Cigna Medical Coverage Policy

Subject **Stem-Cell Transplantation for Inherited Metabolic Disorders**

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Coverage Policy

Cigna covers allogeneic hematopoietic stem-cell transplantation (HSCT) from an appropriately-matched human leukocyte antigen (HLA)-matched donor as medically necessary for the treatment of ANY of the following inherited metabolic disorders:

- Alpha mannosidosis
- Cerebral X-linked Adrenoleukodystrophy
- Farber disease type 2/3
- Gaucher disease types I and 3
- Hunter syndrome (MPS-II), attenuated form
- Hurler syndrome (MPS-IH)
- Krabbe disease (globoid leukodystrophy, GLD)
- metachromatic leukodystrophy (MLD)
- Maroteaux-Lamy syndrome (MPS-VI)
- Sly syndrome (MPS VII)
- Wolman disease
- Niemann-Pick disease type B

Cigna does not cover HSCT for the treatment of ANY of the following inherited metabolic disorders because it is considered experimental, investigational or unproven:

- Scheie syndrome (MPS-IS)
- Niemann-Pick disease type A

- Hunter syndrome (MPS-II), severe form
- Sanfilippo disease (MPS-III)

General Background

Inherited metabolic disorders, also called inborn errors of metabolism or congenital metabolic disorders are rare individually, but common as a group. 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], mucolipidosis); 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. Age of onset, clinical severity and mode of inheritance may vary within each disorder type. Most inherited metabolic disorders affect multiple organs and involve both the central and peripheral nervous systems. They are progressive in nature and frequently fatal in childhood from a combined effect of accumulation of toxic substrate(s) as well as a deficiency of the product of the enzyme reaction. Conditions can vary from an acute life-threatening disease to progressive neurological degeneration, which is ultimately fatal.

The majority of these 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. Allogeneic hematopoietic stem-cell transplantation (HSCT) has been proposed as a treatment option for several of these disorders. HSCT may provide a constant source of enzyme replacement through the engraftment of donor cells. In addition, the donor cells are not impeded by the blood–brain barrier allowing for enzyme delivery to the central nervous system (Prasad, 2008).

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). There are scarce data in the published peer-reviewed scientific literature regarding the safety and effectiveness of autologous HSCT for the treatment of inherited metabolic disorders.

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).

An enzymatically matched normal sibling is the preferred donor for individuals with inherited metabolic disorders; however, unrelated cord blood (CB) has been used with increasing frequency as a graft source for those without a matched sibling donor. CB offers several potential advantages compared with bone marrow or peripheral blood for HSCT, including better availability, greater tolerance for HLA mismatch, lower incidence and severity of graft-versus host disease (GVHD), and reduced likelihood of transmitting viral infections (Boelens, 2010).

Allogeneic HSCT has been suggested as an appropriate treatment option for alpha mannosidosis, cerebral X-linked adrenoleukodystrophy, Farber disease type 2/3, Gaucher disease types I and 3, Hunter syndrome (MPS-II), attenuated form, Hurler syndrome (MPS-IH), Krabbe disease (globoid leukodystrophy, GLD), Maroteaux-Lamy syndrome (MPS-VI), metachromatic leukodystrophy (MLD), Wolman syndrome, Sly syndrome (MPS VII, and Niemann-Pick type B. 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.

On behalf of the Agency for Healthcare Research and Quality (AHRQ), Ratko et al. (2012) published a narrative review/systematic review evaluating the comparative benefits and harms of HSCT versus standard therapies or disease natural history in children with malignant solid tumors, inherited metabolic diseases, and autoimmune diseases. The authors noted evidence was insufficient for most pediatric indications.

The overall grade of evidence strength was classified into the following four categories: high: further research is very unlikely to change confidence in the estimate of effect, moderate: further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate of effect, low: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate, and insufficient: any estimate of effect is very uncertain.

Regarding the effect of HSCT compared to standard therapy, symptom management, or natural disease progression for metabolic disorders in children, AHRQ noted the following:

- Evidence suggesting a benefit of HSCT for overall survival:
  - Wolman's disease compared to disease natural history (high strength)
- Evidence suggesting a benefit of HSCT for neuromuscular symptoms:
  - Farber's disease Type 2/3 compared to symptom management and disease natural history (high strength)
- Evidence suggesting a benefit of HSCT for neurocognitive symptoms:
  - Infantile ceroid lipofuscinosis compared to symptom management or disease natural history (low strength)
  - Attenuated form of MPS (mucopolysaccharoidosis) II (Hunter's disease) compared to enzyme-replacement therapy (ERT) (low strength)
- Evidence suggesting a benefit of HSCT for neurodevelopmental symptoms:
  - Attenuated and severe forms of MPS II (Hunter's disease) compared to ERT (both low strength)
- Evidence suggesting no benefit of single HSCT for overall survival:
  - Niemann-Pick Type A compared to symptom management (low strength)
- Evidence suggesting no benefit of HSCT for neurodevelopmental symptoms:
  - Gaucher Type III compared to ERT (low strength)
  - Juvenile form of GM1, juvenile Tay-Sachs compared to symptom management or disease natural history (both low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
- Evidence suggesting no benefit of HSCT for neurocognitive symptoms:
  - Severe form of MPS II (Hunter's disease) compared to symptom management or disease natural history (low strength)
  - MPS III (Sanfilippo) compared to symptom management, substrate reduction therapy, or disease natural history (low strength)
  - Gaucher Type III compared to ERT (moderate strength)
- Insufficient evidence to draw conclusions on the benefit or harm on overall survival with single allogeneic HSCT compared with symptom management and/or disease natural history for the following indications:
  - mucolipidosis II (I-cell disease)
  - Gaucher disease type II
  - Niemann-Pick type C
  - MPS IV (Morquio syndrome)
  - aspartylglucosaminuria
  - Fabry's disease
  - β-mannosidosis
  - mucolipidosis III
  - mucolipidosis IV
  - glycogen storage disease type II (Pompe disease)
  - Salla disease
  - Adrenomyeloneuropathy
  - galactosialidosis (type unspecified)

- Sandhoff disease (type unspecified)
- Farber's disease type I
- infantile and juvenile GM1
- gangliosidosis
- infantile and juvenile Tay-Sachs
- juvenile ceroid lipofuscinosis

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 allogeneic HSCT. One-year OS was 72% and long-term survival was 68%, with a median follow-up of 24.5 months.

