

# Protocol

## Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

(80122)

*(Formerly Allogeneic Hematopoietic Stem Cell Transplantation for Genetic Diseases and Acquired Anemias)*

<b>Medical Benefit</b>		<b>Effective Date:</b> 04/01/13	<b>Next Review Date:</b> 11/18
<b>Preauthorization</b>	Yes	<b>Review Dates:</b> 04/07, 05/08, 01/10, 01/11, 01/12, 01/13, 01/14, 11/14, 11/15, 11/16, 11/17	

### ***Preauthorization is required and must be obtained through Case Management.***

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: <ul style="list-style-type: none"><li>• With a hemoglobinopathy</li><li>• With a bone marrow failure syndrome</li><li>• With a primary immunodeficiency</li><li>• With inherited metabolic diseases</li><li>• With a genetic disorder affecting skeletal tissue</li></ul>	Interventions of interest are: <ul style="list-style-type: none"><li>• Allogeneic hematopoietic cell transplantation</li></ul>	Comparators of interest are: <ul style="list-style-type: none"><li>• Standard of care</li></ul>	Relevant outcomes include: <ul style="list-style-type: none"><li>• Overall survival</li><li>• Disease-specific survival</li><li>• Symptoms</li><li>• Quality of life</li><li>• Treatment-related morbidity</li></ul>

### **Description**

A number of inherited and acquired conditions have the potential for severe and/or progressive disease. For some conditions, allogeneic hematopoietic cell transplantation (allo-HCT) has been used to alter the natural history of the disease or potentially offer a cure.

### **Summary of Evidence**

For individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome disease, or a genetic disorder affecting skeletal tissue who receive allo-HCT, the evidence includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. The exception has been the use of allo-HCT in the inherited metabolic diseases like Hunter, Sanfilippo, and Morquio syndromes. Allo-HCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Policy**

Allogeneic hematopoietic cell transplantation is considered **medically necessary** for select patients with the following disorders.

*Hemoglobinopathies*

- Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage
- Homozygous beta-thalassemia (i.e., thalassemia major)

*Bone Marrow Failure Syndromes*

- Aplastic anemia including hereditary (including Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond, Diamond-Blackfan syndrome) or acquired (e.g., secondary to drug or toxin exposure) forms.

*Primary Immunodeficiencies*

- Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
- Absent or defective natural killer function (e.g., Chediak-Higashi syndrome)
- Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect).

(See policy guideline #1.)

*Inherited Metabolic Diseases*

- Lysosomal and peroxisomal storage disorders *except* Hunter, Sanfilippo, and Morquio syndromes

(See policy guideline #2.)

*Genetic Disorders Affecting Skeletal Tissue*

- Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease).

**Policy Guidelines**

Individual transplant facilities may have their own additional requirements or protocols that must be met in order for the patient to be eligible for a transplant at their facility.

1. The following guideline lists the immunodeficiencies that have been successfully treated by allo-HCT (Gennery & Cant et al, 2008).

**Lymphocyte Immunodeficiencies**

Adenosine deaminase deficiency

Artemis deficiency

Calcium channel deficiency

CD 40 ligand deficiency

Cernunnos/X-linked lymphoproliferative disease deficiency

CHARGE syndrome with immune deficiency

Common gamma chain deficiency  
Deficiencies in CD45, CD3, CD8  
DiGeorge syndrome  
DNA ligase IV deficiency syndrome  
Interleukin-7 receptor alpha deficiency  
Janus-associated kinase 3 deficiency  
Major histocompatibility class II deficiency  
Omenn syndrome  
Purine nucleoside phosphorylase deficiency  
Recombinase-activating gene 1/2 deficiency  
Reticular dysgenesis  
Winged helix deficiency  
Wiskott-Aldrich syndrome  
X-linked lymphoproliferative disease  
Zeta-chain-associated protein-70 deficiency

**Phagocytic Deficiencies**

Chédiak-Higashi syndrome  
Chronic granulomatous disease  
Griscelli syndrome type 2  
Hemophagocytic lymphohistiocytosis  
Interferon-gamma receptor deficiencies  
Leukocyte adhesion deficiency  
Severe congenital neutropenias  
Shwachman-Diamond syndrome

**Other Immunodeficiencies**

Autoimmune lymphoproliferative syndrome  
Cartilage hair hypoplasia  
CD25 deficiency  
Hyper IgD and IgE syndromes  
Immunodeficiency, centromeric instability, and facial dysmorphism syndrome  
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome  
Nuclear factor- $\kappa$  B (NF- $\kappa$ B) essential modulator deficiency  
NF- $\kappa$ B inhibitor, NF- $\kappa$ B- $\alpha$  deficiency

Nijmegen breakage syndrome

2. In the inherited metabolic disorders, allo-HCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid-cell leukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis, and aspartylglucosaminuria. Allogeneic HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM<sub>1</sub>, gangliosidosis, mucopolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick disease, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes. (Mehta, 2004).

