



# 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 Stem-Cell Transplantation for Inherited Metabolic Disorders**

**Effective Date ..... 7/15/2011**  
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Transplant Donor Charges  
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### INSTRUCTIONS FOR USE

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## Coverage Policy

**CIGNA covers allogeneic hematopoietic stem-cell transplantation (HSCT) from a human leukocyte antigen (HLA)-matched donor (i.e., at least five of six match of the HLA-A, HLA-B, and HLA-DRB1 antigens ) as medically necessary for the treatment of ANY of the following inherited metabolic disorders:**

- Hurler syndrome
- Maroteaux-Lamy syndrome
- Childhood-onset cerebral X-linked adrenoleukodystrophy
- Gaucher disease Type 3 which has failed enzyme replacement therapy
- Krabbe disease in asymptomatic newborns transplanted in the neonatal period
- Late-onset Krabbe disease
- Late infantile and early juvenile metachromatic leukodystrophy (MLD) in asymptomatic patients
- Late juvenile and early adult MLD in patients with adequate neuropsychological function and independence in activities of daily living

**CIGNA does not cover HSCT for the treatment of any other inherited metabolic disorder because it is considered experimental, investigational or unproven.**

## General Background

Inherited metabolic disorders, also called inborn errors of metabolism or congenital metabolic disorders are rare individually, but common as a group. At this time several hundred syndromes have been identified. Most have several forms that vary in age of onset, clinical severity and, often, mode of inheritance. They include a spectrum of disorders caused by a disruption in the metabolic process, primarily caused by deficiency of specific enzymes necessary to complete metabolism or to synthesize essential compounds. Incomplete metabolism results in the inappropriate deposition of metabolites in tissues and organs, causing damage.

There are several types of disorders, including lysosomal storage diseases (e.g., mucopolysaccharidosis [MPS], mucopolididosis); glycogen storage diseases, disorders of carbohydrate metabolism; disorders of amino acid metabolism; organic acidemias; disorders of fatty acid metabolism (e.g., lipidosis), and mitochondrial disorders. Conditions can vary from an acute life-threatening disease to progressive neurological degeneration which is ultimately fatal.

Most of the diseases are inherited in an autosomal dominant pattern, but some may be X-linked (i.e., carried on the X chromosome). Some of these disorders can be treated with diet or enzyme replacement therapy, but many have no cure. Hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment option for several of these disorders.

### **Stem-Cell Transplantation**

Stem-cell transplantation refers to transplantation of HSCs into an individual. HSCT can be either autologous (using the patient's own stem cells) or allogeneic (using stem cells from a donor).

In allogeneic HSCT it is preferable for donors to have a human leukocyte antigen (HLA) type that is identical to the recipient. Matching is performed on the basis of variability at three or more loci of the HLA gene (e.g., HLA-A, HLA-B, HLA-DRB1). Alternative donor sources are being evaluated for individuals with aplastic anemia and Fanconi anemia who do not have an HLA-identical donor. As HLA variability increases, transplant-related morbidity and mortality, including graft rejection and graft-versus-host disease, also increase. Long-term survival after mismatched related donation is inferior to genotypically matched donor transplantation (Young, 2008).

The use of allogeneic HSCT to treat inherited metabolic disorders is based on the theory that replacement of the enzyme-deficient bone marrow with normal donor bone marrow will result in normal cells circulating and secreting the missing enzymes, thereby correcting the defect. The goal is to stabilize the disease process and prolong survival. There is variable benefit to different organ systems. Organs such as the liver and spleen frequently respond favorably; central nervous system improvement occurs slowly because of the slower replacement of microglia with donor-derived cells. HSCT has little effect on bone disease, likely because the replaced enzyme does not penetrate the bone (Peters, 2003).

