



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Genetic Testing for Canavan Disease**

**Effective Date ..... 4/15/2010**  
**Next Review Date ..... 4/15/2012**  
**Coverage Policy Number ..... 0333**

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## Hyperlink to Related Coverage Policies

- Genetic Counseling
- Genetic Disease Screening Panels
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis

### INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer'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 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 supercedes** the information in the Coverage Policies. 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 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. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers genetic testing for Canavan disease as medically necessary for ANY of the following indications:**

- For confirmation of a diagnosis in a symptomatic individual with clinical features suggestive of Canavan disease and an increased level of N-acetylaspartic acid (NAA) but a definitive diagnosis remains uncertain.
- Preconception or prenatal genetic testing to determine carrier status of a prospective biologic parent with the capacity and desire to reproduce when EITHER of the following applies:
  - There is a first- or second-degree relative\* with an identified (aspartoacylase [ASPA]) disease-causing mutation
  - Individual is of Ashkenazi Jewish descent
- For prenatal testing of a fetus (i.e., amniocentesis or chorionic villus sampling [CVS]) or preimplantation genetic diagnosis (PGD) when there is an identified ASPA disease-causing mutation in a first- or second-degree relative\* and at least one parent is known to be heterozygous.

\*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 does not cover molecular genetic testing for Canavan disease in the general population, because such screening is considered not medically necessary or of unproven benefit.**

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## **General Background**

Canavan disease is a neurological birth disorder and one of the most common cerebral degenerative diseases of infancy (National Institute of Neurological Disorders and Stroke [NINDS], 2008). It is one of a group of genetic disorders known as the leukodystrophies, and is caused by a deficiency of the enzyme aspartoacylase (ASPA) encoded by the ASPA gene. Deficiency of this enzyme causes an imperfect growth or development of the myelin sheath around nerve fibers in the brain (NINDS, 2008). Canavan disease is inherited in an autosomal, recessive manner. Canavan disease is usually diagnosed in infants between the ages of three and five months and is characterized by macrocephaly, severe hypotonia, and failure to achieve independent sitting, ambulation, or speech. Hypotonia eventually changes to spasticity, and assistance with feeding becomes necessary. Life expectancy is usually into the teens (Matalon, et al., 2009).

Diagnosis of symptomatic individuals is based on a high concentration of N-acetylaspartic acid (NAA) in the urine. Some individuals with Canavan disease have lower excretion of NAA, but these individuals still have urine concentrations of about five to ten times what is considered normal (Matalon, et al., 2009). NAA concentration is also elevated in the blood and cerebrospinal fluid of children with the disease, but elevated urine concentration of NAA is sufficient for diagnosis of affected individuals (Matalon, et al., 2009).

Treatment of Canavan disease is supportive in nature and directed towards providing adequate nutrition and hydration, managing infectious diseases, and protecting and maintaining the airway (Matalon, et al., 2009).

## **Genetic Testing**

ASPA is the only gene known to be associated with Canavan disease. Three common mutations (E285A, Y231X, and A305E) account for approximately 99% of the disease-causing alleles in Ashkenazi Jewish individuals, and approximately 50–55% of disease-causing alleles in non-Jewish individuals (Matalon, et al., 2009). Preliminary data from limited population screening of Ashkenazi Jewish individuals using the two common Jewish mutations (E285A and Y231X) revealed a carrier rate of 1:40 (Matalon, et al., 2009). The carrier rate in non-Jewish persons is not known but is assumed to be much lower than that found in the Ashkenazi Jewish population.

Clinical indications for molecular genetic testing for Canavan disease include confirmation of the diagnosis, preconception or prenatal carrier testing of prospective biologic parents, prenatal testing of a fetus and preimplantation genetic diagnosis of an embryo. Diagnosis of Canavan disease in a proband is based on the demonstration of increased levels of NAA in the urine. Molecular genetic testing can be used for confirmation of the diagnosis in individuals with non-diagnostic biochemical findings.