Contraindications to Transplantation
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)

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

Mucopolysaccharidoses (MPS): MPS are a group of disorders caused by single-gene defects leading to a deficiency in one of the 11 lysosomal enzymes needed to metabolize glycosaminoglycans, formerly called mucopolysaccharides. As glycosaminoglycans accumulate in the cells, blood, and connective tissues, progressive damage to the skeletal structure and multiple organ systems occurs (Ratko, 2012). Small patient numbers and lack of detailed functional outcome data hamper the development of specific therapy guidelines (Boelens, 2010).

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 prolongation of survival (Ratko, 2012; National Institutes of Neurological Diseases and Stroke [NINDS], 2014b; Boelens, 2010; Prasad, 2009; Sauer, 2009; Hansen, 2008; National Marrow Donor Program [NMDP], 1996-2014; Grewel, 2005; Grigull, 2005; Braunlin, 2003; Malatack, 2003). Data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and the European Group for Blood and Marrow Transplant (EBMT) indicate that > 500 allogeneic HSCTs have been performed worldwide for children with MPS IH since 1980, making it the most commonly transplanted IMD. Some disease manifestations can persist or even progress following HSCT. Although cerebral damage already present before HSCT seems to be irreversible, successful HSCT is able to prevent progressive psychomotor deterioration and improve cognitive function (MPSS, 2011; Boelens, 2010; Prasad, 2009). Due to the morbidity and mortality associated with HSCT, it is currently recommended primarily for children with severe MPS I who may experience some reduction in CNS manifestations (Clark, 2013). Scheie syndrome (IS) is the mildest form of the disease with lifespan in the fourth and fifth decades. Enzyme replacement therapy is considered the first-line treatment. The risks of HSCT may outweigh any benefit, and it is not indicated in the treatment of Scheie syndrome (Peters, 2003).

Literature Review
Although no randomized clinical trials have been reported, several case series, case reports, and retrospective reviews have reported improved symptoms and overall survival outcomes with allogeneic HSCT. According to the National Marrow Donor Program ([NMDP], 2000-2014), 42 allogeneic HSCT were facilitated by the NMDP with a five-year overall survival (OS) of approximately 65%. Data from a narrative review by Ratko et al. (2012) suggest a favorable risk-benefit profile for HSCT for severe cases with stable cardiopulmonary function, if the disease is diagnosed ≤ two years and the development quotient is ≥ 70. Improvements include achievement of normal enzyme activity levels in 67% of patients, and resolution of hepatosplenomegaly. Normal or near normal

intellectual development was reported in 64% of cases. The data also suggest that HSCT results in benefit for individuals with attenuated MPS-IH in which diagnosis is made at > age two.

Professional Societies/Organizations
International Consensus Panel on the Management and Treatment of Mucopolysacchardosis 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.

The National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which note that HSCT is recommended for severe cases with stable cardiopulmonary function, if the disease is diagnosed at 2 years of age or younger and the developmental quotient (DQ) is 70 or greater. HSCT can also be considered in rare attenuated cases in which the diagnosis is made at older than 2 years of age and the DQ is 70 or greater"

Summary for Hurler Syndrome: Although data are not robust, this therapy is considered a standard treatment option for severe Hurler syndrome (MPS IH).

Hunter Syndrome (MPS II): Hunter syndrome is an X-linked recessive disorder, caused by deficiency of the enzyme iduronate sulfatase. HSCT has not demonstrated amelioration of central nervous system (CNS) disease (Peters, 2003; Malatack, 2000). Despite benefits in the somatic features of the disease, the role of HSCT in MPS II remains controversial because of lack of convincing evidence of neurocognitive benefit (Boelens, 2009).

Literature Review
Randomized controlled trial data are lacking and prospective case series reports are limited in the published peer-reviewed scientific literature for this indication. Although HSCT could provide sufficient enzyme activity to slow or stop the progression of the disease, no controlled clinical studies have been conducted in MPSII. In a recent narrative review/systematic review of eight case reports and six case series, Radko et al. (2012) found low strength evidence on neurodevelopmental outcomes which suggests equivalent benefit with single HSCT compared to enzyme replacement therapy (ERT) for severe and attenuated forms of Hunter syndrome (MPS II). Low strength evidence on neurocognitive outcomes suggests no benefit with single HSCT compared to symptom management /natural history for severe MPS II. Low strength evidence on neurocognitive outcomes suggests benefit with single HSCT compared to ERT for attenuated MPS II.

Summary for Hunter Syndrome: Although the data are not robust allogeneic HSCT appears to improve neurodevelopmental and neurocognitive functioning in selected individuals with attenuated Hunter syndrome (MPS II).

Sanfilippo Syndrome (MPS-III): This is the most common form of MPS, with 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. According to Peters (2003), successful HSCT performed early in the disease course does not seem to ameliorate neuropsychological deterioration significantly. Patients with Type IIIA were shown to have progression of central nervous system (CNS) deterioration at the same or faster rate than before transplantation (Shapiro, 1995).

Literature Review
In a recent narrative review/systematic review by Ratko et al. (2012), one case report and four case series were reviewed. Low strength evidence on neurocognitive and neurodevelopmental outcomes suggests no benefit with single HSCT compared to symptom management, substrate reduction therapy, or disease natural history for MPS III.

In a study published by Prasad et al. (2008) 159 children with inherited metabolic diseases underwent HSCT using unrelated cord blood as a donor source. Nineteen patients had Sanfilippo disease. The estimated probability of overall survival (OS) at 180 days, one-, three-, and five-years was 79.0%, 71.8%, 62.7%, and 58.2%, respectively. One year probability of OS was 78% for children with Sanfilippo disease. Of 19 children who underwent transplantation for MPS III, a phenotype with predominant central nervous system (CNS)

involvement, 12 survived and nine had disease stabilization with less impact in cognitive function. Children who underwent transplantation at less than two years of age (n=2) had modest gains in cognitive skills, although they continued to have overall global developmental delay. Study limitations include small patient populations, uncontrolled design and lack of treatment comparator. Further evaluation and publication of the neurocognitive and developmental outcomes of patients with MPS III who have undergone HSCT is critically important (Bolens, 2008).

