INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna companies. Coverage Policies are intended to provide guidance in interpreting certain standard Cigna benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, 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 Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of Cigna. Copyright ©2014 Cigna

Coverage Policy

Please refer to the applicable benefit plan document to determine benefit availability and the terms, conditions and limitations of coverage. Under some benefit plans, coverage for genetic screening and/or testing may be excluded or restricted. If coverage for genetic testing is available, the following conditions of coverage apply.

Cigna covers genetic testing for Gaucher disease as medically necessary for ANY of the following indications:

- carrier testing for EITHER of the following:
  - for the known familial mutation (i.e., testing for the known familial variant) when the individual has a first-, second-, or third degree relative* in whom a disease-causing mutation of gene GBA has been identified
  - with targeted mutation analysis when the individual has a first-, second-, or third degree relative* with the diagnosis of Gaucher disease or is of Ashkenazi Jewish descent

- preconception or prenatal genetic testing to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce for EITHER of the following:
  - for the known familial mutation (i.e., testing for the known familial variant) when one reproductive partner has an identified disease-causing mutation of gene GBA
  - with targeted mutation analysis when one reproductive partner has Gaucher disease or is of Ashkenazi Jewish descent
• prenatal testing for the known familial mutation (i.e., testing for the known familial variant) of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when both members of the reproductive couple have an identified disease-causing mutation of gene GBA

Cigna covers genetic testing with sequence analysis for Gaucher disease as medically necessary when ALL the following criteria are met:

• testing is being performed to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce
• targeted mutation analysis of common variants is negative
• the individual has Gaucher disease or a first-degree relative* who is deceased and had diagnosis of 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.
A third-degree relative is defined as a blood relative with whom an individual shares approximately 12.5% of his/her genes, including the individual's great-grandparents and first-cousins.

Any individual undergoing genetic testing for Gaucher disease should have both pre-and post-test genetic counseling completed by ONE of the following:

• an independent Board-Certified or Board-Eligible Medical Geneticist
• an American Board of Medical Genetics or American Board of Genetic Counseling-certified Genetic Counselor not employed by a commercial genetic testing laboratory (Genetic counselors are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).
• a genetic nurse credentialed as either a Genetic Clinical Nurse (GCN) or an Advanced Practice Nurse in Genetics (APGN) by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC) who is not employed by a commercial genetic testing laboratory (Genetic nurses are not excluded if they are employed by or contracted with a laboratory that is part of an Integrated Health System which routinely delivers health care services beyond just the laboratory test itself).

Cigna does not cover genetic testing for Gaucher disease in the general population, because such screening is considered not medically necessary.

General Background

Gaucher disease 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. 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 Gaucher disease 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, et al., 2013). The diagnosis of Gaucher disease relies on demonstration of deficient glucosylceramidase enzyme activity in peripheral blood leukocytes or other nucleated cells.
Management of Gaucher disease includes: comprehensive baseline evaluation and serial monitoring to evaluate severity and rate of disease progression, symptomatic care, and therapy to reduce glycosylceramide accumulation (National Gaucher Foundation, 2004). Enzyme replacement therapy is available for patients with type 1 Gaucher disease. This therapy decreases liver and spleen size, reduces skeletal abnormalities, and successfully reverses other manifestations of the disorder, including abnormal blood counts (Weinreb, 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 Gaucher disease. Enzyme replacement therapy has changed the natural history of Gaucher disease and eliminated the need for splenectomy in individuals with hypersplenism. For patients not receiving enzyme replacement therapy symptomatic treatment includes partial or total splenectomy. Bone marrow transplantation may be considered for individuals with severe Gaucher disease. Supportive treatment for individuals with Gaucher disease may include: transfusion of blood products for severe anemia and bleeding; analgesics for bone pain; and joint replacement surgery for relief from chronic pain and restoration of function (Pastores, et al., 2013).

**Genetic Testing**

GBA is the only gene known to be associated with Gaucher disease. More than 150 GBA gene mutations have been described. Four mutations 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, et al., 2013).

