Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias

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Replaces 8.01.109

Policy

Allogeneic hematopoietic stem-cell transplantation is considered medically necessary for selected 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) 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)

Inherited Metabolic Disease
- Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes (See Policy Guideline)

Genetic Disorders Affecting Skeletal Tissue
- Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease)
Guideline 1
The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem-cell transplantation (allo-HSCT) (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 CD 45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 (JAK3) deficiency
- Major histocompatibility class II deficiency
- Omenn syndrome
- Purine nucleoside phosphorylase deficiency
- Recombinase-activating gene (RAG) 1/2 deficiency
- Reticular dysgenesis
- Winged helix deficiency
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative disease
- Zeta-chain-associated protein-70 (ZAP-70) deficiency

**Phagocytic Deficiencies**
- Chediak-Higashi syndrome
- Chronic granulomatous disease
- Hemophagocytic lymphohistiocytosis
- Griscelli syndrome, type 2
- 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
- ICF syndrome
- IPEX syndrome
- NEMO deficiency
- NF-κB inhibitor, alpha (κB-alpha) deficiency
- Nijmegen breakage syndrome

**Guideline 2**
In the inherited metabolic disorders, allogeneic HSCT 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 HSCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HSCT has not generally been effective in Hunter, Sanfilippo, or Morquio syndromes. (Mehta, 2004).

The experience with reduced-intensity conditioning (RIC) and allogeneic HSCT for the diseases listed in this policy 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 (GVHD). Several Phase II/III trials are ongoing examining the role of this type of transplant for these diseases, as outlined in the clinical trial section under each disease type.

**Coding**

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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<tbody>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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<table>
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<tr>
<th>HCPCS</th>
<th>Description</th>
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<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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 of pre and post transplant care in the global definition</td>
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</table>
A number of inherited and acquired conditions have the potential for severe and/or progressive disease. For some conditions, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been used to alter the natural history of the disease or potentially offer a cure.

The evidence for allo-HSCT in select individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome diseases, or a genetic disorder affecting skeletal tissue includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, hospitalizations, medication use, resource utilization, and treatment-related mortality and 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 with the use of allo-HSCT in the inherited metabolic diseases Hunter, Sanfilippo, and Morquio syndromes. Allo-HSCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases.

Background
Hematopoietic stem-cell transplantation (HSCT) 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 HSCT 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.

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Immunologic compatibility between infused stem cells and the recipient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on 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 Allogeneic HSCT
The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. 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 allogeneic HSCT 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 allotransplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablution 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, 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 allogeneic HSCT.

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. (1) 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 males and 48 for females. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea, and HSCT, the latter being the only possibility for cure.(1)

**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 myelogenous leukemia. 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.(2) In Fanconi anemia, HSCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HSCT, with cure of the marrow failure and amelioration of the risk of leukemia.(2)

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

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.(3) 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 acute myelogenous leukemia. 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.(3)

**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.(4) 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.(4) 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. (4) Bone marrow transplant 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.(5)

**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.(6) 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.(6) Hurler syndrome usually leads to premature death by 5 years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don’t 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. The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells, for example microglial cells in the brain and Kupffer cells in the liver.(6)

Allogeneic HSCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in the Table 1.(6) 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 1,000 transplants have been performed worldwide.(6)

Table 1. Lysosomal and Peroxisomal Storage Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Other Names</th>
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</thead>
<tbody>
<tr>
<td>Sphingolipidosis</td>
<td>Fabry’s, Faber’s, Gaucher’s I-III, GM1, gangliosidosis, Niemann-Pick disease A and B, Tay-Sachs disease, Sandhoff’s disease, Globoid leukodystrophy, Metachromatic leukodystrophy</td>
<td>Lipogranuomatosis, Krabbe disease, MLD</td>
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<td>Glycoproteinosis</td>
<td>Aspartylglucosaminuria, Fucosidosis, alpha-Mannosidosis, beta-Mannosidosis, Mucolipidosis III and IV</td>
<td>Sialidosis, Type III-Batten disease</td>
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<td>Other lipidoses</td>
<td>Niemann-Pick disease C, Wolman disease, Ceroid lipofuscinosis</td>
<td>Glycogen storage, GSD type II, Pompe</td>
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<tr>
<td>Glycogen storage</td>
<td>GSD type II, Pompe</td>
<td>Multiple enzyme deficiency</td>
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<tr>
<td>Lysosomal transport defects</td>
<td>Cystinosis, Sialic acid storage disease, Salla disease</td>
<td>I-cell disease, Galactosialidosis, Mucolipidosis type II</td>
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<tr>
<td>Peroxisomal storage disorders</td>
<td>Adrenoleukodystrophy, Adrenomyeloneuropathy</td>
<td>ALD, AMN, Adrenoleukodystrophy</td>
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</table>

Infantile Malignant Osteopetrosis
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.(7) 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. Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately 6 months of age, and severe hematologic malfunction with bone marrow failure.(7) Seventy percent of these patients die before the age of 6 years, often of recurrent infections.(7) HSCT is the only curative therapy for this fatal disease.

Hematopoietic stem-cell transplantation for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis is addressed in a separate policy. (See Related Policies)
**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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**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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**Benefit Application**

N/A

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**Rationale**

This policy was updated with an electronic search of the NCBI PubMed database from July 15, 2013, through October 27, 2015.

