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

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Section: Transplants

Place(s) of Service: Outpatient; Inpatient

Precertification is required for this service.

I. Description

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 radiation therapy. 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.

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 human
leukocyte antigens (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 lymphoablation.

**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. 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.

**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. 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.

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

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia. 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.

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. The most severe defects (collectively known as severe combined immunodeficiency, or SCID) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells. Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the life span 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. 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.

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. 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. 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 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.

Allogeneic HSCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1. 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.

**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. 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. Seventy percent of these patients die before the age of 6 years, often of recurrent infections. HSCT is the only curative therapy for this fatal disease.

**Table 1. Lysosomal and Peroxisomal Storage Disorders**

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Other Names</th>
</tr>
</thead>
</table>
| 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’s  
Farber’s  
Gaucher’s I-III  
GM₁ gangliosidosis  
Niemann-Pick disease A and B  
Tay-Sachs disease  
Sandhoff’s disease  
Globoid leukodystrophy  
Metachromatic leukodystrophy | Lipogranulomatosis  
Krabbe disease  
MLD |
| Glycoproteinosis       | Aspartylglucosaminuria  
Fucosidosis  
alpha-Mannosidosis  
beta-Mannosidosis  
Mucolipidosis III and IV | Sialidosis |
| Other lipidoses        | Niemann-Pick disease C |
### II. Criteria/Guidelines

Allogeneic hematopoietic stem cell transplantation is covered (subject to Administrative Guidelines) for selected patients with the following disorders:

<table>
<thead>
<tr>
<th>Glycogen storage</th>
<th>Wolman disease</th>
<th>Ceroid lipofuscinosis</th>
<th>Type III-Batten disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple enzyme deficiency</td>
<td>Galactosialidosis</td>
<td>Mucolipidosis type II</td>
<td>I-cell disease</td>
</tr>
<tr>
<td>Lysosomal transport defects</td>
<td>Cystinosis</td>
<td>Sialic acid storage disease</td>
<td>Salla disease</td>
</tr>
<tr>
<td>Peroxisomal storage disorders</td>
<td>Adrenoleukodystrophy</td>
<td>Adrenomyeloneuropathy</td>
<td>ALD AMN</td>
</tr>
</tbody>
</table>

II. Policy Guidelines

1. The following lists the immunodeficiencies that have been successfully treated by allogeneic HSCT:
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 (IκB-alpha) deficiency
- Nijmegen breakage syndrome
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 been effective in Hunter, Sanfilippo, or Morquio syndromes. 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.

IV. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA’s Precertification Request and mail or fax the form as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
</tr>
<tr>
<td>38209</td>
<td>; Thawing of previously frozen harvest, with washing</td>
</tr>
<tr>
<td>38210</td>
<td>; Specific cell depletion within harvest, T-cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>; Red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>; Platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>; Plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>; Cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow, aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38242</td>
<td>Allogeneic donor lymphocyte infusions</td>
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<td>86812 - 86822</td>
<td>Histocompatibility studies code range</td>
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**HCPCS Code**  
**Description**

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0265</td>
<td>Cryopreservation, freezing and storage of cells for therapeutic use, each cell line</td>
</tr>
<tr>
<td>G0266</td>
<td>Thawing and expansion of frozen cells for therapeutic use, each cell line</td>
</tr>
<tr>
<td>G0267</td>
<td>Bone marrow or peripheral stem-cell harvest, modification or treatment to eliminate cell type(s) (e.g., T cells, metastatic carcinoma)</td>
</tr>
<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy administration code range</td>
</tr>
<tr>
<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 peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical, surgical, diagnostic and emergency services)</td>
</tr>
</tbody>
</table>