Summary for Sanfilippo Syndrome: There is insufficient evidence to demonstrate the effectiveness of allogeneic hematopoietic stem-cell transplantation (HSCT) for the treatment of Sanfilippo disease (MPS III). The role of this therapy has not yet been demonstrated for this indication.

Morquio Syndrome (MPS-IV): There are two types of MPS-IV, caused by a deficiency of the enzymes galactosamine-6-sulphatase (Type IVA) and beta-galactosidase (Type IVB). Individuals with MPS IV typically have preserved intellectual function.

Literature Review
Controlled clinical trial data are lacking and data from prospective studies are limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of HSCT for the treatment of Morquio syndrome (MPS IV). At this time, there is no role for HCT since skeletal deformities are not improved by HSCT (Malatack, 2003; Peters, 2003). In a recent systematic review by Ratko et al. (2012), two case reports were reviewed. The authors noted the body of evidence on neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management for MPS IV (Morquio syndrome) is insufficient to draw conclusions.

Summary for Morquio Syndrome (MPS IV): Data demonstrating improved health outcomes are very limited in the published, peer reviewed scientific literature. The role of HSCT has not 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. Enzyme replacement therapy (ERT) has proven to be a successful treatment for MPS VI, and is recommended as first-line therapy for all cases of MPS VI. If enzyme replacement fails, then HSCT is recommended. All phenotypes of MPS VI are associated with reduced life expectancy and should therefore be considered candidates for HSCT or ERT (Peters, 2003). Allogeneic hematopoietic stem-cell transplantation (HSCT) has been used successfully to treat MPS IV in some individuals, demonstrating successful engraftment and improved enzymatic functioning post transplantation (Ratko, 2012; Turbeville, 2011; Malatack, 2003; Lee, 2000; Alvaro, 1998). As in other MPS disorders, HSCT has not been able to effectively treat skeletal abnormalities (MPSS, 2011).

Literature Review
Controlled trial data are lacking and there are limited case series and case reports with small patient populations in the published peer-reviewed scientific literature. 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. Transplantation is considered a therapeutic alternative for MPS VI, however, it has been relegated to a second-line therapy since the introduction of ERT. Systemic problems have responded well to ERT without the risks associated with HSCT (Giugliani, 2010).

Using data from the Center for International Blood and Marrow Transplant Research (CIBMTR), Tuberville (2011) reported results of a retrospective analysis of 45 patients who received an allogeneic HSCT for MPS IV between 1982 and 2007. The probability of survival (95% CI) was 78% at 100 days, 66% at one- and three-years post-transplant.

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: Peters et al. (2003) published joint guidelines which note 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

Summary for Maroteaux-Lamy Syndrome (MPS IV): Although data are not robust, allogeneic 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. In most severe cases, neonatal jaundice and hydrops fetalis are present at birth, and survival is a few months. In less severe cases, growth retardation is evident in the first two years of life (Ratko, 2012).

Literature Review
Controlled trial data are lacking and prospective case reports are limited in the published peer-reviewed scientific literature regarding the safety and effectiveness of this therapy for the treatment of Sly syndrome (MPS VII). Peters et al. (2003) notes that MPS VII can in certain circumstances, be ameliorated by hematopoietic stem-cell transplantation (HSCT) provided that the neuropsychological and clinical status of the patient is good at the time of transplant. In a narrative review by Ratko et al. (2012), data were very limited regarding the effectiveness of allogeneic HSCT for this indication. However, the authors noted "Overall there appears to be a favorable risk-benefit profile for the treatment of MPS VII with HSCT only in cases with severe physical disabilities."

Summary for Sly Syndrome: Although data are limited, allogeneic HSCT seems a reasonable treatment option for select individuals with MPS VII given the ultimately poor prognosis of children with this disease.

Sphingolipidosis: Lipidoses are disorders of lipid metabolism that lead to abnormal accumulation of fats in certain body tissues. Disorders include Gaucher disease, Niemann-Pick disease, and Krabbe disease.

Gaucher Disease: Gaucher disease is a disorder of lipid metabolism, resulting in an accumulation of abnormal glucocerebrosides in reticuloendothelial cells. According to the National Institutes of Neurological Diseases and Stroke ([NINDS], 2013), there are three forms, types I-III.

Allogeneic hematopoietic stem-cell transplantation (HSCT) has been studied in Gaucher disease, however, HSCT is not regarded as first-line therapy because of the low morbidity associated with enzyme replacement therapy (ERT) (Peters, 2003).Type I disease responds to HSCT with normalization of splenic function and is effective in alleviating most symptoms of Gaucher Type I, including skeletal symptoms in the early onset severe form of Type I (Ratko, 2012). Type II disease responds to HSCT with resolution of peripheral but not central nervous system (CNS) symptoms of the disease, and Type III disease (Norbottnian) responds to HSCT with reversal of peripheral organ symptoms and stabilization and slowing of neurological deterioration (Boelens, 2008; Malatack, 2003; Peters, 2003). National Institute for Neurological Disorders and Stroke ([NINDS], 2013c) notes "Currently there is no specific treatment available for most of the lipid storage disorders but highly effective enzyme replacement therapy is available for patients with type 1 Gaucher disease and some patients with type 3 Gaucher disease."

Literature Review
In a recent narrative review by Ratko et al. (2012), the authors noted that HSCT may be considered for Gaucher Type I if there is a persistence or progression of severe bone pain or if access to ERT is limited. Cure of Gaucher Type I can be achieved with HSCT if engraftment is successful and complications from the procedure are minimal. The data suggested no benefit of HSCT on neurodevelopmental symptoms for Gaucher type III disease compared to ERT, but a moderate strength of evidence to support HSCT for neurocognitive symptoms. There was insufficient information to determine the impact of HSCT on Gaucher type II disease.

Somaraju et al. (2012) reported results of a systematic review of the literature. The authors reported that no randomized controlled trial (RCT), quasi-RCT or controlled clinical trial on the efficacy of HSCT for Gaucher disease was identified for inclusion in the study. The research evidence on which to base clinical decisions is limited to case reports.

Professional Societies/Organizations
National Institute of Neurological Disorders and Stroke (NINDS): Regarding Gaucher disease the NINDS (2013c) notes that currently there is no specific treatment available for most of the lipid storage disorders but highly effective enzyme replacement therapy is available for patients with type 1 Gaucher disease and some patients with type 3 Gaucher disease.NINDS (2013) also notes that bone marrow transplantation can reverse the non-neurological effects of Type 1 disease, but it carries a high risk and is rarely performed.