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**Hemoglobinopathies**

Two 2010 review articles summarize the experience to date with hematopoietic stem-cell transplant (HSCT) and the hemoglobinopathies. (9-12)

More than 3000 patients worldwide have been treated for β-thalassemia with allogeneic HSCT (allo-HSCT). (11) Overall survival (OS) rates have ranged from 65% to 98% at 5 years, up to 87% at 15 years, up to 89% at 20 years, and thalassemia-free survival has been reported to be as high as 86% at 6 years. (13) The Pesaro risk stratification system classifies patients with thalassemia who plan to undergo allo-HSCT into risk groups I through III based on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with 2 risk factors, and III with all 3 risk factors). (14) The outcome of allo-HSCT in more than 800 patients with thalassemia according to risk stratification has shown overall and event-free survival (EFS) of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III. (14)

A 2015 study of 489 patients with nonmalignant hematologic disorders who underwent allo-HSCT between May 1997 and April 2012 included 152 patients with β-thalassemia. (15) Mean age at transplantation was 5.7 years (range, 1.1-23 years). At the time of transplantation, 26 (17%) patients had Pesaro class I, 103 (68%) had class II, and 23 (15%) had class III; 132 patients received peripheral blood stem cells and 20 received bone marrow grafts. Mean times to neutrophil and platelet engraftment were 21.4 days (range, 8-69 days) and 32.8 days (range, 7-134 days), respectively. The incidence of graft rejection was significantly lower in patients who received peripheral blood stem cells than in those who received bone marrow grafts (9% vs 25%; p=0.036). Acute graft-versus-host-disease (GVHD) grade II-IV occurred in 15% of β-thalassemia patients and chronic GVHD occurred in 12%. The incidence of transplant-related mortality for this group was 18%. After a median follow-up period of 12 years, the OS for these patients was 82.4%. Disease-free survival (DFS) of the whole group of β-thalassemia patients was 72.4% (74% in the peripheral blood stem cell transplantation group vs 64% in the bone marrow stem cell transplantation group; p=0.381), which may be attributed to the higher incidence of graft rejection in bone marrow groups.
Approximately 500 to 600 patients with sickle cell disease have undergone allo-HSCT, and most of the experience with allo-HSCT and sickle cell disease comes from 3 major clinical series. (1,11) The largest series to date consists of 87 symptomatic patients, most of whom received donor allografts from siblings who are human leukocyte antigen (HLA) identical. The results from this series (16) and the 2 others (17,18) were similar, with rates of OS ranging from 92% to 94% and EFS from 82% to 86%, with a median follow-up ranging from 0.9 to 17.9 years. (1)

Experience with reduced-intensity preparative regimens (reduced-intensity conditioning [RIC] and allogeneic HSCT for the hemoglobinopathies) is limited to a small number of patients. Challenges have been with high rates of graft rejection (10%-30%), (9) and, in adult patients, severe graft-versus-host-disease (GVHD) has been observed with the use of RIC regimens. (10)

In a recent report, 30 patients aged 16 to 65 years with severe sickle cell phenotype enrolled in a RIC allogeneic HSCT study, consisting of alemtuzumab (1 mg/kg in divided doses), total body irradiation (300 cGy), sirolimus, and infusion of unmanipulated filgrastim mobilized peripheral blood stem cells from HLA-matched siblings. (19) The primary endpoint was treatment success at 1 year after the transplant, defined as a full donor-type hemoglobin for patients with sickle cell disease and transfusion independence for patients with thalassemia. Secondary endpoints included the level of donor leukocyte chimerism; incidence of acute and chronic GVHD; and sickle cell-thalassemia disease-free survival (DFS), immunologic recovery, and changes in organ function. Twenty-nine patients survived a median 3.4 years (range, 1-8.6), with no nonrelapse mortality. One patient died from intracranial bleeding after relapse. The normalized hemoglobin and resolution of hemolysis among engrafted patients were accompanied by stabilization in brain imaging, a reduction of echocardiographic estimates of pulmonary pressure, and allowed for phlebotomy to reduce hepatic iron. A total of 38 serious adverse events were reported: pain and related management, infections, abdominal events, and sirolimus-related toxic effects.

Bernardo et al. reported the results of 60 thalassemia patients (median age, 7 years; range, 1-37) who underwent allogeneic HSCT after an RIC regimen based on the treosulfan. (20) Before transplant, 27 children were assigned to risk class 1 of the Pesaro classification, 17 to class 2, and 4 to class 3; 12 patients were adults. Twenty patients were transplanted from an HLA-identical sibling and 40 from an unrelated donor. The cumulative incidence of graft failure and transplantation-related mortality was 9% and 7%, respectively. Eight patients experienced grade II-IV acute GVHD, the cumulative incidence being 14%. Among 56 patients at risk, 1 developed limited chronic GVHD. With a median follow-up of 36 months (range, 4-72), the 5-year probability of survival and thalassemia-free survival were 93% and 84%, respectively. Neither the class of risk nor the donor used influenced outcome.