**ICD-10-CM Code**  
**Description**

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>D56.1</td>
<td>Beta thalassemia</td>
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<tr>
<td>D57.00 – D57.819</td>
<td>Sickle-cell disorders code range</td>
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<tr>
<td>D61.01 – D61.89</td>
<td>Other aplastic anemias and other bone marrow failure syndromes code range (includes Fanconi anemia)</td>
</tr>
<tr>
<td>D70.0</td>
<td>Congenital agranulocytosis (includes Kostmann’s disease)</td>
</tr>
<tr>
<td>D71</td>
<td>Functional disorders of polymorphonuclear neutrophils (includes chronic granulomatous disease)</td>
</tr>
<tr>
<td>D81.0 – D81.9</td>
<td>Combined immunodeficiencies code range</td>
</tr>
<tr>
<td>D82.0 – D82.9</td>
<td>Immunodeficiency associated with other major defects code range (includes Wiskott-Aldrich and X-linked lymphoproliferative syndromes)</td>
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<tr>
<td>E70.330</td>
<td>Chediak-Higashi syndrome</td>
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<tr>
<td>E71.50 - E71.548</td>
<td>Peroxisomal disorders code range (includes childhood cerebral X-linked adrenoleukodystrophy)</td>
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<tr>
<td>E75.25</td>
<td>Metachromatic leukodystrophy</td>
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<tr>
<td>ICD-10-PCS Code</td>
<td>Description (ICD-10-PCS codes are only used for inpatient services)</td>
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<tr>
<td>E76.01</td>
<td>Hurler’s syndrome</td>
</tr>
<tr>
<td>E76.29</td>
<td>Other mucopolysaccharidoses (includes Maroteaux-Lamy syndrome)</td>
</tr>
<tr>
<td>E77.01</td>
<td>Defects in glycoprotein degradation (includes aspartylglucosaminuria, mannosidosis and fucosidosis)</td>
</tr>
<tr>
<td>Q78.2</td>
<td>Osteopetrosis (includes Albers-Schonberg syndrome)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10-PCS Code</th>
<th>Description (ICD-10-PCS codes are only used for inpatient services)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30243G1, 30243X1, 30243Y1</td>
<td>Percutaneous transfusion, central vein, bone marrow or stem cells, nonautologous, code list</td>
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<tr>
<td>07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ, 07DS0ZZ, 07DS3ZZ</td>
<td>Surgical, lymphatic and hemic systems, extraction, bone marrow, code list</td>
</tr>
</tbody>
</table>

V. Scientific Background

**Hemoglobinopathies**

Review articles summarize the experience to date with hematopoietic stem cell transplant (HSCT) and the hemoglobinopathies.

More than 3,000 patients worldwide have been treated for beta-thalassemia with allogeneic hematopoietic stem-cell transplant (HSCT). 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. The Pesaro risk stratification system classifies patients with thalassemia who are to undergo allogeneic HSCT into risk groups I through III 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). The outcome of allogeneic HSCT in more than 800 patients with thalassemia according to risk stratification has shown overall and event-free survival of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III.¹

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. 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 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 series16 and the 2 others17,18 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.

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 included high rates of graft rejection (10–30%), and, in adult patients, severe graft-versus-host-disease (GVHD) has been observed with the use of RIC regimens.

A 2014 published article reported results from 30 patients aged 16 to 65 years with severe sickle cell phenotype who were enrolled in an RIC allo-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 end point 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 end points included the level of donor leukocyte chimerism; incidence of acute and chronic GVHD; and sickle cell–thalassemia DFS, immunologic recovery, and changes in organ function. Twenty-nine patients survived a median 3.4 years (range, 1-8.6 years), 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 and colleagues reported the results of 60 thalassemia patients (median age, 7 years; range, 1-37) who underwent allogeneic HSCT after a RIC regimen based on the treosulfan. Before transplant, 27 children were assigned to risk class 1 of the Pesaro risk stratification system, 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 2014 report on RIC HSCT, 98 patients with class 3 thalassemia were transplanted with related or unrelated donor stem cells.21 Seventy-six of patients less than 10 years of age received a
conventional myeloablative conditioning regimen (cyclophosphamide, busulfan, ± fludarabine). The remaining 22 patients were 10 years of age or older with hepatomegaly and in several instances, additional comorbidity problems, who underwent HSCT with a novel RIC regimen (fludarabine and busulfan). Rates of 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 group that received myeloablative conditioning. Furthermore, graft failures occurred in 6 patients in the myeloablated group (8%), although 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 or any method of HSCT in patients with sickle cell disease.