National Marrow Donor Program (NMDP), International Bone Marrow Transplant Registry, Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which note that hematopoietic stem-cell transplantation (HSCT) may be indicated in patients with Type 3 Gaucher disease who have neurological deterioration or pulmonary compromise while on enzyme replacement therapy. These organizations also note that 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).

Summary for Gaucher Disease: Although data are not robust, allogeneic HSCT appears to be an acceptable treatment option for Gaucher types I and III.

Krabbe Disease: Krabbe disease, also called galactosylceramide lipidosis or globoid-cell leukodystrophy, is the deficiency of the enzyme galactocerebroside beta-galactosidase which causes progressive destruction of myelin and the nervous system. The optimal treatment for Krabbe disease is still being developed. HSCT is the only available therapy with potential to improve neurocognitive function, increase survival and alter the natural history of the disease (Boelens, 2008). HSCT is recommended for the severe early onset form of the disease if the disease is diagnosed antenatally, so that HSCT can be performed during the neonatal period, prior to the onset of symptoms. Screening for the disease is recommended in particular for families who have had a child previously diagnosed with the disease, allowing for an antenatal diagnosis and an early transplantation. HSCT is recommended for patients with the late onset form of disease if symptoms have not become severe (Ratko, 2012). HSCT in presymptomatic infants and older individuals with mild symptoms may improve and preserve cognitive function, but peripheral nervous system function may deteriorate (Wenger, 2011).

Literature Review
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.

Krivit et al. (1998) described the use of allogeneic HSCT to treat five children with GLD. Four children received marrow from a human leukocyte antigen (HLA)-identical sibling. One child was treated with unrelated cord blood transplant from a 1 HLA-DR mismatch donor. Two children with late-onset GLD who had substantial neurologic disability, including ataxia, tremors, motor incoordination, and gait dysfunction, showed resolution of their symptoms. Most children had improvement in MRI, and cerebrospinal fluid (CSF) protein levels.

Professional Societies/Organizations
National Institute for Neurological Disorders and Stroke (NINDS): NINDS (2011a) notes there is no cure for Krabbe disease. Results of a very small clinical trial of patients with infantile Krabbe disease found that children who received umbilical cord blood stem cells from unrelated donors prior to symptom onset developed with little neurological impairment. Results also showed that disease progression stabilized faster in patients who receive cord blood compared to those who receive adult bone marrow. Bone marrow transplantation has been shown to benefit mild cases early in the course of the disease.

National Marrow Donor Program (NMDP), International Bone Marrow Transplant Registry, Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which note 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_2 gangliosidoses, including Tay-Sachs disease.

Summary for Krabbe Disease: There is sufficient evidence in the published, peer-reviewed scientific literature to demonstrate improved health outcomes with the use of allogeneic HSCT for the treatment of Krabbe disease.

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.

Literature Review
More than 100 transplants have been performed for this disorder. Despite this number, the lack of graft-outcome and long-term follow-up studies makes it difficult to draw firm conclusions regarding the efficacy of hematopoietic stem-cell transplantation (HSCT) in metachromatic leukodystrophy (MLD) (Boelens, 2008).

Prasad et al. (2008) reported results of a study involving 159 children with inherited metabolic diseases who underwent HSCT using unrelated cord blood as a donor source. Five-year overall survival in 15 mainly symptomatic MLD patients was 58%. Those patients transplanted with advanced disease had worse outcomes.

Professional Societies/Organizations
National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which 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.

National Institute for Neurological Disorders and Stroke (NINDS): NINDS (2012b) notes that bone marrow transplantation may delay progression of the disease in some infantile-onset cases.

Summary for MLD: 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.

Literature Review
Data are limited to small, uncontrolled case reports and case series. In a recent comparative effectiveness review by Ratko (2012) the authors note “overall there appears to be a favorable risk-benefit profile for the treatment of patients with HSCT who have severe symptoms from Niemann-Pick Type B, particularly those with severe liver disease or pulmonary disease. The procedure will ideally be performed as early in the disease process as possible for maximum benefit.” Regarding treatment of individuals with type A disease low strength evidence on survival suggests no benefit with single HSCT compared to symptom management. Ratko (2012) also notes “The body of evidence on neurocognitive and neurodevelopmental outcomes with single HSCT compared to symptom management or natural history of Niemann-Pick C is insufficient to draw conclusions.”

Professional Societies/Organizations
National Institutes of Neurological Disorders and Stroke (NINDS): The NINDS (2014) notes “There is currently no cure for Niemann-Pick disease. Children usually die from infection or progressive neurological loss. Bone marrow transplantation has been attempted in a few patients with type B, and encouraging results have been reported. The development of enzyme replacement and gene therapies might also be helpful for those with type B.”

National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which note that HSCT is recommended for Niemann-Pick Type B patients with early severe liver disease or pulmonary symptoms; however, HSCT is considered experimental therapy for patients with neurologic symptoms. Regarding type A, Peters notes Type A is not amenable to effective treatment with HSCT because of its rapid progression.

Summary for Niemann-Pick Disease
There is insufficient evidence to support the safety and effectiveness of allogeneic HSCT for the treatment of Niemann-Pick disease type A. The role of this therapy has not yet been established for this indication. Treatment of individuals with NP type B is considered an acceptable treatment option.

Adrenoleukodystrophy (X-ALD): 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. The severity and extent of symptoms determines the course of treatment. Studies have shown that an MRI Loes severity score of 2-3 in boys younger than 10 years of age, will most likely develop progressive cerebral disease and are therefore candidates for hematopoietic stem-cell transplantation (HSCT). Bolens et al. (2008) notes "X-ALD has a variable clinical presentation, and HSCT is indicated only in those individuals with clear evidence of early cerebral inflammatory disease. It is not indicated for asymptomatic individuals who have no cerebral involvement on testing because the risks of HSCT are considered too great. Nor is it indicated for those individuals with advanced cerebral disease because HSCT does not reverse, and may even worsen, established disease."

Literature Review
Outcomes following HSCT have varied from complete resolution of symptoms to having no effect. Disease status prior to the procedure is the best predictor of outcomes (Ratko, 2012).The most successful outcomes are when the HSCT has been performed prior to the onset of neurologic symptoms.