In a recent report on RIC HSCT, 98 patients with class 3 thalassemia were transplanted with related or unrelated donor stem cells. (21) Seventy-six of the patients age 10 years or younger received a conventional myeloablative conditioning regimen (cyclophosphamide [Cy], busulfan, + fludarabine [Flu]). The remaining 22 patients, who were older than 10 years, had hepatomegaly and in several instances additional comorbidity problems, underwent HSCT with a novel RIC regimen (fludarabine and busulfan). EFS (86% vs 90%, respectively), and OS (95% vs 90%, respectively) were not significantly different between the groups. However, a higher incidence of serious treatment-related complications was observed in the myeloablative conditioned group. Further, graft failures occurred in 6 patients in the myeloablative group (8%), but none occurred in the RIC group.

A Cochrane systematic review published in 2013 identified no randomized controlled trials (RCTs) that assessed a risk or benefit of any method of HSCT in patients with sickle cell disease. (22)

**Bone Marrow Failure Syndromes**

Two 2010 review articles summarize the experience to date with HSCT and the bone marrow failure syndromes. (9,23-25)

**Fanconi Anemia**

In a summary of allogeneic HSCT from matched related donors over the past six years in Fanconi anemia, totaling 103 patients, OS ranged from 83% to 88%, with transplant-related mortality ranging from 8% to 18.5% and average chronic GVHD of 12%. (26)

The outcomes in patients with Fanconi anemia and an unrelated donor allogeneic HSCT have not been as
promising. The European Group for Blood and Marrow Transplantation (EBMT) working party has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median 2-year survival was 28%±8%. (3) Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. (3) The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 96 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year OS rates were 13% and 52%, respectively, in patients who received non-fludarabine versus fludarabine-based regimens. (3)

Zanis-Neto et al. reported the results of 30 patients with Fanconi anemia treated with RIC regimens, consisting of low-dose Cy. (27) Seven patients were treated with Cy at 80 mg/kg and 23 with 60 mg/kg. Grade 2-3 acute GVHD rates were 57% and 14% for patients who received the higher and lower doses, respectively (p=0.001). Four of the 7 patients who received the higher dose were alive at a median of 47 months (range, 44-58 months), and 22 of 23 given the lower dose were alive at a median of 16 months (range, 3-52 months). The authors concluded that a lower dose of Cy conditioning had lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the CIBMTR, Wagner et al. reported that Flu-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year OS (52% vs. 13%, respectively; p<0.001) compared with non-fludarabine regimens. (28)

**Other**

Results with allogeneic HSCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis. (3) Currently, nonmyeloablative conditioning regimens with Flu are being explored; however, very few results have been published. (3)

Outcomes after allogeneic HSCT were recently reported in 34 patients with dyskeratosis congenita who underwent transplantation between 1981 and 2009. (29) The median age at transplantation was 13 years (range, 2-35). Approximately 50% of transplantations were from related donors. The day-28 probability of neutrophil recovery was 73% and the day-100 platelet recovery was 72%. The day-100 probability of grade II to IV acute GVHD and the 3-year probability of chronic GVHD were 24% and 37%, respectively. The 10-year probability of survival was 30%; 14 patients were alive at last follow-up. Ten deaths occurred within 4 months from transplantation because of graft failure (n=6) or other transplantation-related complications; 9 of these patients had undergone transplantation from mismatched related or from unrelated donors. Another 10 deaths occurred after 4 months; 6 of them occurred more than 5 years after transplantation, and 4 of these were attributed to pulmonary failure. Transplantation regimen intensity and transplantations from mismatched related or unrelated donors were associated with early mortality. Transplantation of grafts from HLA-matched siblings with Cy-containing non-radiation regimens was associated with early low toxicity. Late mortality was attributed mainly to pulmonary complications and likely related to the underlying disease.

Experience with allogeneic HSCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease. (3) Gesaro et al. reported 26 patients with Shwachman-Diamond syndrome from the EBMT registry given HSCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (MDS-AML) (n=9); or another diagnosis (n=1). (30) Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n=6), mismatched related (n=1), or unrelated graft (n=19). Graft failure occurred in 5 (19%) patients, and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, OS was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

In Diamond-Blackfan anemia, allogeneic HSCT is an option in corticosteroid-resistant disease. (3) In a report from the Diamond-Blackfan anemia registry, 20 of 354 registered patients underwent allogeneic HSCT, and the five-year survival rates were 87.5% when recipients received HLA-identical sibling grafts but were poor in recipients of alternative donors. (3) The CIBMTR reported the results in 61 patients who underwent HSCT between 1984 and 2000. (31) Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of OS after transplantation for patients transplanted from an HLA-identical sibling donor (vs. an alternative donor) was 78% versus 45% (p=0.01) at one year and 76% versus 39% (p=0.01) at three years, respectively.

A randomized Phase III trial compared 2 different conditioning regimens in high-risk aplastic anemia patients
Patients in the Cy plus anti-thymocyte globulin (ATG) arm (n=39) received Cy at 200 mg/kg; those in the Cy-Flu-ATG group (n=40) received Cy at 100 mg/kg and Flu at 150 mg/m2. No difference in engraftment rates was reported between arms. Infection with an identified causative organism and sinusoidal obstruction syndrome, hematuria, febrile episodes, and death from any cause tended to be more frequent in the Cy-ATG arm but did not differ significantly between arms. OS at 4 years did not differ between the Cy-ATG and Cy-Flu-ATG arms (78% vs. 86%, respectively, p=0.41). Although this study was underpowered to detect real differences between the conditioning regimens, the results suggest an RIC regimen with Cy-Flu-ATG appears to be as safe as a more traditional myeloablative regimen comprising Cy-ATG in allogeneic HSCT.