Gaucher disease is inherited in an autosomal recessive manner. Targeted mutation analysis can be used to identify carriers among at-risk family members. 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. Molecular genetic testing of a proband may be considered for genetic counseling purposes, primarily for carrier detection among at-risk relatives (Pastores, et al., 2013). Sequence analysis of the GBA coding region may be used to detect mutations in affected individuals in whom mutation analysis has identified only a single mutation.

Carrier testing by assay of enzyme activity is unreliable due to overlap in enzyme activity between carriers and noncarriers. 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 (Pastores, et al., 2013).

Carrier testing in at-risk individuals may be performed when there is an affected family member with known disease-causing mutation. When the individual is of Ashkenazi Jewish descent, preconception or prenatal genetic testing to determine carrier status of a prospective biologic parent should include testing for the four mutations (mutation: N370S, 84GG, L444P 2, IVS2+1), that for approximately 90% of the disease-causing mutations in this population, also referred to as the American College of Medical Genetics (ACMG) 4 mutation panel (Gross, et al., 2008; Pastores, et al., 2013).

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. Prenatal of the fetus testing relies upon analysis 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 diagnosis and preimplantation genetic diagnosis may be performed (Pastores, et al., 2013).

Genetic testing should be undertaken only after independent genetic counseling has been provided to patients in order to assist in complex clinical decision-making. Post-genetic testing counseling should be planned. The genetic counseling should be provided by an independent specialty-trained genetics professional such as a medical geneticist or a genetic counselor who is an American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counseling professional who is unaffiliated with the genetic testing lab performing the test(s).
Professional Societies/Organizations

American College of Medical Genetics (ACMG): the ACMG practice guidelines for carrier screening in individuals of Ashkenazi Jewish descent, include the following recommendations regarding genetic testing for Gaucher disease (Gross, et al., 2008):

- Prenatal/preconception carrier screening and carrier screening for Gaucher disease be offered for to all Ashkenazi Jews who are pregnant or considering pregnancy
- Carrier screening for these disorders should include testing for the specific mutations related to the conditions, which will results in a carrier detection rate of 95% for most disorders
- The offering of such testing should ideally take place before pregnancy, thereby giving individuals time to make appropriate reproductive decisions based on their own personal choices and cultural backgrounds. Currently, the majority of testing takes place in the primary care obstetrical setting and not in the medical genetic specialty environment. However, regardless of the clinical setting, adequate counseling should be provided to anyone considering testing so that choices are informed.
- If only one member of a couple is of Ashkenazi Jewish background, then testing should still be offered with the Jewish member of the couple being tested first.

American College of Obstetricians and Gynecologists (ACOG) (2009): The ACOG guidance for preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent include recommendations that genetic testing for Gaucher is available and some individuals may inquire about the availability of carrier screening for this disorder. They recommend that patient education materials be made available so that interested patients can make an informed decision regarding these tests and that patients may benefit from genetic counseling.

Use Outside of the US
No relevant information found

Summary
Gaucher disease is an autosomal recessive metabolic disorder caused by mutations in gene GBA. Genetic testing may be used to identify carriers among at-risk family members. Clinical uses of molecular genetic testing for Gaucher disease include the identification of specific disease-causing point mutations, carrier testing, prenatal testing and preimplantation genetic diagnosis.

Coding/Billing Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81251</td>
<td>GBA (glucosidase, beta, acid) (eg, Gaucher disease) gene analysis, common variants (eg, N370S, 84GG, L444P, IVS2+1G&gt;A)</td>
</tr>
<tr>
<td>81403</td>
<td>Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of &gt;10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)</td>
</tr>
<tr>
<td></td>
<td>- Known familial variant, not otherwise specified, for gene listed in Tier 1 or Tier 2, DNA sequence analysis, each variant exon</td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td></td>
<td>- genetic testing for Gaucher Disease with sequence analysis.</td>
</tr>
</tbody>
</table>

References


