



# 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 Niemann-Pick Disease**

**Effective Date ..... 3/15/2010**  
**Next Review Date..... 3/15/2012**  
**Coverage Policy Number ..... 0299**

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## Hyperlink to Related Coverage Policies

- Genetic Counseling
- Genetic Disease Screening Panels
- Genetic Testing of Heritable Disorders
- Preimplantation Genetic Diagnosis
- Stem-Cell Transplant for Metabolic Disorders

### 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 Niemann-Pick disease (NPD) as medically necessary when ANY of the following criteria are met:**

- For diagnostic testing in **EITHER** of the following situations:
  - in symptomatic individuals with clinical features suggestive of NPD and abnormal biochemical testing, but for whom conventional studies have been completed and a definitive diagnosis remains uncertain
  - in individuals with nondiagnostic or variant biochemical findings when confirmation by molecular genetic testing is necessary to confirm the diagnosis.
- For carrier testing of at-risk family members (first- or second-degree\* relatives) once the mutations have been identified in the proband and the individual has both the capacity and desire to reproduce.
- For prenatal testing or preimplantation genetic diagnosis (PGD) when two disease-causing mutations in the gene have been identified in an affected family member.

\*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 genetic testing for Niemann-Pick disease in the general population, because such screening is considered not medically necessary or of unproven benefit.**

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## General Background

Niemann-Pick disease (NPD) is an autosomal recessive disorder caused by various allelic/gene mutations. There are thought to be six types of NPD (i.e., A, B, C, D, E, F), based on the genetic cause and the signs and symptoms exhibited by the patient; however, according to Vanier (2002), classifying type D as a distinct entity is no longer justified. Little is known about the rarer Types E and F (National Institutes of Health [NIH], 2009; National Center for Biotechnology Information [NCBI], 2009; NCBI, 2007).

NPD types A (NP-A) and B (NP-B) are caused by mutations of gene SMPD1, characterized by abnormal lipid metabolism, due to a deficiency of acid sphingomyelinase (ASM) activity. Lipid, mainly sphingomyelin, accumulates in reticuloendothelial and other cell types throughout the body. The accumulation of lipids in the ganglion cells of the central nervous system leads to cell death (NCBI, 2009). The clinical phenotype ranges from a severe infantile form with neurologic degeneration resulting in death usually by 3 years of age (i.e., Type A) to a later-onset nonneurologic or visceral form (i.e., Type B) that is compatible with survival into adulthood. Forms intermediate to these two extremes occur as a continuum of neurologic findings in those who survive early childhood (McGovern, 2009). Type A occurs in all races and ethnicities, but higher rates are seen in the Ashkenazi (Eastern European) Jewish population (NIH, 2009).

Niemann-Pick disease type C (NP-C), subdivided into types C1 (NP-C1) and C2 (NP-C2), and NPD type D (NP-D) are lipid storage disorders and involve disruption in the transport of cholesterol between cells, characterized by progressive neurodegeneration. NP-D and NP-C1 are caused by mutations of the same gene (i.e., NPC1); NP-C2 is caused by mutations of a separate gene (i.e., NPC2). NP-C has a highly variable clinical phenotype. In the classic childhood-onset form, development is normal for the first several years, with the appearance of symptoms between two to four years. In the childhood-onset form, death usually occurs at age five to 15. Adult-onset forms, with insidious onset and slower progression, have also been reported (NCBI, 2009, NCBI, 2007). Type C Niemann-Pick disease has been reported in all ethnic groups but it is most common among Puerto Ricans of Spanish descent, while Type D has only been found in the French Canadian population of Nova Scotia. (NIH, 2009).

There is currently no cure for NPD. Treatment is primarily supportive in nature, and varies with symptoms and type of disease.

### Clinical Diagnosis

The diagnosis of NPD types A and B can be made reliably by measurement of ASM enzyme activity in peripheral blood lymphocytes or cultured skin fibroblasts. When compared to controls, affected individuals typically have less than 10% residual enzyme activity (McGovern and Schuchman, 2006). Definitive diagnosis of NP-C requires demonstration of abnormal intracellular cholesterol homeostasis in cultured fibroblast by biochemical testing and positive filipin staining (Patterson, 2006).

Molecular genetic testing is performed to confirm the diagnosis in individuals with nondiagnostic or variant biochemical findings. Clinical uses of molecular genetic testing for all types of NPD include confirmation of the diagnosis, carrier testing and prenatal diagnosis. Methods of molecular genetic testing for NPD include mutation analysis and sequence analysis. Sequence analysis of the SMPD1 gene detects mutations in 99% of individuals with enzymatically confirmed ASM deficiency. Three mutations of the SMPD1 gene account for about 90% of the NP-A disease-causing alleles in the Ashkenazi Jewish population. One mutation accounts for 90% of the NP-B mutant alleles in individuals from the Maghreb region of North Africa, 100% of the mutant alleles in

individuals from Grand Canaria Island, and about 20–30% of the mutant alleles in Americans of North African descent (McGovern and Schuchman, 2006).