A 2015 study analyzed outcomes reported to the EBMT of children with idiopathic aplastic anemia, according to treatment received. (33) Front-line immunosuppressive therapy (IST) was compared with front-line HSCT from an HLA-matched family donor (MFD), to evaluate the outcomes of patients who, after having failed IST, underwent rescue HSCT, and to compare their outcomes with front-line HSCT and those who did not fail IST (IST with no subsequent transplant). Additional outcomes that were evaluated were the cumulative incidence of posttherapy tumors and prognostic factors that may affect the outcome of the disease. Included in the analysis were records from 563 consecutive children (313 males and 250 females [age range, 0-12 years]) diagnosed between January 2000 and December 2009. Geographical origin, if known, was distributed as follows: 383 patients from Europe, 51 from Africa, 51 from the Middle East, 2 from Australia, and 1 from Brazil. The median age at diagnosis was 7.8 years (range, 0.01-11.9 years). A total of 167 children received front-line IST (consisting of ATG plus cyclosporine); of these, 91 (55%) failed IST as front-line treatment and underwent subsequent rescue HSCT (HSCT post-IST failure) whereas IST was the only treatment received (IST alone) for 76 patients. Three-year probability of OS and EFS for the whole population was 90% and 86%, respectively. The 3-year OS was 91% (SE=2%) after MFD front-line HSCT versus 87% (SE=3%) after first-line IST (p=0.18). The 3-year probability of OS after HSCT post-IST failure was 83%, after MFD front-line HSCT 91% and after IST alone 97% (p=0.017). A subgroup analysis showed no significant difference between IST alone and MFD front-line HSCT (p=0.21), but significantly higher OS of both MFD front-line HSCT (p=0.02) and IST alone (p=0.047) over HSCT post-IST failure.

In the 2015 study cited earlier, which examined 489 patients with nonmalignant hematologic disorders who underwent allo-HSCT, 273 patients with severe aplastic anemia were included. (15) Of these subjects, 212 were male and 61 were female, and the mean age at transplantation was 19.7 years (range, 1.5-51 years). Mean times to neutrophil and platelet engraftment were 13.9 days (range, 10-26 days) and 14.1 days (range, 8-83 days), respectively. Graft rejection occurred in1% of patients. Acute GVHD grade II-IV occurred in 15% and chronic GVHD occurred in 28% of patients. The incidence of transplant-related mortality was 22%. At 8 years, OS and DFS were both 74%. Conditioning regimens differed among the patients, with 181 receiving fludarabine and cyclophosphamide and 92 receiving cyclophosphamide and ATG. No statistically significant differences between conditioning groups were observed in terms of mean time to neutrophil engraftment and incidence of extensive chronic GVHD (p=0.136 and 0.651, respectively). Mean time to platelet engraftment was significantly longer in the cyclophosphamide/ATG group (p=0.016). The incidence of transplant-related mortality in the fludarabine/cyclophosphamide group was 17%, which was significantly lower than in the cyclophosphamide/ATG group (33%; p=0.002). After a median follow-up of 8 years, OS was statistically significantly better in the fludarabine/cyclophosphamide group than in the cyclophosphamide/ATG group of patients (80% vs 64%, respectively; p=0.021).

Primary Immunodeficiencies

Two 2010 review articles summarize experience to date with HSCT and the primary immunodeficiencies. (34,35) Additional individual studies are reported next.

Outcomes of HSCT in patients with chronic granulomatous disease (CGD) were compared with those in patients with CGD who were given conventional treatment. (36) Forty-one patients in Sweden were diagnosed with CGD between 1990 and 2012. From 1997 to 2012, 14 patients with CGD, aged 1 to 35 years, underwent HSCT and received grafts either from an HLA-matched sibling donor or a matched unrelated donor. Thirteen of the 14 (93%) transplanted patients were reported alive and well at publication. The mean age at transplantation was 10.4 years, and the mean survival time was 7.7 years. In contrast, 7 of 13 men or boys with X-linked CGD who were treated conventionally died from complications of CGD at a mean age of 19 years, while the remaining patients suffered life-threatening infections.
A prospective study in 16 centers in ten countries worldwide enrolled patients aged 0 to 40 years with CGD treated with RIC HSCT consisting of high-dose Flu, serotherapy or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration. (37) Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related-donors or HLA-9/10 or HLA-10/10 matched unrelated-donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at 2 years, incidence of acute and chronic GVHD, achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least 6 months of follow-up. A total 56 patients (median age 12.7 years) with chronic granulomatous disease were enrolled; 42 patients (75%) had high-risk features (i.e., intractable infections and auto inflammation),(25) (45%) were adolescents and young adults (age 14-39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At median follow-up of 21 months, OS was 93% (52/56) and EFS was 89% (50/56). The 2-year probability of OS was 96% (95% confidence interval [CI], 86.46 to 99.09) and of EFS was 91% (79.78 to 96.17). Graft-failure occurred in 5% (3/56) of patients. The cumulative incidence of acute GVHD of grade III to IV was 4% (2/56) and of chronic GVHD was 7% (4/56). Stable (>=90%) myeloid donor chimerism was documented in 52 (93%) surviving patients.