Several uncontrolled case series and retrospective reviews demonstrate improved survival outcomes with allogeneic HSCT (Beam, 2007; Mahmood, 2007; Peters, 2004; Shapiro, 2000). 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.

Prasad et al. (2008) reported outcomes of 12 boys with X-ALD who received allogeneic HSCT. With a median follow-up of 3.3 years the probability of overall survival was OS was 71.9%.This study included three patients transplanted at a very young age (2.6–3.5 years) before the onset of clinical symptoms. These children continued to develop at a normal rate for three-five years post transplant.

Professional Societies/Organizations
National Institute for Neurological Disorders and Stroke (NINDS): According to NINDS (2013), 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.

Summary for Adrenoleukodystrophy: 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.

Wolman Disease: According to NINDS (2011a), Wolman disease results from lysosomal acid lipase deficiency, causing accumulation of cholesteryl esters and triglycerides in the cells and tissues. Enzyme replacement therapy is currently under active investigation for this disease. Fewer than 80 cases have been identified. Symptoms appear immediately, within the first week of life, and include failure to thrive, jaundice, anemia, relentless vomiting, abdominal distention, steatorrhea, and hepatosplenomegaly. Because of the failure to absorb nutrients, severe malnutrition occurs and life expectancy is less than 6 months (Ratko, 2012).

Literature Review
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.

In a recent systematic review by Ratko et al. (2012) high-strength evidence suggests a benefit of HSCT compared to disease natural history. Evidence for this review consists of two case series and two case reports involving eight patients. Two died from the procedure and 1 died from disease progression. Four have survived

and have been followed for 0.3 to 11 years, with normal or near normal functioning. For three patients who have survived long-term follow-up from 4 to 11 years, HSCT altered the course of Wolman disease.

Summary for Wolman Disease:
Although data are limited in size and study design, there is some support for the benefit of HSCT compared with natural disease progression. Allogeneic HSCT is an acceptable treatment option for this indication.

Farber's Disease
Farber's disease is a rare autosomal recessive disorder characterized by a deficiency in ceramidase, resulting in the accumulation of ceramide in various tissues, the central nervous system, and most notably the joints. Fifty cases of this disease have been reported in the literature. Life expectancy is two years of age in type I. Progressive neurological failure is the usual cause of death. The milder form is type 2/3, which has no associated neurological symptoms. Lifespan for type 2/3 is into teen years.

Literature Review
In a recent narrative review Ratko et al. (2012) reviewed three case series with seven total patients. Two patients had type I disease, five had type 2/3. No treatment-related mortality was reported in the seven patients with Farber disease undergoing HSCT. High strength evidence on number of subcutaneous nodules and number of joints with limited range of motion suggests a benefit with single HSCT compared to symptom management or disease natural history for Farber's disease.

Summary
Given the rare occurrence of this disease, it is unlikely that large prospective controlled trials will be forthcoming. Allogeneic HSCT is an accepted treatment option for this indication.

Alpha Mannosidosis
Alpha-mannosidosis is a rare autosomal recessive disease caused by a deficiency in the enzyme α-mannosidase, resulting in the accumulation of oligosaccharides in the liver, bone marrow, and central nervous system. Symptoms include mental retardation, impaired hearing, and deterioration of previously acquired developmental skills. A severe infantile form, Type I, has an onset of symptoms occurring before 12 months of age resulting in progressive deterioration. Type II is the less severe form, with symptoms beginning in late childhood to adulthood. Life expectancy can extend through the fifth decade of life (Ratko, 2012; Malm, 2013)

Literature Review
Less than 20 cases have been reported worldwide. Data are limited to small case series and case reports. Results have shown favorable outcomes, with resolutions in organomegaly, bony disease, and either stabilization or improvement of neuropsychologic symptoms (Ratko, 2012).

Professional Societies/Organizations
National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group: Peters et al. (2003) published joint guidelines which note that allogeneic HSCT is recommended for all patients with severe Type I form prior to the onset of significant symptoms, and recommended for Type II patients if early neurocognitive deficits are present.

Summary for Alpha-Mannosidosis
Given the rare occurrence of this disorder it is unlikely that randomized clinical trials will be undertaken. Allogeneic HSCT is an acceptable treatment option for this disorder.

Use Outside of the US: No relevant information

Summary
Inherited metabolic disorders are rare individually but common as a group. Some disorders may be treated with enzyme replacement therapy but for many no treatment has been established. The use of allogeneic HSCT is supported for several indications by a practice guideline published on behalf of the National Marrow Donor Program, International Bone Marrow Transplant Registry, and the Working Party on Inborn Errors of the European Bone Marrow Transplant Group (2003). 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: 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 when used to report allogeneic bone marrow or blood-derived stem-cell procedures:

CPT®* Codes	Description
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, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
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, allogeneic
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation, per donor
38242	Allogeneic lymphocyte infusions

HCPCS Codes	Description
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 of pre-and post-transplant care in the global definition

References

1. Alvaro F, Toogood I, Fletcher JM, Clements P, Rawling T, To B. Allogeneic CD34 selected peripheral stem cell transplant for Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI): rapid Haemopoietic and biochemical reconstitution. Bone Marrow Transplant. 1998 Feb;21(4):419-21.

2. Beam D, Poe MD, Provenzale JM, Szabolcs P, Martin PL, Prasad V, et al. Outcomes of unrelated umbilical cord blood transplantation for X-linked adrenoleukodystrophy. Biol Blood Marrow Transplant. 2007 Jun;13(6):665-74.Epub 2007 Apr 6.

3. Boelens JJ. Trends in haematopoietic cell transplantation for inborn errors of metabolism. J Inherit Metab Dis. 2006 Apr-Jun;29(2-3):413-20.

4. Boelens JJ, Aldenhoven M, Purtill D, Ruggeri A, Defor T, Wynn R, et al. Outcomes of transplantation using various hematopoietic cell sources in children with Hurler syndrome after myeloablative conditioning. Blood. 2013 May 9;121(19):3981-7. Epub 2013 Mar 14.

5. Boelens JJ, Prasad VK, Tolar J, Wynn RF, Peters C. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. Pediatr Clin North Am. 2010 Feb;57(1):123-45.