**Online site ClinicalTrials.gov**

A nonrandomized Phase II/III trial is recruiting patients with a high-risk hemoglobinopathy to undergo an allogeneic HSCT using a preparative regimen to achieve stable mixed chimerism. Patients will either receive a myeloablative preparative regimen or a nonmyeloablative one if they do not have an HLA-identical sibling donor or are otherwise ineligible for a myeloablative regimen. Primary outcome measure is regimen-related toxicity, and secondary outcome measures include incidence of chimerism and GVHD, quality of life, and overall and disease-free survival. Estimated enrollment is 30 with a study completion date of June 2016 (NCT00176852). Several Phase II trials are also recruiting patients with a hemoglobinopathy for allogeneic HSCT, including with RIC.

**Bone marrow failure syndromes**

Review articles summarize the experience to date with HSCT and bone marrow failure syndromes.

**Fanconi anemia**

In a summary of patients with Fanconi anemia who received allogeneic HSCT from matched related donors over the past 6 years prior to publication, totaling 103 patients, overall survival (OS) ranged from 83–88%, with transplant-related mortality ranging from 8–18.5% and average chronic GVHD of 12%.

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%. Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year OS rates were 13% and 52% in patients who received nonfludarabine- versus fludarabine-based regimens.

Zanis-Neto and colleagues reported the results of 30 patients with Fanconi anemia treated with RIC) regimens, consisting of low-dose cyclophosphamide. Seven patients were treated with cyclophosphamide 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 cyclophosphamide 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 and colleagues reported that fludarabine-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year OS (52% vs. 13%, respectively; p less than 0.001) compared with non-fludarabine based regimens.

**Other**

Results with allogeneic HSCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis. Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results are available at this time.

Outcomes after allo-HSCT were reported in 34 patients with dyskeratosis congenita who underwent transplantation between 1981 and 2009. Median age at transplantation was 13 years (range, 2-35 years). 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% and at the time of publication, 14 patients were still 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 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 cyclophosphamide-containing nonradiation 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. Cesaro and colleagues reported 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Bone Marrow Transplantation 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). 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. In a report from the Diamond-Blackfan anemia registry, 20 of 354 registered patients underwent allogeneic HSCT, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts but were poor in recipients of alternative donors. The CIBMTR reported the results in to the International Bone Marrow Transplant Registry of 61 patients with Diamond-Blackfan anemia who underwent HSCT between 1984 and 2000. 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 (versus an alternative donor) was 78% versus 45% (p=0.01) at 1 year and 76% versus 39% (p=0.01) at 3 years, respectively.

A randomized Phase III trial compared 2 different conditioning regimens in high-risk aplastic anemia patients (n=79) who underwent allogeneic HSCT. Patients in the cyclophosphamide (Cy) plus anti-thymocyte globulin (ATG) arm (n=39) received Cy at 200 mg/kg; those in the Cy-fludarabine (Flu)-ATG group (n=40) received Cy at 100 mg/kg and Flu at 150 mg/m^2 (NCT01145976). 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. Overall survival 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 conventional myeloblative 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 Frontline immunosuppressive therapy (IST) was compared with frontline 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 frontline 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 frontline IST (consisting of ATG plus cyclosporine); of these, 91 (55%) failed IST as frontline 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 frontline 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 frontline HSCT 91% and after IST alone 97% (p=0.017). A subgroup analysis showed no significant difference between IST alone and MFD frontline HSCT (p=0.21), but significantly higher OS of both MFD frontline 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 in 1% 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
Review articles summarize experience with HSCT and the primary immunodeficiencies. Additional individual studies are reported next.

In patients with chronic granulomatous disease (CGD), outcomes of HSCT were compared with those of conventional treatment in a study of 41 patients in Sweden who were diagnosed with CGD between 1990 and 2012.36 From 1997 to 2012, 14 patients (aged 1 to 35 years) underwent HSCT and received grafts either from an HLA-matched sibling donor or a matched unrelated donor. Thirteen (93%) of the 14 transplanted patients were reported alive and well at publication in 2013. 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 remainder suffered life-threatening infections.