HSCT using HLA-identical sibling donors can correct underlying primary immunodeficiencies, such as severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies, in approximately 90% of cases. (38) According to a European series of 475 patients collected between 1968 and 1999, survival rates for SCID were approximately 80% with a matched sibling donor, 50% with a haploidentical donor, and 70% with a transplant from an unrelated donor. (38) Since 2000, OS for patients with SCID who have undergone HSCT is 71%. (4)

Hassan et al. reported a multicenter retrospective study, which analyzed the outcome of HSCT in 106 patients with adenosine deaminase deficient-SCID who received a total of 119 transplants. (39) HSCT from matched sibling and family donors had significantly better OS (86% and 81%) in comparison with HSCT from matched unrelated (66%; p<0.05) and haploidentical donors (43%; p<0.001). Superior OS was also seen in patients who received unconditioned transplants in comparison with myeloablative procedures (81% vs. 54%; p<0.003) although in unconditioned haploidentical donor HSCT, non-engraftment was a major problem. Long-term immune recovery showed that regardless of transplant type, overall T cell numbers were similar, although a faster rate of T cell recovery was observed following matched sibling and family donor HSCT. Humoral immunity and donor B-cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HSCT.

For Wiskott-Aldrich syndrome, an analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes. (40) Fifty-five transplants were from HLA-identical sibling donors, with a five-year probability of survival of 87% (95% CI: 74% to 93%); 48 were from other relatives, with a five-year probability of survival of 52% (37% to 65%); and 67 were from unrelated donors with a five-year probability of survival of 71% (58% to 80%; p<0.001).

Moratto et al. retrospectively reported the long-term outcome and donor-cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HSCT in the period 1980 to 2009. (41) OS was 84.0% and was even higher (89.1% 5-year survival) for those who received HSCT since the year 2000, reflecting recent improvement of outcome after transplantation from mismatched family donors and for patients who received HSCT from an unrelated donor at older than 5 years. Patients who went to transplantation in better clinical condition had a lower rate of post-HSCT complications. Retrospective analysis of lineage-specific donor-cell engraftment showed that stable full-donor chimerism was attained by 72.3% of the patients who survived for at least 1 year after HSCT. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte counts and post-HSCT autoimmunity, and myeloid donor cell chimerism below 50% was associated with persistent thrombocytopenia.

For patients with genetic immune/inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the current results with allogeneic HSCT are 60% to 70% 5-year DFS.

For patients with other immunodeficiencies, OS rates are 74%, with even better results (90%) with well-matched donors for defined conditions, such as chronic granulomatous disease. (4)

Studies so far indicate that RIC regimens may have an important role in treating patients with primary immunodeficiency. (35) In the absence of prospective or larger registry studies, it is not possible to prove superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae, e.g., infertility and growth retardation, may be avoided or reduced. Currently, RIC HSCT
using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (>5 years of age), and chronic granulomatous disease with ongoing inflammatory or infective complications. Minimal intensity conditioning HSCT may be particularly suited to unrelated donor HSCT in young SCID patients with significant comorbidities.

X-linked lymphoproliferative disease type 1 (XLP1) is a rare, deadly immune deficiency caused by mutations in SH2D1A. Allogeneic HSCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. A recent study reported an 8-year single-center experience.(42) Sixteen consecutive patients diagnosed with XLP1 underwent allogeneic HSCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, Flu, and melphalan. Fourteen of 16 patients received 8/8 HLA-matched unrelated or related bone marrow grafts, whereas 2 patients received mismatched unrelated grafts. All patients had hematopoietic recovery. No cases of hepatic veno-occlusive disease or pulmonary hemorrhage were reported. One patient (6%) developed acute GVHD and later also developed chronic GVHD (6%). Five patients (31%) developed mixed chimerism. One-year survival estimated by Kaplan-Meier analysis was 80%, with long-term survival estimated at 71%. There were no occurrences of lymphoma after HSCT.

**Inherited Metabolic Diseases**

Two 2010 review articles summarize the experience to date with HSCT and the inherited metabolic diseases.(43,44)

In the past 25 years, HSCT has been performed in approximately 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders.(6) Most (>80%) have been in patients with mucopolysaccharidosis I (MPS I; Hurler syndrome), other MPS syndromes (MPS II, MPS IIIA and B, MPS VI), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid leukodystrophy.(6) With the exception of Hurler and globoid cell leukodystrophy, most published data are single-case reports or small series with short follow-up.(45) The benefit of allogeneic HSCT appears limited to select subsets of patients with few types of lysosomal storage diseases and is not effective in patients who have developed overt neurologic symptoms or in those with aggressive infantile forms.(45)