6. Boelens JJ, Rocha V, Aldenhoven M, Wynn R, O'Meara A, Michel G, et al. Risk factor analysis of outcomes after unrelated cord blood transplantation in patients with hurler syndrome. Biol Blood Marrow Transplant. 2009 May;15(5):618-25.

7. Braunlin EA, Stauffer NR, Peters CH, Bass JL, Berry JM, Hopwood JJ, et al. Usefulness of bone marrow transplantation in the Hurler syndrome. Am J Cardiol. 2003 Oct 1;92:882-6.

8. Cable C, Finkel RS, Lehkey TJ, Biassou NM, Wiggs EA, Bunin N, et al. Unrelated umbilical cord blood transplant for juvenile metachromatic leukodystrophy: a 5-year follow-up in three affected siblings. Mol Genet Metab. 2011 Feb;102(2):207-9.

9. Caniglia M, Rana I, Pinto RM, Fariello G, Caruso R, Angioni A, et al. Allogeneic bone marrow transplantation for infantile globoid-cell leukodystrophy (Krabbe's disease). Pediatr Transplantation. 2002;6:427-31.

10. Chan KW, Wong LTK, Applegarth D, Davidson AGF. Bone marrow transplantation in Gaucher's disease: effect of mixed chimeric state. Bone Marrow Transplant. 1994;14:327-30.

11. Clark LA, Heppner J. Mucopolysaccharidosis Type I. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. SourceGeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. 2002 Oct 31 [updated 2011 Jul 21]. Accessed Jul 6, 2014. Available at URL address: http://www.ncbi.nlm.nih.gov/pubmed/20301341

12. de Ru MH, Boelens JJ, Das AM, Jones SA, van der Lee JH, Mahlaoui N, et al. Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus procedure. Orphanet J Rare Dis. 2011 Aug 10;6:55.

13. Escolar ML, Poe MD, Provenzale JM, Richards KC, Allison J, Wood S, et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med. 2005 May 19;352(20):2069-81.

14. Gassas A, Raiman J, White L, Schechter T, Clarke J, Doyle J. Long-term adaptive functioning outcomes of children with inherited metabolic and genetic diseases treated with hematopoietic stem cell transplantation in a single large pediatric center: a parent's perspective. J Pediatr Hematol Oncol. 211 Apr;33(3):216-20.

15. Giugliani R, Federhen A, Rojas MV, Vieira T, Artigalás O, Pinto LL, et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. Genet Mol Biol. 2010 Oct;33(4):589-604.

16. Grewal SS, Krivit W, Defor TE, Shapiro EG, Orchard PJ, Abel SL, et al. Outcome of second hematopoietic cell transplantation in Hurler syndrome. Bone Marrow Transplant. 2002 Mar;29(6):491-6.

17. Grewal SS, Shapiro E, Braunlin E, Charnas L, Krivit W, Orchard P, et al. Continued neurocognitive development and prevention of cardiopulmonary complications after successful BMT for I-cell disease: a long-term follow-up report. Bone Marrow Transplant. 2003 Nov;32(9):957-60.

18. Grewal SS, Wynn R, Abdenur JE, Burton BK, Gharib M, Haase C, et al. Safety and efficacy of enzyme replacement therapy in combination with hematopoietic stem cell transplantation in Hurler syndrome. Genet Med. 2005 Feb;7(2):143-6.

19. Grigull L, Beilken A, Schrappe M, Das A, Luecke T, Sander A, et al. Transplantation of allogeneic CD34-selected stem cells after fludarabine-based conditioning regiment for children with mucopolysaccharidosis IH (M. Hurler). Bone Marrow Transplant. 2005 Feb;35(3):265-9.

20. Grewal SS, Barker JN, Davies SM, Wagner JE. Unrelated donor hematopoietic cell transplantation: marrow or umbilical cord blood? Blood. 2003 Jun 1;101(11):4233-44.

21. Hansen MD, Filopovich AH, Davies SM, Mehta P, Bleesing J, Jodele S, et al. Allogeneic hematopoietic cell transplantation (HCT) in Hurler's syndrome using a reduced intensity preparative regimen. Bone Marrow Transplant. 2008 Feb;41(4):349-53. Epub 2007 Nov 19.

22. Hsu YS, Hwu WL, Huang SF, Lu MY, Chen RL, Lin DT, et al. Niemann-Pick disease type C (a cellular cholesterol lipidosis) treated by bone marrow transplantation. Bone Marrow Transplant. 1999;24:103-7.

23. Klein KA, Krivit W, Whitley CB, Peters C, Cool VA, Fuhrman M, et al. Poor cognitive outcome of eleven children with Sanfilippo syndrome after bone marrow transplantation and successful engraftment. Bone Marrow Transplant. 1995;15:S176.

24. Krivit W, Peters C, Dusenbery K, Ben-Yoseph Y, Ramsay NKC, Wagner JE, et al. Wolman disease successfully treated by bone marrow transplantation. Bone Marrow Transplant. 2000;26:567-70.

25. Krivit W, Shapiro EG, Peters C, Wagner JE, Cornu G, Kurtzberg J, et al. Hematopoietic stem-cell transplantation in globoid-cell leukodystrophy. N Engl J Med. 1998;338(16):1119-26.

26. Lee V, Li CK, Shing MM, Chik KW, Lam CW, Tsang KS, et al. Umbilical cord blood transplantation for Maroteaux-Lamy syndrome (mucopolysaccharidosis type VI). Bone Marrow Transplant. 2000 Aug;26(4):455-8.

27. Maccotta L, Sherr EH. Hematopoietic stem cell transplantation for the treatment of childhood cerebral X-linked adrenoleukodystrophy. Nat Clin Pract Neurol. 2008 Mar;4(3):130-1. Epub 2008 Jan 22.

28. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. Lancet Neurol. 2007 Aug;6(8):687-92.

29. Malatack JJ, Consolini DM, Bayever E. The status of hematopoietic stem cell transplantation in lysosomal storage disease. Pediatr Neurol. 2003 Nov;29(5):391-403.