The experience with reduced-intensity conditioning (RIC) and allogeneic HCT for the diseases listed in this protocol has been limited to small numbers of patients, and have yielded mixed results, depending upon the disease category. In general, the results have been most promising in the bone marrow failure syndromes and primary immunodeficiencies. In the hemoglobinopathies, success has been hampered by difficulties with high rates of graft rejection, and in adult patients, severe graft versus host disease. Phase 2/3 trials are ongoing examining the role of this type of transplant for these diseases.

### Medicare Advantage

If a transplant is needed, we arrange to have the Medicare-approved transplant center review and decide whether the patient is an appropriate candidate for the transplant.

### Background

Hematopoietic cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Allogeneic HCT (allo-HCT) refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Cord blood is discussed in greater detail in the Placental and Umbilical Cord Blood as a Source of Stem Cells Protocol.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is a critical factor for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

#### *Preparative Conditioning for Allo-HCT*

The conventional practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC allogeneic transplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition.

## *Genetic Diseases and Acquired Anemias*

### Hemoglobinopathies

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of  $\beta$ -thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function. The only definitive cure for thalassemia is to correct the genetic defect with allo-HCT.

Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin and, unlike thalassemia major, has a variable course of clinical severity.<sup>1</sup> Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for men and 48 for women. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea, and allo-HCT, the latter being the only possibility for cure.<sup>1</sup>

### Bone Marrow Failure Syndromes

Aplastic anemia in children is rare and is most often idiopathic and less commonly, due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently, this disease terminates in a myelodysplastic syndrome or acute myeloid leukemia (AML). Most patients with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age.<sup>2</sup> In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

Dyskeratosis congenita is characterized by marked telomere dysregulation with clinical features of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia.<sup>3</sup> Early mortality is associated with bone marrow failure, infections, pulmonary complications, or malignancy.

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome.<sup>3</sup> Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially AML. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow, with 30% of patients also having a variety of physical anomalies.<sup>3</sup>

### Primary Immunodeficiencies

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes.<sup>4</sup> The most severe defects (collectively known as severe combined immunodeficiency [SCID]) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells.<sup>4</sup> Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood.<sup>4</sup> Bone marrow transplantation is the only definitive cure, and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function.<sup>5</sup>

Inherited Metabolic Diseases

Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait.<sup>6</sup> Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic substrate and a deficiency of the product of the enzyme reaction.<sup>6</sup> Hurler syndrome usually leads to premature death by five years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier.<sup>6</sup> The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells (e.g., microglial cells in the brain and Kupffer cells in the liver).<sup>6</sup>

Allogeneic HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1.<sup>6</sup> The first stem cell transplant for an inherited metabolic disease was performed in 1980 in a patient with Hurler syndrome. Since that time, more than 1000 transplants have been performed worldwide.<sup>6</sup>

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS)	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler, Scheie, H-S Hunter Sanfilippo A-D Morquio A-B Maroteaux-Lamy Sly
Sphingolipidosis	Fabry Farber Gaucher types 1 and 3 GM <sub>1</sub> gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff disease Globoid cell leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis       Krabbe disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis Alpha-mannosidosis Beta-mannosidosis Mucopolidosis III and IV	    Sialidosis
Other lipidoses	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis	  Type III-Batten disease
Glycogen storage	GSD type II	Pompe
Multiple enzyme deficiency	Galactosialidosis Mucopolidosis type II	 I-cell disease

Category	Diagnosis	Other Names
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

### Genetic Disorders Affecting Skeletal Tissue

Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow.<sup>7</sup> Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease). Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately six months of age, and severe hematologic malfunction with bone marrow failure.<sup>7</sup> Seventy percent of these patients die before the age of six years, often of recurrent infections.<sup>7</sup> HCT is the only curative therapy for this fatal disease.

HCT for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis, is considered separately in the Hematopoietic Cell Transplantation for Autoimmune Diseases Protocol.

### **Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

### **References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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