Hurler syndrome is a lysosomal storage disease that if left untreated, results in progressive multisystem morbidity including neurodevelopmental deterioration, severe orthopedic manifestations, and cardiopulmonary complications leading to death in early childhood. Although enzyme replacement therapy is available, HSCT remains the only treatment that delivers the deficient enzyme to the central nervous system (CNS).(46) Impressive results have been observed with allogeneic HSCT in Hurler syndrome. The benefits that have been observed include improvements in neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others.(6) Survival of engrafted Hurler syndrome patients has been radically changed from that of untransplanted patients, with long-term survival data indicating that lifespan can be extended by many decades.(47) An analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%.(48)

In 2015, an international retrospective analysis reported long-term results from 217 patients with Hurler syndrome who successfully underwent allo-HSCT between 1985 and 2011.(46) Median follow-up was 9.2 years (range, 3-23 years), median age at diagnosis was 9 months (range, 0-42 months), and median age at transplant was 16 months (range, 2-47 months). Primary study end points were neurodevelopmental outcomes and growth; secondary end points included outcomes involving several different organ systems. Pre-HSCT, 56.9% of patients showed normal neurodevelopment and 26.6% showed only mildly impaired neurodevelopment. At last follow-up post-HSCT, normal or only mildly impaired neurodevelopment was observed in 26.9% and 28.3% of the patients, respectively, and 44.9% suffered from moderate to severely impaired neurodevelopment. Predictors of better outcomes posttransplant were higher baseline developmental and intelligence quotients (IQs) pretransplant, younger age at transplant, and a normal α-L-iduronidase enzyme level posttransplant.

Experience with allogeneic HSCT and a reduced-intensity preparative regimen has been reported in seven patients with Hurler syndrome.(49) Six of the patients received transplants from unrelated donors, and one received the transplant from a sibling. All patients had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the seven children were alive at a median of 1,014 days (range: 726–2,222 days) post-transplant.
The few patients with Maroteaux-Lamy and Sly syndrome who have received transplants have shown promising results, with clinical improvement post-transplant.\(^{(47)}\)

Outcomes with the leukodystrophies and allogeneic HSCT have been variable but somewhat promising. In boys and men with X-linked adrenoleukodystrophy; outcomes have depended on disease status at transplant and transplant-related complications,\(^{(47)}\) but reports of preservation of neuropsychologic and neurologic function have been presented.

Miller et al. reported the results of 60 boys who underwent allogeneic HSCT for cerebral adrenoleukodystrophy between 2000 and 2009.\(^{(50)}\) The median age at HSCT was 8.7 years; conditioning regimens and allograft sources varied. At HSCT, 50% demonstrated a Loes radiographic severity score of 10 or more, and 62% showed clinical evidence of neurologic dysfunction. A total of 78% (n=47) are alive at a median 3.7 years after HSCT. The estimate of 5-year survival for boys with Loes score less than 10 at HSCT was 89%, whereas that for boys with Loes score of 10 or more was 60% (p=0.03). The 5-year survival estimate for boys absent of clinical cerebral disease at HSCT was 91%, whereas that for boys with neurologic dysfunction was 66% (p=0.08). The cumulative incidence of transplantation-related mortality at day 100 was 8%. Post-transplantation progression of neurologic dysfunction depended significantly on the pre-HSCT Loes score and clinical neurologic status.

Fewer than 40 patients with Globoid-cell leukodystrophy have undergone allogeneic HSCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.\(^{(47)}\)

Many patients with metachromatic leukodystrophy who have undergone allogeneic HSCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival.\(^{(47)}\)

Mynarek et al. reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HSCT.\(^{(51)}\) Patients were diagnosed with the disease at a median age of 2.5 years (range, 1.1-23 years) and underwent HSCT at a median age of 3.6 years (1.3-23.1 years). After a median follow-up of 5.5 years (2.1-12.6 years), OS was 88%. One patient died 76 days after HSCT from sepsis, GVHD, and pulmonary hemorrhage, and another patient died on day 135 due to viral infections and multi-organ failure. Before HSCT, the extent of developmental delay in the 17 patients varied over a wide range. After HSCT, patients made developmental progress; however, normal development was not achieved. Hearing ability improved in some but not all of the patients.

Hunter syndrome is composed of two distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged life span, minimal to no central nervous system involvement, and a slow progression.\(^{(47)}\) Experience with allogeneic HSCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly.\(^{(47)}\) Some authors suggest that HSCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits.\(^{(47)}\)

Eight patients with Hunter syndrome received an allogeneic HSCT between the ages of 3 and 16 years.\(^{(52)}\) In six cases, the donor was a sibling with identical HLA status, in one case, the donor was unrelated HLA-compatible, and in one case, the donor was a mismatched unrelated donor. The severity of disease before transplant was rated by assessing the age at diagnosis, behavior, and intelligence quotient (IQ) at the time of graft and genotype. Five patients were considered to have severe central nervous system involvement (i.e., diagnosis before the age of 4 years and an IQ <80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years and normal IQ), and 1 as intermediate (i.e., diagnosis after the age of four years and IQ between 80 and 90). After follow-up ranging from seven to 17 years, all were still alive with the exception of one patient who died of unrelated causes. Successful engraftment was achieved in all patients and cardiovascular abnormalities stabilized in all patients, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. Neuropsychological outcome was variable: the two patients with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four patients with the severe form of the syndrome deteriorated after the graft, and their IQ/developmental quotient had declined below 50 at the time of the last evaluation. Of the patients with the severe form, three lost the ability to walk in their early teens, two lost language at nine and 11 years, and two developed epilepsy. The remaining two patients with the severe form required special schooling and had poor social and language skills.