One NP-C1 mutation accounts for 15–20% of disease-causing alleles in Western Europe and the United States (Millat, 2005). Detection rates using sequence analysis may be comparable to those found by mutation scanning, which has identified NP-C1 mutations in 90% and NP-C2 mutations in 4% of individuals. Most individuals with NP-C1 are compound heterozygotes with mutations unique to their families (Greer, 1998).

### **Testing Strategy**

Although there is no cure for NPD, genetic testing for NPD allows an opportunity for supportive medical treatment and reproductive planning, as well as the opportunity for preparation of the family for an individual with this disorder.

**Diagnosis:** Biochemical testing establishes the diagnosis of ASM deficiency (e.g., NP-A, NP-B) when peripheral blood lymphocytes or cultured skin fibroblasts demonstrate enzyme activity <10% of controls. Molecular genetic testing is used to confirm the diagnosis of ASM deficiency.

Biochemical testing demonstrating abnormal intracellular cholesterol homeostasis in cultured fibroblasts is the mainstay of diagnosis for NP-C1 and NP-C2 and may be supported by ultrastructural changes on skin or rectal biopsy. Molecular genetic testing is used primarily to confirm the diagnosis in individuals with variant biochemical findings.

**Carrier Detection:** Biochemical testing is unreliable in defining the heterozygous state in all types of NPD because of significant overlaps with the findings within controls. DNA analysis of the SMPD1, NP-C1 or NP-C2 genes may be used for carrier testing of at-risk family members if the mutations have been identified in the proband.

**Prenatal Testing:** Biochemical prenatal testing is available for NP-C when the proband has a classic biochemical phenotype (not a variant phenotype which requires a more complex assay that is not applicable to prenatal diagnosis), and for NP-A and NP-B by using fetal cells obtained either by amniocentesis at age 15–18 weeks' gestation or by chorionic villus sampling at about age 12 weeks' gestation (Patterson, 2006). Prenatal molecular genetic testing for all types of NPD is possible by analysis of DNA of fetal cells obtained either by amniocentesis at age 15–18 weeks' gestation or by CVS at about age 12 weeks' gestation when two disease causing alleles have been identified in an affected family member.

**Preimplantation Genetic Diagnosis (PGD):** PGD is available for families in which the disease-causing mutations have been identified in an affected family member.

### **Professional Societies/Organizations**

**American College of Obstetricians and Gynecologists (ACOG):** ACOG (2009) published Committee Opinion Paper Number 442 (Replaces No. 298, August 2004), which notes that individuals of Ashkenazi Jewish descent may inquire about the availability of carrier screening for disorders, including Niemann-Pick Type A. When only one partner is of Ashkenazi Jewish descent, that individual should be screened first. The Opinion also notes if it is determined that this individual is a carrier, the other partner should be offered screening. Individuals with a positive family history of one of these disorders should be offered carrier screening for the specific disorder and may benefit from genetic counseling. When both partners are carriers of one of these disorders, they should be referred for genetic counseling and offered prenatal diagnosis.

**American College of Medical Genetics (ACMG):** On behalf of the Professional Practice and Guidelines Committee, the ACMG notes that Niemann-Pick disease is a test for which carrier screening should be offered.

### **Summary**

Niemann-Pick disease (NPD) is an inherited autosomal recessive disorder characterized by varying degrees of disability. The primary goals of genetic testing for NPD are for confirmation of the diagnosis in order to establish a supportive treatment plan and for reproductive planning with carrier testing, prenatal diagnosis, and preimplantation genetic diagnosis (PGD).

## 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 (i.e., DNA or RNA)
83892	Molecular diagnostics; enzymatic digestion, each enzyme treatment
83894	Molecular diagnostics; separation by gel electrophoresis (e.g., agarose, polyacrylamide), each nucleic acid preparation
83898	Molecular diagnostics; amplification, target, each nucleic acid sequence
83900	Molecular diagnostics; amplification, target, multiplex, first 2 nucleic acid sequences
83901	Molecular diagnostics; amplification, target, multiplex, each additional nucleic acid sequence beyond 2 (List separately in addition to code for primary procedure)
83904	Molecular diagnostics; mutation identification by sequencing, single segment, each segment
83905	Molecular diagnostics; mutation identification by allele specific transcription, single segment, each segment
83912	Molecular diagnostics; interpretation and report

<b>HCPCS Codes</b>	<b>Description</b>
S3849	Genetic testing for Niemann-Pick disease

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
272.7	Lipidoses

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

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## Policy History

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<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	3/15/2008	0299	Genetic Testing for Niemann-Pick Disease

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