A prospective study in 16 centers across 10 countries worldwide enrolled CGD patients aged 0 to 40 years to examine the effects of an RIC regimen prior to HSCT, consisting of high-dose fludarabine, serotherapy, or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration. 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 of 56 patients (median age 12.7 years) were included; 42 (75%) patients had high-risk features (ie, intractable infections and autoinflammation) and 25 (45%) were adolescents and young adults (age range, 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% and EFS was 89%. 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% of patients. The cumulative incidence of acute GVHD grade III-IV was 4% and of chronic GVHD was 7%. Stable (≥90%) myeloid donor chimerism was documented in 52 (93%) surviving patients.

HSCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies, such as SCID, Wiskott-Aldrich syndrome and other prematurely lethal X-linked immunodeficiencies, in approximately 90% of cases. 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. A report from 2008 found an OS rate for patients with SCID who have undergone HSCT to be 71%.

Hassan and colleagues 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. HSCT from matched sibling and family donors had significantly better OS (86% and 81%) in comparison to HSCT from matched unrelated (66%; p<0.05) and haploidentical donors (43%; p<0.0001). Superior OS was also seen in patients who received unconditioned transplants in comparison to 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. Fifty-five transplants were from HLA-identical sibling donors, with a 5-year probability of survival of 87% (95% confidence interval [CI]: 74–93%); 48 were from other relatives, with a 5-year probability of survival of 52% (37–65%); and 67 were from unrelated donors with a 5-year probability of survival of 71% (58–80%; p<0.001).

Moratto and colleagues retrospectively reported the long-term outcome and donor-cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HSCT in the period 1980-2009. Overall survival 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 <50% was associated with persistent thrombocytopenia.
For patients with genetic immune/inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the current results with allogeneic HSCT are 60–70% 5-year disease-free survival.

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.

Studies so far indicate that RIC regimens may have an important role in treating patients with primary immunodeficiency. 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 (older than 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. Allo-HSCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. One study reported an 8-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allo-HSCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, fludarabine, 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. 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**

Review articles summarize the experience with HSCT and the inherited metabolic diseases.

In the past 25 years, HSCT has been performed in approximately 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders. The majority (more than 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. With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up. 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.
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). Impressive results have been observed with allo-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. 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. An analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%.

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. 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 7 patients with Hurler syndrome. Six of the patients received transplants from unrelated donors, and 1 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 7 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.

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, but reports of preservation of neuropsychologic and neurologic function have been made.

Miller and colleagues reported the results of 60 boys who underwent allogeneic HSCT for cerebral adrenoleukodystrophy (cALD) between 2000 to 2009. The median age at HSCT was 8.7 years; conditioning regimens and allograft sources varied. At HSCT, 50% demonstrated a Loes radiographic severity score ≥10, 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 <10 at HSCT was 89%, whereas that for boys with Loes score ≥10 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.

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.

Mynarek and colleagues reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HSCT. 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 2 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. Experience with allogeneic HSCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly. Some authors suggest that HSCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits.

Eight patients with Hunter syndrome received an allogeneic HSCT between the ages of 3 and 16 years. In 6 cases, the donor was a sibling with identical HLA status, in 1 case, the donor was unrelated HLA-compatible, and in 1 case, the donor was a mismatched unrelated donor. The severity of disease prior to 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 less than 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 4 years and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive with the exception of 1 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 2 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, 3 lost the ability to walk in their early teens, 2 lost language at 9 and
11 years, and 2 developed epilepsy. The remaining 2 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. The literature addressing the use of HSCT in Sanfilippo disease consists of 2 case reports. Vellodi and colleagues reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HSCT and were followed up for 9 years. 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.

**Infantile Malignant Osteopetrosis**
A review article summarizes the experience with HSCT and osteopetrosis.

The success of allo-HSCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a 5-year DFS of 73% to 79% versus transplantation with an unrelated or mismatched donor of 13% to 45%.

A retrospective analysis of 122 children who received an allogeneic HSCT for autosomal recessive osteopetrosis between 1980 and 2001 reported 5-year disease-free survival of 73% for recipients of a genotype HLA-identical HSCT (n=40), 43% for those of a phenotype HLA-identical or 1 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).

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

**Table 2. Summary of Key Trials**

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### Summary

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.

### VI. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.
This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VII. References

with aplastic anemia and hypoplastic myelodysplastic syndrome. Ann Hematol. Sep 2012; 91(9):1459-1469. PMID 22526363