Experience with allogeneic HSCT in patients with MPS III (Sanfilippo syndrome) has shown no alteration in the course of neuropsychologic deterioration seen in these patients.\(^{(47)}\) The literature addressing the use of HSCT in Sanfilippo disease consists of two case reports.\(^{(53,54)}\) Vellodi et al. reported the outcomes of twin girls diagnosed
with MPS III who underwent allogeneic HSCT and were followed up for nine years.(53) At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next 8 years, both girls had a steady decline in cognitive development, and both functioned in the area of significant developmental delay. The authors postulated that a possible reason for continued deterioration in the twins, despite the demonstration of full chimerism, was a very low level of enzyme throughout the years after transplant. One other patient with MPS III who had received a transplant was 5.3 years old at the time of the transplant and continued to regress post-transplant.(54)

**Infantile Malignant Osteopetrosis**
A 2010 review article summarizes the experience to date with HSCT and osteopetrosis.(55)

The success of allogeneic HSCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a five-year DFS of 73% to 79% versus transplantation with an unrelated or mismatched donor of 13% to 45%.(7)

A retrospective analysis of 122 children who received an allogeneic HSCT for autosomal recessive osteopetrosis between 1980 and 2001 reported five-year DFS of 73% for recipients of a genotype HLA-identical HSCT (n=40), 43% for those of a phenotype HLA-identical or one HLA-antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20), and 24% for patients who received an HLA-haplotype-mismatch graft from a related donor (n=41).(56)

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 2.

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<th>NCT No.</th>
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<td>In-vivo T-cell Depletion and Hematopoietic Stem Cell Transplantation for Life-Threatening Immune Deficiencies and Histiocytic Disorders</td>
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<td>NCT00775931</td>
<td>Allogeneic Hematopoietic Stem Cell Transplantation For Severe Osteopetrosis</td>
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<td>Oct 2015</td>
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<td>NCT00176852</td>
<td>Allogeneic Hematopoietic Stem Cell Transplant for Patients With High Risk Hemoglobinopathy Using a Preparative Regimen to Achieve Stable Mixed Chimerism</td>
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<td>Jun 2016</td>
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<td>NCT01087398</td>
<td>Hematopoietic Stem Cell Transplantation for Malignant Infantile Osteopetrosis</td>
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<td>NCT01019876</td>
<td>Risk-Adapted Allogeneic Stem Cell Transplantation For Mixed Donor Chimerism In Patients With Selected Non-Malignant Diseases</td>
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<td>May 2013</td>
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<td>NCT00023192</td>
<td>Treatment of Chronic Granulomatous Disease With Allogeneic Stem Cell Transplantation Versus Standard of Care</td>
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<td>Jun 2014 (completed)</td>
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<td>NCT00383448</td>
<td>Treatment of High Risk, Inherited Lysosomal And Peroxisomal Disorders by Reduced Intensity Hematopoietic Stem Cell Transplantation</td>
<td>39</td>
<td>Sep 2014 (completed)</td>
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**Summary of Evidence**
The evidence for allogeneic hematopoietic stem cell transplantation (allo-HSCT) in select individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome diseases, or a genetic disorder affecting skeletal tissue includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, hospitalizations, medication use, resource utilization, and
treatment-related mortality and 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 with the use of allo-HSCT in the inherited metabolic diseases Hunter, Sanfilippo, and Morquio syndromes. Allo-HSCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases.

**Clinical Input Received From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society (3 reviewers) and 3 academic medical centers while this policy was under review in 2009. There was general agreement with the policy statements. In particular, the reviewers were specifically asked to address the issue of the use of HSCT in the inherited metabolic diseases, except for Hunter, Sanfilippo, and Morquio syndromes; 4 reviewers agreed with the current policy statement, 1 disagreed, and 1 did not address this specific question.

**Practice Guidelines and Position Statements**

**European Blood and Marrow Transplantation Inborn Error Working Party et al**

In 2014, an international expert panel, the European Blood and Marrow Transplantation Inborn Error Working Party and the Paediatric Diseases Working Party, provided consensus-based recommendations on indications for HSCT and transplant management in the hemoglobinopathies.(11)

** Pediatric Haemato-Oncology Italian Association**

In 2015, the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association issued guidelines on the diagnosis and treatment of acquired aplastic anemia in childhood.(57)

**U.S. Preventive Services Task Force Recommendations**

Allogeneic HSCT is not a preventive service.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