HSCT has been suggested as an appropriate treatment option for Hurler syndrome, Maroteaux-Lamy syndrome, adrenoleukodystrophy (ALD), Gaucher syndrome, Krabbe disease, and Metachromatic dystrophy (MLD). Given the rare incidence of these disorders, randomized clinical trials are not likely and few prospective studies are available in the peer-reviewed, published scientific literature. Although data are not robust, allogeneic HSCT is considered an acceptable treatment option for these indications.

In a retrospective analysis of the Cord Blood Transplantation Study, Martin et al. (2006) reported improved overall survival (OS) compared with the natural course of the disease in a cohort of 69 individuals with various lysosomal and peroxisomal storage disorders who received umbilical cord blood as a donor source for allogeneic HSCT. One-year OS was 72%. Long-term survival was 68%, with a median follow-up of 24.5 months.

A discussion of some of the more common inherited metabolic disorders follows:

### **Mucopolysaccharidoses (MPS):**

- **Hurler Syndrome (MPS-IH):** Hurler syndrome is caused by a deficiency of the enzyme alpha-L-iduronase. Allogeneic HSCT may improve some of the symptoms of the disease, including the preservation of cognitive function and development in the normal range, and prolong survival (National Institutes of Neurological Diseases and Stroke [NINDS], 2011a;h; Sauer, 2009; Hansen, 2008; National Marrow Donor Program [NMDP], 2008; Grewel, 2005; Grigull, 2005; Braunlin, 2003; Malatack, 2003).

The clinical success of hematopoietic stem-cell transplantation (HSCT) depends on the age of the child at transplantation, the degree of clinical involvement, the child's cardiopulmonary status and neurologic development, the type of donor, and the ability to achieve stable engraftment. To help prevent developmental delays, a HSCT generally should be performed at a very young age, preferably before age two.

Although no randomized clinical trials have been reported, several case series have reported improved symptoms and overall survival outcomes with allogeneic HSCT. This therapy is considered a reasonable treatment option for Hurler syndrome.

- **Scheie Syndrome (MPS-IS):** This syndrome, also caused by the absence of the enzyme  $\alpha$ -L-iduronidase, can be considered a mild form of Hurler syndrome. Enzyme replacement therapy is available to treat this disorder. As symptoms are mild and lifespan is into the fourth or fifth decade, and the risks of HSCT may outweigh any benefit, this therapy is not indicated in the treatment of Scheie syndrome (Peters, 2003).

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of Scheie syndrome (MPS-IS). The role of this therapy has not yet been established for this indication.

- **Hunter Syndrome (MPS-II):** Hunter syndrome is an X-linked disease, causing a deficiency of the enzyme iduronate sulfatase. HSCT has not demonstrated amelioration of central nervous system (CNS) disease (Peters, 2003; Malatack, 2000).

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of Hunter syndrome (MPS-II). The role of this therapy has not yet been established for this indication.

- **Sanfilippo Syndrome (MPS-III):** This is the most common form of MPS. There are four subtypes, A through D, caused by four unique enzyme deficiencies. There is no specific treatment for this disorder. Individuals with this syndrome have not been shown to benefit from HSCT. Patients with Type IIIA were shown to have progression of CNS deterioration at the same or faster rate than before transplantation (Shapiro, 1995).

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of Sanfilippo syndrome (MPS III). The role of this therapy has not yet been established for this indication.

- **Morquio Syndrome (MPS-IV):** There are two types, caused by a deficiency of the enzymes galactosamine-6-sulphatase (Type IVA) and beta-galactosidase (Type IVB). Individuals with MPS IV exhibit severe dysostosis multiplex, but typically have preserved intellectual function. At this time, there is no role for HCT since skeletal deformities can not be helped to any appreciable extent by HSCT (Malatack, 2003; Peters, 2003).

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of Morquio syndrome (MPS IV). The role of this therapy has not yet been established for this indication.

- **Maroteaux-Lamy Syndrome (MPS-VI):** This syndrome is an uncommon type of MPS, caused by a deficiency of the enzyme N-acetylglucosamine-4-sulphatase. Allogeneic hematopoietic stem-cell transplantation (HSCT) has been used successfully to treat MPS IV in some individuals (Malatack, 2003; Lee, 2000; Alvaro, 1998). Patients demonstrated successful engraftment and improved enzymatic functioning post transplantation.

