705 phenotype is variable, individuals who undergo carrier testing may be identified as being homozygous. Prenatal testing for pregnancies at increased risk is available and relies upon assay of glucosylceramidase enzymatic activity and mutation analysis when the underlying gene defects are known.

Testing Strategy for a Proband

Assay of glucosylceramidase enzyme activity in leukocytes or of the nucleated cells is the confirmatory diagnostic test. Molecular genetic testing and the identification of two disease-causing alleles provides additional confirmation of the diagnosis, but should not be used in place of biochemical testing. As the diagnosis of GD can be confirmed through biochemical testing performed on the peripheral blood leukocytes, it is not necessary to perform a bone marrow examination.

Molecular genetic testing of a proband may be considered for genetic counseling purposes, primarily for carrier detection among at-risk relatives (Pastores, 2005).

Carrier Detection

Measurement of glucosylceramidase enzyme activity in peripheral blood leukocytes is unreliable for carrier determination due to significant overlap in residual enzyme activity between obligate carriers and general (noncarrier) population.

Mutation analysis can be used to identify carriers among at-risk first- or second-degree family members once the disease-causing mutations of the GBA gene have been identified in the proband. The purpose of testing asymptomatic individuals at substantially increased risk is medical follow-up and potential treatment as well as lifestyle and reproductive planning (Pastores, 2005).

Prenatal Testing

Prenatal testing is available for pregnancies at increased risk. Prenatal testing relies upon analysis of glucosylceramidase enzymatic activity of fetal cells obtained by chorionic villus sampling (CVS) at about 10–12 weeks' gestation or by amniocentesis usually performed at about 15–18 weeks' gestation. If the

disease-causing GBA mutations have been identified in both parents or in a previously affected sibling, prenatal testing results can be confirmed by mutation analysis of the GBA gene performed on fetal DNA obtained by CVS or amniocentesis (Pastores, 2005).

Management

Management issues include: 1) comprehensive baseline evaluation and serial monitoring to evaluate severity and rate of disease progression, 2) symptomatic care, and 3) therapy to reduce glycosylceramide accumulation (National Gaucher Foundation, 2004).

Enzyme replacement therapy (ERT) is available for patients with type 1 GD. This therapy decreases liver and spleen size, reduces skeletal abnormalities, and successfully reverses other manifestations of the disorder, including abnormal blood counts (Weintraub, 2002). There is currently no effective treatment for severe brain damage that may occur in patients with types 2 and 3. There is no permanent cure for GD. ERT has changed the natural history of GD and eliminated the need for splenectomy in individuals with hypersplenism. Individuals not receiving ERT and certain other individuals may still require symptomatic treatment such as:

- Partial or total splenectomy may be provided for individuals with massive splenomegaly with significant areas of infarction and persistent severe thrombocytopenia with high risk of bleeding.
- Transfusion of blood products may be given for severe anemia and bleeding. Anemia and clotting problems unresponsive to ERT should prompt investigations for an intercurrent disease process. Evaluation by a hematologist is recommended prior to any major surgical or dental procedures.
- Analgesics may be provided for bone pain. Persistent bone pain in individuals receiving enzyme replacement therapy should prompt evaluations to exclude the possibility of a mechanical problem (e.g., pathologic fracture or joint collapse secondary to osteonecrosis, degenerative arthritis).
- Joint replacement surgery may be undertaken for relief from chronic pain and restoration of mobility.

Gene therapy is under investigation. It involves the introduction of the GBA gene into hematopoietic stem cells. In limited trials, there has been evidence of some enzyme production by transduced cells, but it does not appear to be sustained or result in a permanent cure (Pastores, 2005).

Summary

Gaucher disease (GD) is an autosomal recessive metabolic disorder in which harmful quantities of a fatty substance called glucocerebroside accumulate in the spleen, liver, lungs, bone marrow and, in rare cases, the brain. 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 provides additional confirmation of the diagnosis but should not be used in place of biochemical testing.

Measurement of glucosylceramidase enzyme activity in peripheral blood leukocytes is unreliable for carrier determination due to significant overlap in residual enzyme activity between obligate carriers and the general (i.e., noncarrier) population. Mutation analysis can be used to identify carriers among at-risk family members once the disease-causing mutations of the GBA gene have been identified in the proband.

If the disease-causing GBA mutations have been identified in both parents or in a previously affected sibling, prenatal testing results can be confirmed by mutation analysis of the GBA gene performed on fetal deoxyribonucleic acid (DNA) obtained by chorionic villus sampling (CVS) or amniocentesis.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

| CPT [®] * Codes | Description |
|--------------------------|-------------------|
| | No specific codes |

| HCPCS Codes | Description |
|-------------|-------------------------------------|
| S3848 | Genetic testing for Gaucher disease |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------|-------------|
| 272.7 | Lipidosis |

*Current Procedural Terminology (CPT[®]) © 2007 American Medical Association: Chicago, IL.

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