Appendix

N/A

History

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<td>02/01/00</td>
<td>Add to Therapy Section - New policy. Policy represents revision of original 7.03.10. Myelofibrosis and myelodysplasia, originally included in that policy, are now addressed in policy CP.MP.BC.8.01.21. Policy replaced CP.MP.BC.8.01.22, with policy statement on remaining indications unchanged.</td>
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<td>11/12/07</td>
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<td>05/13/08</td>
<td>Cross Reference Update - No other changes</td>
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<td>12/08/09</td>
<td>Replace policy - Policy updated and extensively edited based on literature search. Except for one change, the intent of the policy statements is unchanged. The change in the policy statement is that treatment of Hunter, Sanfilippo, and Morquio syndromes are not included in the list of lysosomal and peroxisomal storage diseases where allo-HSCT may be considered medically necessary and are now considered not medically necessary. References added. On hold for notification, release to publish on May 10, 2010.</td>
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<td>12/14/2010</td>
<td>Replace policy - Policy updated and extensively edited with information on use of reduced-intensity conditioning based upon literature search. References 9, 10, 15, 18, 19, 21, 22, 25, 26, 30 and 33 have been added; the policy statements remain unchanged. Reviewed and approved by OAP on November 18, 2010.</td>
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<td>01/24/12</td>
<td>Code 38232 added.</td>
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<td>Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.</td>
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<td>Update to Related Policies Titles: 8.01.17, 8.01.20, 8.01.21, 8.01.29, 8.01.30, 8.01.31, 8.01.35, and 8.01.520.</td>
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11/27/12 Replace policy - Policy updated with literature search; references 15, 25 and 27 added; no change in policy statements. HCPCS codes G0265 – G0267 removed as these are deleted codes as of 2008.
02/01/13 Update Related Policies, change title of policy 8.01.21.
03/20/13 The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.
09/30/13 Update Related Policies. Change title to 8.01.31.
02/27/14 Update Related Policies. Change title to 8.01.30.
03/11/14 Coding Update. Codes 41.02, 41.03, and 41.05 were removed per ICD-10 mapping project; these codes are not utilized for adjudication of policy.
03/21/14 Update Related Policies. Add 8.01.15 and delete 8.01.514.
04/18/14 Update Related Policies. Remove 8.01.20 and add 8.01.529.
06/24/14 Update Related Policies. Delete 8.01.35 and 8.01.42 and add 8.01.530 and 8.01.532
11/10/14 Annual Review. Policy updated with literature review through July 31, 2014; references 15, 17, 23, 29-30, and 35 added; no change in policy statements. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not relate to adjudication.
02/03/15 Update Related Policies. Remove 8.01.23, 8.01.28 and 8.01.30.
11/10/15 Annual Review. Policy updated with literature search; reference 48 added; no change in policy statement.
04/12/16 Annual Review. Policy updated with literature review through October 27, 2015; references 11-13, 15, 24-25, 33, 46, and 57 added. Policy statements unchanged.
08/09/16 Update Related Policies. Remove 8.01.27 as it was archived.
09/30/16 Coding Update. Remove CPT 86817 from coding section.
11/04/16 Coding update. Removed codes that are transplant benefit related.
04/01/17 Update Related Policies; updated some of the titles. Minor formatting update.
08/01/17 Updated title of Related Policy 8.01.511.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA).
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Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5992. TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة. قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة. قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة. قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة، قد يحيى هذا الإشعار معلومات هامة.

Oromo (Cushite):


Français (French):


Kreyòl ayisyen (Creole):

Avis sila a gen Enfòmasyon Enpòtan ladan. Avis sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan osawa konsènan kouvèti asirans lan atravé Premera Blue Cross. Kapab genyen dat ki enpòtan nan avisi sila a. Ou ka gen pou pran kék akson avan setend dat limit pou ka bente kouvèti asirans sante w la osawa pou yo ka ede w avèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asitans nan lang ou pale a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):


Hmong (Hmong):


Illoko (Ilocano):

Daytoy a Pakdaa ket naglaon iti Napateg nga Impormasjon. Daytoy a pakdaa mabalini nga adda ket naglaon iti napateg nga impormasjon maipanggpep iti aplikasyonwyo wenny coverage babaen iti Premera Blue Cross. Daytoy ket mabalini dagiti importante a petsa iti daytoy a pakdaa. Mabalini nga adda rumbeng nga aramidey nga adda saksay dagiti partikular a naituding nga aldaw tapno mapagtalainedeyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasjon ken tulong iti bukodyo a pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).
Japanese (Japanese): この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている情報が重要である場合をご確認ください。健康保険や保険サポートを維持するには、特定の期限までに行動を取られなければなりません。このガイダンスによる情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean): 본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지는 귀하의 신청에 관하여 그리고 Premera Blue Cross를 통한 커버리지를 개선하기 위한 정보를 포함하고 있습니다. 본 통지서에는 책임이 있는 벌이가 있을 수 있습니다. 귀하의 신청을 개선하기 위해서 일정한 미각까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 준비에 귀하의 안내에 부담없이 읽을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하실시오.

Русский (Russian): Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish): Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas claras en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).


ไทย (Thai): ประกาศนี้มีข้อมูลที่สำคัญเกี่ยวกับการสมัครหรือขอบเขตการประกันสุขภาพของคุณ Premera Blue Cross และมีความจำเป็นในการให้คุณทราบ คุณควรดำเนินการในกำหนดเวลาที่ระบุไว้เพื่อจะได้รับการประกันสุขภาพของคุณในกรณีที่มีการป่วย คุณมีสิทธิ์ที่จะได้รับการสนับสนุนและการช่วยเหลือในกรณีที่มีการป่วยได้ โทร. 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian): Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхування через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує ймовірність того, що Вам треба буде здійснити певні кроки у конкретному кінцевому строкі для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).