Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

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<td>MM.07.001</td>
<td>May 22, 2019</td>
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I. Summary
A number of inherited and acquired conditions have the potential for severe and/or progressive disease. For some conditions, allogeneic hematopoietic cell transplantation (allo-HCT) has been used to alter the natural history of the disease or potentially offer a cure.

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

For individuals who have an inherited metabolic syndrome disease (specifically those including Hunter, Sanfilippo, and Morquio syndromes) who receive allo-HCT, the evidence includes case reports. The relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. Use of allo-HCT to treat patients with Hunter, Sanfilippo, or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

A. Hemoglobinopathies
   1. 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
   2. Homozygous beta-thalassemia (i.e., thalassemia major)

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

D. Inherited metabolic disease
   Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes

E. Genetic disorders affecting skeletal tissue
   Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease);

The following guideline lists immunodeficiencies that have been successfully treated by allogeneic hematopoietic cell transplantation (allo-HCT)

**Lymphocyte immunodeficiencies**
- Adenosine deaminase deficiency
- Artemis deficiency
- Calcium channel deficiency
- CD40 ligand deficiency
- Cernunnos/X-linked lymphoproliferative disease deficiency
- CHARGE syndrome with immune deficiency
- Common gamma chain deficiency
- Deficiencies in CD45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV
- 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-KB inhibitor, alpha (IKB-alpha) deficiency
- Nijmegen breakage syndrome

For inherited metabolic disorders, allo-HCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid-cell leukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis, and aspartylglucosaminuria. Allogeneic HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes (Mehta, 2004).

The experience with reduced-intensity conditioning RIC and allo-HCT 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 adults, severe graft versus host disease (GVHD). Several Phase II/III trials are ongoing or completed examining the role of this type of transplant for these diseases, as outlined in the Ongoing and Unpublished clinical trials section.

III. 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, or use iExchange as indicated along with the required documentation.

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<th>CPT Codes</th>
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<tr>
<td>38205</td>
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<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing</td>
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<tr>
<td>38209</td>
<td>; Thawing of previously frozen harvest, with washing</td>
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<td>; Specific cell depletion within harvest, T-cell depletion</td>
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<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
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<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>
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<td>Beta thalassemia</td>
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<td>Sickle-cell disorders code range</td>
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<td>Other aplastic anemias and other bone marrow failure syndromes code range (includes Fanconi anemia)</td>
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<td>D70.0</td>
<td>Congenital agranulocytosis (includes Kostmann’s disease)</td>
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<td>D71</td>
<td>Functional disorders of polymorphonuclear neutrophils (includes chronic granulomatous disease)</td>
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<td>Combined immunodeficiencies code range</td>
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<td>Immunodeficiency associated with other major defects code range (includes Wiskott-Aldrich and X-linked lymphoproliferative syndromes)</td>
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<td>Peroxisomal disorders code range (includes childhood cerebral X-linked adrenoleukodystrophy)</td>
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<td>07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ, 07DS0ZZ, 07DS3ZZ</td>
<td>Surgical, lymphatic and hemic systems, extraction, bone marrow, code list</td>
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### IV. Background

#### Genetic Diseases and Acquired Anemias

**Hemoglobinopathies**

Thalassemias result from variants in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of b-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. 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 men and 48 for women.

**Treatment**

The only definitive cure for thalassemia is to correct the genetic defect with allogeneic hematopoietic cell transplantation (allo-HCT).

Three major therapeutic options are available for sickle cell disease: chronic blood transfusions, hydroxyurea, and allo-HCT, the latter being the only possibility for cure.

**Bone Marrow Failure Syndromes**

Aplastic anemia in children is rare; most often, it is 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 myelodysplastic syndrome or acute myeloid 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.

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.

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome. 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 myeloid 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.

**Treatment**
In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of human leukocyte antigen (HLA)-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

**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) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells.

**Treatment**
Without treatment, patients with severe combined immunodeficiency 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. Bone marrow transplantation is the only definitive cure, and the treatment of choice for severe combined immunodeficiency 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.

**Treatment**
Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in the 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 (eg, microglial cells in the brain and Kupffer cells in the liver).