In guidelines provided in a joint statement from the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group (Peters, 2003), reported benefits of allogeneic HSCT for the treatment of Maroteaux-Lamy syndrome include enzymatic and biochemical correction, resolution of hepatosplenomegaly, stabilization of cardiopulmonary function and improvement of visual acuity and joint mobility.

As this is a rare disorder and generally fatal by early adulthood, it is unlikely that additional evidence in the form of randomized clinical trials will become available. Based on the improvement of outcomes found in

case reports, allogeneic hematopoietic stem-cell transplantation (HSCT) is a reasonable treatment option for the Maroteaux-Lamy syndrome.

- **Sly Syndrome (MPS-VII):** This extremely rare syndrome is caused by a deficiency of the enzyme beta-glucuronidase. The use of HSCT for the treatment of Sly syndrome has been shown to be effective in animal models; however, experience with this therapy in humans is limited (Sands, 1995).

Data are lacking regarding the safety and effectiveness of this therapy for the treatment of Sly syndrome. The role of HSCT has not yet been established for this indication.

**Mucopolysaccharidoses:** The mucopolysaccharidoses (ML) (i.e., types I-IV) result from enzyme deficiencies leading to abnormal storage of carbohydrates, lipids and proteins in cellular structures called lysosomes; thus, these diseases are also known as lysosomal storage diseases. This abnormal storage can lead to significant organ damage. According to the National Institute of Neurological Disorders and Stroke ([NINDS], 2010i), there is currently no cure for ML and treatment is supportive.

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of the mucopolysaccharidoses. The role of this therapy has not yet been established for this indication.

**Lipidoses:** Lipidoses are disorders of lipid metabolism that lead to abnormal accumulation of fats in certain body tissues.

- **Adrenoleukodystrophy:** Adrenoleukodystrophy and adrenomyeloneuropathy are rare X-linked recessive metabolic disorders that result in the accumulation of very long-chain fatty acids in the nervous system, adrenal gland, and testes. Damage to the myelin sheath, an insulating membrane which surrounds nerve cells in the brain is a characteristic finding.
- According to the NINDS (2009 b), transplantation can provide long-term benefit to boys who have early evidence of X-ALD, but the procedure carries risk of mortality and morbidity and is not recommended for those whose symptoms are already severe or who have the adult-onset or neonatal forms.

Several uncontrolled case series and retrospective reviews demonstrate improved survival outcomes with allogeneic HSCT (Beam, 2007; Mahmood, 2007; Peters, 2004; Shapiro, 2000). Five-year survival probabilities were 54%–56%. Peters et al. (2004) evaluated the outcomes of HSCT provided to 126 boys with childhood cerebral adrenoleukodystrophy. The five- and eight-year survival probabilities were 56%, compared to 40% five-year survival rate for boys with cerebral adrenoleukodystrophy who did not receive transplantation.

As this is a rare disorder and generally fatal by early adolescence, it is unlikely that additional evidence in the form of randomized clinical trials will become available. Based on the improvement of outcomes found in multicenter case reports and retrospective reviews, allogeneic HSCT is a reasonable treatment option for childhood-onset cerebral X-linked adrenoleukodystrophy.

- **Fabry's Disease:** Fabry's disease is an X-linked deficiency of the enzyme alpha-galactosidase-A, leading to incomplete lipid metabolism and the accumulation of glycolipid in many tissues. According to the NINDS (2010b), treatment is primarily supportive.

Data are lacking regarding the safety and effectiveness of HSCT for the treatment of Fabry's disease. The role of this therapy has not yet been established for this indication.

- **Gaucher Disease:** Gaucher disease is a disorder of lipid metabolism, resulting in an accumulation of abnormal glucocerebrosides in reticuloendothelial cells. According to the NINDS (2008d), there are three forms, types I-III.