DNA mutation analysis of the ASPA gene can be used for preconception or prenatal carrier testing to identify carriers among at-risk family members. Carrier testing in at-risk individuals may be performed when there is an affected family member with known disease-causing mutation or the individual is of Ashkenazi Jewish descent. Carrier detection using biochemical assay is not routinely available because it relies on a complex enzyme assay in cultured skin fibroblasts. Carrier testing provides the opportunity for reproductive planning.

Prenatal testing is performed during pregnancy to determine if a developing fetus is at risk for inheriting identifiable genetic diseases or traits. Diagnosis is made through the testing of amniotic fluid, fetal cells and fetal and/or maternal blood cells via chorionic villus sampling (CVS) at about 10–12 weeks of gestation or by amniocentesis at 16–18 weeks of gestation. The ASPA disease-causing mutation of an affected family member must be identified before prenatal testing can be performed.

Preimplantation genetic diagnosis may be available for families in which both of the ASPA disease-causing mutation has been identified in an affected family member. This technique allows for determination of genotype of an embryo before implantation takes place, providing the opportunity to exclude embryos with genetic abnormalities before the initiation of pregnancy.

### **Professional Societies/Organizations**

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

- Carrier screening for Canavan disease should be offered 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 result in a carrier detection rate 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.

The ACMG position statement on carrier testing for Canavan disease recommends that carrier testing for this disorder be offered before pregnancy. If only one partner is of Ashkenazi Jewish descent, he/she should be offered carrier testing, and the couple should be counseled regarding the limitations and benefits of carrier testing and prenatal diagnosis for this situation. If a family member is affected, the proband mutation(s) should be defined, and the relatives should be offered screening for this mutation(s). This screening could be combined with screening for Tay-Sachs disease, as both disorders are more common in the same ethnic group (ACMG, 1998).

**American College of Obstetricians and Gynecologists (ACOG):** ACOG guidance for preconception and prenatal carrier screening for genetic diseases in individuals of Eastern European Jewish descent include the following recommendations regarding genetic testing for Canavan disease (ACOG, 2009):

- Carrier screening for Canavan disease 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.
- When only one partner is of Ashkenazi Jewish descent, that individual should be screened first. If it is determined that this individual is a carrier, the other partner should be offered screening. However, the couple should be informed that the carrier frequency and the detection rate in non-Jewish individuals is unknown for this condition. Therefore, it is difficult to accurately predict the couple's risk of having a child with the disorder.
- Individuals with a positive family history of this disorder should be offered carrier screening for the specific disorder and may benefit from genetic counseling.
- When both partners are carriers of this disorder, they should be referred for genetic counseling and offered prenatal diagnosis. 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 or amniocentesis.

### **Summary**

Canavan Disease is inherited in an autosomal recessive manner caused by a deficiency of the enzyme aspartoacylase (ASPA) encoded by the ASPA gene. Clinical indications for molecular genetic testing for this disorder include confirmation of the diagnosis, preconception or prenatal genetic testing of a prospective biologic parent to determine carrier status, prenatal testing of a fetus and preimplantation genetic diagnosis of an embryo.

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## **Coding/Billing Information**

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

**Covered when medically necessary:**

<b>CPT<sup>®*</sup> Codes</b>	<b>Description</b>
83890	Molecular diagnostics; molecular isolation or extraction, each nucleic acid type (ie, DNA or RNA)
83891	Molecular diagnostics; isolation or extraction of highly purified nucleic acid, each nucleic acid type (ie, DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83896	Molecular diagnostics; nucleic acid probe, each
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83909	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis), each nucleic acid preparation
83912	Molecular diagnostics; interpretation and report
83914	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay [OLA], single base chain extension [SBCE], or allele-specific primer extension [ASPE])

<b>HCPCS Codes</b>	<b>Description</b>
S3851	Genetic testing for Canavan disease

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
330.0	Leukodystrophy

**\*Current Procedural Terminology (CPT<sup>®</sup>) © 2010 American Medical Association: Chicago, IL.**

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## References

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## Policy History

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<b>Pre-Merger Organizations</b>	<b>Last Review Date</b>	<b>Policy Number</b>	<b>Title</b>
CIGNA HealthCare	4/15/2008	0333	Genetic Testing for Canavan Disease

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