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

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<tr>
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<th>Diagnosis</th>
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<td>Morquio syndrome A-B</td>
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<td>Adrenomyeloneuropathy</td>
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**Genetic Disorders Affecting Skeletal Tissue**

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

**Hematopoietic Cell Transplantation**
HCT refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Allo-HCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Cord blood is discussed in greater detail in evidence review evidence review 7.01.50.

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

**Preparative Conditioning for Allo-HCT**
The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. Reduced-intensity conditioning refers to chemotherapy regimens that seek to reduce adverse events secondary to bone marrow toxicity. These regimens partially eradicate the patient’s hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo reduced-intensity conditioning with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for reduced-intensity conditioning allogeneic transplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition.
HCT for autoimmune diseases, such as rheumatoid arthritis or multiple sclerosis, is considered separately in evidence review BCBSA Medical Policy #8.01.25.

**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 Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**V. RATIONALE**
This evidence review was created in December 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through November 15, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and
whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

**Clinical Context and Test Purpose**

The purpose of allogeneic hematopoietic cell transplantation (allo-HCT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a hemoglobinopathy. The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with a hemoglobinopathy?

The following PICOTS were used to select literature to inform this review.

- **Patients**
  The relevant population of interest are individuals with a hemoglobinopathy.

- **Interventions**
  The therapy being considered is allo-HCT.

- **Comparators**
  Comparators of interest include standard of care.

- **Outcomes**
  The general outcomes of interest are overall survival (OS), disease-specific survival, symptoms, quality of life, and treatment-related morbidity.

- **Timing**
  Follow-up at 3- and 12- years is of interest for allo-HCT to monitor relevant outcomes.

- **Setting**
  Patients with a hemoglobinopathy are actively managed by hematologists and primary care providers in an outpatient clinical setting. Patients with a hemoglobinopathy undergoing hematopoietic cell transplantation (HCT) are actively managed in the inpatient clinical setting.

- **Study Selection Criteria**
  Methodologically credible studies were selected using the following principles:
  To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
  a. In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
b. To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

c. Studies with duplicative or overlapping populations were excluded.

HEMOGLOBINOPATHIES
Review articles summarize the experience to date with HCT and the hemoglobinopathies.

β-Thalassemia
More than 3000 patients worldwide have been treated for β-thalassemia with allo-HCT. The 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 plan to undergo allo-HCT into risk groups 1 through 3 based on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class 1 having no risk factors, class 2 with two risk factors, and class 3 with all three risk factors). The outcome of allo-HCT in more than 800 patients with thalassemia according to risk stratification has shown OS and event-free survival (EFS) rates of 95% and 90% for Pesaro class 1, 87% and 84% for class 2, and 79% and 58% for class 3.

A 2015 study of 489 patients with nonmalignant hematologic disorders who underwent allo-HCT between 1997 and 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 1, 103 (68%) had class 2, and 23 (15%) had class 3; 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, III, and 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 rate for these patients was 82.4%. The disease-free survival (DFS) rate for the whole group of β-thalassemia patients was 72.4% (74% in the peripheral blood cell transplantation group vs 64% in the bone marrow cell transplantation group; p=0.381), which might be attributed to the higher incidence of graft rejection in bone marrow groups.

Bernardo et al (2012) reported on the results of 60 thalassemia patients (median age, 7 years; range, 1-37 years) who underwent allo-HCT after a reduced-intensity conditioning (RIC) regimen based on treosulfan. Before the transplant, 27 children were assigned to 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 a human leukocyte antigen (HLA)-identical sibling and 40 from an unrelated donor. The cumulative incidence of graft failure and transplantation-related mortality were 9% and 7%, respectively. Eight patients experienced grade II, III, or IV acute GVHD, the cumulative incidence being 14%. Among 56 patients at risk, one developed limited chronic GVHD. With a median follow-up of 36 months (range, 4-72 months), 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 outcomes.