Allogeneic hematopoietic stem-cell transplantation (HSCT) has been studied in Gaucher disease: Type I disease responds to HSCT with normalization of splenic function, Type II disease responds to HSCT with resolution of peripheral but not central nervous system (CNS) symptoms of the disease, and Type III

disease responds to HSCT with reversal of peripheral organ symptoms and stabilization and slowing of neurological deterioration (Malatack, 2003; Peters, 2003).

In guidelines provided in a joint statement from the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group, HSCT may be indicated in patients with Type III Gaucher disease who have neurological deterioration or pulmonary compromise while on enzyme replacement therapy (Peters, 2003). The National Institute of Neurological Disorders and Stroke ([NINDS], 2009d) notes that bone marrow transplantation can reverse the non-neurological effects of Type 1 disease, but it carries a high mortality rate due to imperfect donor matches.

- **Krabbe Disease:** Krabbe disease, also called galactosylceramide lipidosis or globoid-cell leukodystrophy, is the deficiency of the enzyme galactocerebroside beta-galactosidase that causes progressive destruction of myelin and the nervous system. The optimal treatment for Krabbe disease is still being developed. The NINDS (2008c) notes that bone marrow transplantation has been shown to benefit mild cases early in the course of the disease.

Escolar et al. (2005) compared the results of 11 asymptomatic newborns and 14 symptomatic children, all with infantile Krabbe disease who underwent transplantation using unrelated donor umbilical cord blood. Rates of engraftment and survival for the symptomatic children were 100% and 43%, respectively, at a median follow-up of 3.4 years. Survival among the asymptomatic newborns was better than among the symptomatic infants ( $p=0.01$ ). The newborns who were transplanted before symptoms developed had a positive alteration of disease; however, children who underwent transplantation after the development of symptoms showed very little improvement in symptoms.

- **Metachromatic Leukodystrophy:** Metachromatic leukodystrophy (MLD) is caused by a deficiency of the enzyme arylsulfatase A, causing metachromatic lipids to accumulate in the white matter of the central nervous system, peripheral nerves, kidney, spleen and other visceral organs. MLD includes late infantile, juvenile, and adult subtypes.

Guidelines produced by a collaboration of the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group recommend hematopoietic stem-cell transplantation (HSCT) in patients with MLD who are pre-symptomatic or who have good neuropsychological function and independence in activities of daily living (Peters, 2003). NINDS (2010h) notes that bone marrow transplantation may delay progression of the disease in some cases.

Although data are not robust, several case series have reported improved symptoms and overall survival outcomes with allogeneic HSCT. This therapy is considered a reasonable treatment option for selected individuals with metachromatic leukodystrophy.

**Niemann-Pick Disease:** There are thought to be six types of this disease (i.e., A, B, C, D, E, F), which is characterized by abnormal lipid metabolism. Treatment is primarily supportive in nature, and varies with symptoms and type of disease.

Data regarding the safety and effectiveness of allogeneic HSCT are limited to small, uncontrolled case reports. The role of this therapy has not yet been established for this indication.

- **Sandhoff Disease:** Sandhoff disease is a lysosomal storage disorder, causing severe neurodegeneration. It is considered by some to be a variant of Tay-Sachs disease. NINDS (2007k) notes that there is no specific treatment for this disorder other than supportive care.

Data are lacking regarding the safety and effectiveness of allogeneic HSCT for the treatment of Sandhoff disease. The role of this therapy has not yet been established for this indication.

- **Tay-Sachs Disease:** Tay-Sachs disease is a severe deficiency of hexosaminidase A, which results in the inappropriate storage of GM<sub>2</sub> ganglioside in the central nervous system (CNS). The National Institute of

Neurological Disorders and Stroke [NINDS], 2010c; 2007i) notes that supportive treatment is appropriate for individuals with this disease. Stem-cell transplantation has been explored but has not been shown to reverse or slow damage to the central nervous system. Guidelines produced by a collaboration of the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group indicate that HSCT does not appear to successfully treat any form of GM<sub>2</sub> gangliosidosis, including Tay-Sachs disease (Peters, et al., 2003).