30. Malm G, Gustafsson B, Berglund G, Lindstrom M, Naess K, Borgstrom B, et al. Outcome in six children with mucopolysaccharidosis type IH, hurler syndrome, after haematopoietic stem cell transplantation (HSCT). Acta Paediatr. 2008 Apr 29. [Epub ahead of print]

31. Malm D, Nilssen Ø. Editors Alpha-Mannosidosis. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. 2001 Oct 11 [updated 2012 May 03].Accessed Jul 6, 2014. Available at URL address: http://www.ncbi.nlm.nih.gov/books/NBK1396/

32. Martin PL, Carter SL, Kernan NA, Sahdev I, Wall D, Pietryga D, et al. Results of the cord blood transplantation study (COBLT): outcomes of unrelated donor umbilical cord blood transplantation in pediatric patients with lysosomal and peroxisomal storage diseases. Biol Blood Marrow Transplant. 2006 Feb;12(2):184-94.

33. Meuleman N, Vanhaelen G, Tondreau T, Lewalle P, Kwan J, Bennani J, et al. Reduced intensity conditioning haematopoietic stem cell transplantation with mesenchymal stromal cells infusion for the treatment of metachromatic leukodystrophy: a case report. Haematologica. 2008 Jan;93(1):e11-3.

34. Miller WP. Rothman SM, Nascene D, Kivisto T, DeFor TE, Zieglar RS, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. 2011 Aug 18;1187):1970-8.

35. Mitchell R, Nivison-Smith I, Anazodo A, Tiedemann K, Shaw PJ, Teague L, et al. Outcomes of haematopoietic stem cell transplantation for inherited metabolic disorders: a report from the Australian and New Zealand Children's Haematology Oncology Group and the Australasian Bone Marrow Transplant Recipient Registry. Pediatr Transplant. 2013 Sep;17(6):582-8.

36. Muenzer J, Wrath JE, Clarke LA, International Consensus Panel on Management and Treatment of Muccopolysaccharidoses I. Mucopolysaccharidosis I: management and treatment guidelines. Pediatrics. 2009 Jan; 123(1):19-29.

37. Mullen CA, Thompson JN, Richard LA, Chan KW. Unrelated umbilical cord blood transplantation in infancy for mucopolysaccharidosis type IIB (Hunter syndrome) complicated by autoimmune hemolytic anemia. Bone Marrow Transplant. 2000 May;25(10):1093-7.

38. National Institute of Neurological Disorders and Stroke. (a) [NINDS] Acid lipase disease information page. Updated 2014 Apr 16. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/acid_lipase/acid_lipase.htm

39. National Institute of Neurological Disorders and Stroke (a) [NINDS] Adrenoleukodystrophy information page. Updated 2012 Oct 22. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/adrenoleukodystrophy/adrenoleukodystrophy.htm

40. National Institute of Neurological Disorders and Stroke. (b) [NINDS] Fabry's disease information page. Updated 2013 Sep 23. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/fabrys/fabrys.htm

41. National Institute of Neurological Disorders and Stroke. (b) [NINDS] Generalized gangliosidoses information page. Updated 2014 Apr 16. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/gangliosidoses/Gangliosidoses.htm

42. National Institute of Neurological Disorders and Stroke. (c) [NINDS] Gaucher’s disease information page. Updated 2013 Jul 5. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/gauchers/gauchers.htm

43. National Institute of Neurological Disorders and Stroke. (a) [NINDS] Krabbe’s disease information page. Updated 2011 Oct 6. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/krabbe/krabbe.htm#Is_there_any_treatment

44. National Institute of Neurological Disorders and Stroke. (c) [NINDS] lipid storage diseases fact sheet. Updated 2014 Apr 16. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/lipid_storage_diseases/detail_lipid_storage_diseases.htm

45. National Institute of Neurological Disorders and Stroke. (b) [NINDS] Metachromatic leukodystrophy information page. Updated 2012 Oct 22. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/metachromatic_leukodystrophy/metachromatic_leukodystrophy.htm

46. National Institute of Neurological Disorders and Stroke. (d) [NINDS] Mucolipidoses information page. Updated 2014 Apr 16. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/mucolipidoses/mucolipidoses.htm

47. National Institute of Neurological Disorders and Stroke. (e) [NINDS] Mucopolysaccharidoses information page. Updated 2014 Apr 16. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/mucopolysaccharidoses/mucopolysaccharidoses.htm#Is_there_any_treatment

48. National Institute of Neurological Disorders and Stroke. (b) [NINDS] Sandhoff information page. Updated 2011 Oct 6. Accessed Jul 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/sandhoff/sandhoff.htm

49. National Institute of Neurological Disorders and Stroke. (c) [NINDS] Tay-Sachs information page. Updated 2011 Oct 6. Accessed Jun 6, 2014. Available at URL address: http://www.ninds.nih.gov/disorders/taysachs/taysachs.htm

50. National Marrow Donor Program. Physician Resources. Diseases treatable by hematopoietic cell transplantation. 1996-2014 National Marrow Donor Program. Accessed Jul 6, 2014. Available at URL address: https://bethematchclinical.org/

51. National Marrow Donor Program. Physician Resources. Transplant outcomes by disease and disease stage. 1996-2014. National Marrow Donor Program. Accessed Jul 6, 2014. Available at URL address: http://marrow.org/Physicians/When_to_Transplant/Outcomes_by_Disease.aspx#other

52. National MPS Society. MPS fact sheet. ©2011. Accessed Jun 6, 2014. Available at URL address: http://www.mpssociety.org

53. Peters C, Charnas LR, Tan Y, Ziegler RS, Shapiro EG, DeFor T, et al. Cerebral X-linked adrenoleukodystrophy: the international hematopoietic transplantation experience from 1982-1999. Blood. 2004 Aug 1;104(3):881-8.

54. Pastores GM, Hughes DA. Gaucher Disease. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. SourceGeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. 2000 Jul 27 [updated 2013 Sep 19]. Accessed Jul 6, 2014. Available at URL address: http://www.ncbi.nlm.nih.gov/books/NBK1269/

55. Peters C, Balthazor M, Shapiro EG, King RJ, Kollman C, Hegland JD, et al. Outcome of unrelated donor bone marrow transplantation in 40 children with Hurler syndrome. Blood. 1996 Jun 1;87(11):4894-902.

56. Peters C, Shapiro EG, Anderson J, Henslee-Downey PJ, Klemperer MR, Cowan MJ, et al. Hurler syndrome: II. Outcome of HLA-genotypically identical sibling and HLA-haploidentical related donor bone marrow transplantation in fifty-four children. Blood. 1998 Apr 1;91(7):2601-8.