In a 2014 report on RIC HCT, 98 patients with class 3 thalassemia were transplanted with related or unrelated donor stem cells. Seventy-six of patients less than 1ten years of age received a conventional myeloablative conditioning regimen (cyclophosphamide, busulfan, with or without fludarabine). The remaining 22 patients were 10 years of age or older with hepatomegaly and, in several instances, additional comorbidity problems, who underwent HCT with a novel RIC regimen (fludarabine and busulfan). Rates of EFS (86% vs 90%, respectively), and OS (95% vs 90%, respectively) did not differ significantly between groups. However, a higher incidence of serious treatment-related complications
was observed in the group that received myeloablative conditioning. Furthermore, graft failures occurred in six patients in the myeloablated group (8%), although none occurred in the RIC group.

**Sickle Cell Disease**
A Cochrane systematic review published in 2013 identified no RCTs that assessed risk or benefit of any method of HCT in patients with sickle cell disease.

Approximately 500 to 600 patients with sickle cell disease have undergone allo-HCT, and most of the experience with allo-HCT and sickle cell disease comes from 3 major clinical series. The largest series to date consists of 87 symptomatic patients, most of whom received donor allografts from siblings who are HLA-identical. The results from that series and the 2 others 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 (RIC and allo-HCT 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 GVHD, which has been observed with the use of RIC regimens.

Hsieh et al (2014) reported on results from 30 patients aged 16 to 65 years with severe sickle cell phenotype who were enrolled in a RIC allo-HCT study, consisting of alemtuzumab (1 mg/kg in divided doses), total body irradiation (300 centigray), sirolimus, and infusion of unmanipulated filgrastim-mobilized peripheral blood stem cells from HLA-matched siblings. The primary endpoint was treatment success at one year after the transplant, defined as 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 DFS, immunologic recovery, and changes in organ function. Twenty-nine patients survived a median of 3.4 years (range, 1-8.6 years), with no nonrelapse mortality. One patient died from intracranial bleeding after relapse. 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.

**Section Summary: Hemoglobinopathies**
The use of allo-HCT to treat patients with β-thalassemia or sickle cell disease has been shown to improve OS, EFS, or DFS.

**Clinical Context and Test Purpose**
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a bone marrow failure syndrome.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with a bone marrow failure syndrome?

The following PICOTS were used to select literature to inform this review.

- **Patients**
  The relevant population of interest are individuals with a bone marrow failure syndrome.
- **Interventions**
  The therapy being considered is allo-HCT.
- **Comparators**
  Comparators of interest include standard of care.
- **Outcomes**
The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity.

- **Timing**
  Follow-up at 1.1- and 8-year is of interest for allo-HCT to monitor relevant outcomes.

- **Setting**
  Patients with a bone marrow failure syndrome are actively managed by hematologists and primary care providers in an outpatient clinical setting. Patients with bone marrow failure syndrome undergoing HCT are actively managed in the inpatient clinical setting.

- **Study Selection Criteria**
  Methodologically credible studies were selected using the following principles:
  - To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
  - In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
  - To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
  - Studies with duplicative or overlapping populations were excluded.

**Bone Marrow Failure Syndromes**

Review articles summarize the experience to date on the use of HCT to treat bone marrow failure syndromes.

**Fanconi Anemia**

In a 2008 summary of patients with Fanconi anemia who received allo-HCT from matched related donors over 6 years (total n=103 patients), OS rates ranged from 83% to 88%, with transplant-related mortality ranging from 8% to 18.5% and average chronic GVHD of 12%.

The outcomes in patients with Fanconi anemia and an unrelated donor allo-HCT have not been as promising. The European Group for Blood and Marrow Transplantation has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median 2-year survival was 28%.3, Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplant Research analyzed 98 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- or fludarabine-based regimens.

Zanis-Neto et al (2005) reported on the results of 30 patients with Fanconi anemia treated with RIC regimens, consisting of low-dose cyclophosphamide.27, Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade II or III 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 resulted in lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the Center for International Blood and Marrow Transplant Research, Wagner et al (2007) reported that fludarabine-based (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year OS rates (52% vs 13%, respectively; p<0.001) compared with non-fludarabine-based regimens.
Dyskeratosis Congenita

Results with allo-HCT in dyskeratosis congenita have been disappointing because of severe late effects, including diffuse vasculitis and lung fibrosis. Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results have been published.