Data are lacking in the published peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of Tay-Sachs disease. The role of this therapy has not yet been established for this indication.

- **Wolman Disease:** According to the NINDS (2010a), Wolman disease results from lysosomal acid lipase deficiency, causing accumulation of cholesteryl esters and triglycerides in the cells and tissues. Also according to the NINDS, there is no treatment for this disease.

Tolar et al. (2009) reported on the results of four patients with Wolman disease who received allogeneic HSCT. Two patients survived four years and eleven years, respectively. Survivors showed resolution of diarrhea within weeks after engraftment, normalized hepatic function, improved hepatosplenomegaly, and in one patient normal adrenal function. The older patient had normal adaptive functions but mild to moderate neurocognitive deficiencies thought to be secondary to treatment and other medical problems. The younger patient had age appropriate neurodevelopmental and adaptive abilities.

Data are limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of allogeneic HSCT for this disease. The role of this therapy has not yet been established for this indication.

### **Contraindications**

Many factors affect the outcome of a tissue transplant. The patient selection process is designed to obtain the best result for each patient. Relative contraindications to HSC transplantation include, but are not limited to:

- poor cardiac function (ejection fraction less than 45%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal)
- poor renal function (creatinine clearance less than 50 mL/min)
- poor pulmonary function (diffusion capacity [DLCO] less than 60% of predicted)
- presence of human immunodeficiency virus or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1)

### **Professional Societies/Organizations**

**National Marrow Donor Program (NMDP), International Bone Marrow Transplant Registry, Working Party on Inborn Errors of the European Bone Marrow Transplant Group:** In guidelines provided in a joint statement from the National Marrow Donor Program, the International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group, Peters (2003) noted that HSCT may be indicated in patients with Type 3 Gaucher disease who have neurological deterioration or pulmonary compromise while on enzyme replacement therapy. The Guidelines also noted that HSCT does not appear to successfully treat any form of GM<sub>2</sub> gangliosidosis, including Tay-Sachs disease (Peters, 2003).

**National Institute of Neurological Disorders and Stroke (NINDS):** The NINDS supports the use of allogeneic HSCT as a treatment for some patients with Krabbe disease (2010f).

**International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I:** Muenzer et al. (2009) published Guidelines which noted when it is successful, hematopoietic stem cell transplantation (HSCT) using either bone marrow or umbilical cord stem cells can prevent and/or reverse many but not all of the clinical features of severe MPS I." It must be performed early in the disease course, before developmental deterioration begins.

### **Summary**

Although data are not robust, the published peer-reviewed scientific literature supports the safety and effectiveness of allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of selected inherited metabolic disorders.

## Coding/Billing Information

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

**Covered when medically necessary when used to report allogeneic bone marrow or blood-derived stem-cell procedures:**

<b>CPT<sup>®*</sup> Codes</b>	<b>Description</b>
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

<b>HCPCS Codes</b>	<b>Description</b>
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150 <sup>†</sup>	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days or pre-and post-transplant care in the global definition

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
272.7	Lipidoses
277.5	Mucopolysaccharidosis
277.86	Peroxisomal disorders
330.0	Leukodystrophy

**Experimental/Investigational/Unproven/Not Covered when used to report bone marrow or blood-derived stem-cell procedures for any other inherited metabolic disorder:**

<b>CPT* Codes</b>	<b>Description</b>
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation
38240	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic
38242	Bone marrow or blood-derived peripheral stem cell transplantation; allogeneic donor lymphocyte infusions

<b>HCPCS Codes</b>	<b>Description</b>
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem cell transplantation, allogeneic
S2150†	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days or pre-and post-transplant care in the global definition

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
330.1	Cerebral lipidoses

\*Current Procedural Terminology (CPT®) © 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	7/15/2008	0386	Stem-Cell Transplant for Inherited Metabolic Disorders

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