57. Peters C, Steward CG; National Marrow Donor Program; International Bone Marrow Transplant Registry; Working Party on Inborn Errors, European Bone Marrow Transplant Group. Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. Bone Marrow Transplant. 2003 Feb;31(4):229-39.

58. Prasad VK, Kurtzberg J. Cord blood and bone marrow transplantation in inherited metabolic diseases: scientific basis, current status and future directions. Br J Haematol. 2010 Feb;148(3):356-72.

59. Prasad VK, Mendizabal A, Parikh SH, Szabolcs P, Driscoll TA, Page K, et al. Unrelated donor umbilical cord blood transplantation for inherited metabolic disorders in 159 pediatric patients from a single center: influence of cellular composition of the graft on transplantation outcomes. Blood. 2008 Oct 1;112(7):2979-89.

60. Ratko TA, Belinson SE, Brown HM, Noorani HZ, Chopra RD, Marbella A, et al. Hematopoietic Stem-Cell Transplantation in the Pediatric Population [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US).); 2012 Feb. Report No.: 12-EHC018-EF. AHRQ Comparative Effectiveness Reviews.

61. Ringden O, Remberger M, Svahn BM, Barkholt L, Mattsson J, Aschan J, et al. Allogeneic hematopoietic stem cell transplantation for inherited disorders: experience in a single center. Transplantation. 2006 Mar 15;81(5):718-25.

62. Sands MS, Erway LC, Vogler C, Sly WS, Birkenmeier EH. Syngeneic bone marrow transplantation reduces the hearing loss associated with murine mucopolysaccharidosis Type VII. Blood. 1995 Sep 1;86(5):2033-40.

63. Sauer M, Meissner B, Fuchs D, Gruhn B, Kabish H, Erttmann R, et al. Allogeneic blood SCT for children with Hurler's syndrome: results from the German multicenter approach MPS-HCT 2005. Bone Marrow Transplant. 2009 Mar;43(5):375-81.

64. Scarpa M. Mucopolysaccharidosis Type II. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. Source GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2014. 2007 Nov 6 [updated 2011 Feb 22]. Accessed Jul 6, 2014. Available at URL address: http://www.ncbi.nlm.nih.gov/books/NBK1274/

65. Shah AJ, Kapoor N, Crooks GM, Parkman R, Weinberg KI, Wilson K, et al. Successful hematopoietic stem cell transplantation for Niemann-Pick disease type-2. Pediatrics. 2005 Oct;116(4):1022-5.

66. Shapiro EG, Krivit W, Lockman L, Jambaque I, Peters C, Cowan M, et al. Long-term effect of bone marrow transplantation for childhood-onset cerebral X-linked adrenoleukodystrophy. Lancet. 2000 Aug 26;356:713-18.

67. Somaraju UR, Tadepalli K. Hematopoietic stem cell transplantation for Gaucher disease. Cochrane Database Syst Rev. 2012 Jul 11;7:CD006974.

68. Souillet G, Guffon N, Maire I, Pujol M, Taylor P, Sevin F, et al. Outcome of 27 patients with Hurler's syndrome transplanted from either related or unrelated haematopoietic stem cell sources. Bone Marrow Transplant. 2003 Jun;31(12):1105-17.

69. Spranger J. Muccopolysacharoidoses. In: Kleigman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, editors. Nelson textbook of pediatrics, 19th ed. Philadelphia: Elsevier; 2011.

70. Staba SL, Escolar ML, Poe M, Kim Y, Martin PL, Szabolcs P, et al. Cord-blood transplants from unrelated donors in patients with Hurler's syndrome. N Engl J Med. 2004 May 6;350(19):1960-9.

71. Tokimasa S, Ohta H, Takizawa S, Kusuki S, Hashii Y, Sakaii N, et al. Umbilical cord-blood transplantations from unrelated donors in patients with inherited metabolic diseases: Single-institute experience. Pediatr Transplant. 2008 Sep;12(6):672-6.

72. Tolar J, Grewal SS, Bjoraker KJ, Whitley CB, Shapiro EG, Charnas L, et al. Combination of enzyme replacement and hematopoietic stem cell transplantation as therapy for Hurler syndrome. Bone Marrow Transplant. 2008 Mar;41(6):531-5. Epub 2007 Nov 26.

73. Tolar J, Petryk A, Khan K, Bjoraker KJ, Jessurun J, Dolan M, et al. Long-term metabolic, endocrine, and neuropsychological outcome of hematopoietic cell transplantation for Wolman disease. Bone Marrow Transplant. 2009 Jan;43(1):21-7.

74. Turbeville S, Nicely H, Rizzo JD, Pederson TL, Orchard PJ, Horwitz ME, et al. Clinical outcomes following hematopoietic stem cell transplantation for treatment of mucopolysaccharidosis VI. Mol Genet Metab. 2011 Feb;102(2):111-5.

75. Victor S, Coulter JB, Besley GT, Ellis I, Desnick RJ, Schuchman EH, et al. Niemann-Pick disease: sixteen-year follow-up of allogeneic bone marrow transplantation in a type B variant. J Inherit Metab Dis. 2003;26:775-85.

76. Wada R, Tifft CJ, Proia RL. Microglial activation precedes acute neurodegeneration in Sandhoff disease and is suppressed by bone marrow transplantation. Proc Natl Acad Sci U S A. 2000 Sep 26;97(20):10954-9.

77. Wenger DA. Krabbe disease. In: Pagon RA, Bird TD, Dolan CR, Stephens K, Adam MP, ed. Gene Reviews [internet]. Seattle (WA): University of Washington, Seattle; 1993-2014 2000 Jun 19 [updated 2011 Mar 30]. Accessed Jul 6, 2014. Available at URL address: http://www.ncbi.nlm.nih.gov/books/NBK1238/

78. Wynn R. Stem cell transplantation in inherited metabolic disorders. Hematology Am Soc Hematol Educ Program. 2011;2011:285-91.

79. Wynn RF, Wraith JE, Mercer J, O'Meara A, Tylee K, Thornley M, et al. Improved metabolic correction in patients with lysosomal storage disease treated with hematopoietic stem cell transplant compared with enzyme replacement therapy. J Pediatr. 2009 Apr;154(4):609-11.