Outcomes after allo-HCT were reported in 2013 for 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, III, or 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 14 patients were still alive at last follow-up. Ten deaths occurred within four months from transplantation because of graft failure (n=6) or other transplantation-related complications; nine of these patients had undergone transplantation from mismatched related or unrelated donors. Another ten deaths occurred after four months; six of which occurred more than five years after transplantation, and four of deaths 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.

Shwachman-Diamond Syndrome

Experience with allo-HCT in Shwachman-Diamond syndrome is limited because very few patients have undergone allogeneic transplants for this disease.3, Cesaro et al (2005) reported on 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Marrow Transplantation registry, who received HCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myeloid leukemia (n=9); or another diagnosis (n=1).30 Various preparative regimens were used; most included 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, the OS rate was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that the presence of myelodysplastic syndrome-acute myeloid leukemia or use of total body irradiation-based conditioning regimens were factors associated with a poorer outcome.

Diamond-Blackfan Syndrome

In Diamond-Blackfan syndrome, allo-HCT is an option in corticosteroid-resistant disease.3, In a report from the Diamond-Blackfan Anemia Registry (2008), 20 of 354 registered patients underwent allo-HCT, and the 5-year survival rate was 87.5% when recipients received HLA-identical sibling grafts but was poor in recipients of alternative donors. Another team of investigators (2005) examined outcomes reported to the International Bone Marrow Transplant Registry between 1984 and 2000 for 61 patients with Diamond-Blackfan syndrome who underwent HCT. 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% vs 45% (p=0.01) at 1 year and 76% vs 39% (p=0.01) at 3 years, respectively.

Aplastic Anemia

A randomized phase 3 trial (2012) compared 2 conditioning regimens in patients (n=79) with high-risk aplastic anemia who underwent allo-HCT.32 Patients in the cyclophosphamide plus anti-thymocyte globulin (ATG) arm (n=39) received cyclophosphamide at 200 mg/kg; those in the cyclophosphamide-fludarabine-ATG arm (n=40) received cyclophosphamide at 100 mg/kg and fludarabine at 150 mg/m2.
No difference in engraftment rates was reported between arms. Infections with an identified causative organism and sinusoidal obstruction syndrome, hematuria, febrile episodes, and death from any cause tended to be more frequent among those receiving cyclophosphamide-ATG but did not differ significantly between treatment arms. For example, at 4 years, OS rates did not differ significantly between the cyclophosphamide-ATG (78%) and the cyclophosphamide-fludarabine-ATG arms (86%; \( p=0.41 \)). Although this study was underpowered to detect real differences between the conditioning regimens, the results suggested that a RIC regimen with cyclophosphamide-fludarabine-ATG appears to be as safe as a more conventional myeloablative regimen using cyclophosphamide plus ATG in allo-HCT.

A 2015 study analyzed outcomes reported to the European Group for Blood and Marrow Transplantation of children with idiopathic aplastic anemia, according to treatment received.33, Front-line immunosuppressive therapy (IST) was compared with front-line HCT from an HLA-matched family donor, to evaluate the outcomes of patients who, after having failed IST, underwent rescue HCT, and to compare their outcomes using front-line HCT with 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 might affect the outcome of the disease. Included in the analysis were records from 563 consecutive children (313 boys, 250 girls [age range, 0-12 years]) diagnosed between 2000 and 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 rescue HCT (HCT post-IST failure) whereas IST was the only treatment received (IST alone) for 76 patients. The 3-year probability of OS and EFS for the whole population was 90% and 86%, respectively. The 3-year OS rate was 91% after matched family donor front-line HCT and 87% after first-line IST (\( p=0.18 \)). The 3-year probability of OS after HCT post-IST failure was 83%, 91% after matched family donor front-line HCT, and 97% after IST alone (\( p=0.017 \)). A subgroup analysis showed no significant difference between IST alone and matched family donor front-line HCT (\( p=0.21 \)), but significantly longer OS of both matched family donor front-line HCT (\( p=0.02 \)) and IST alone (\( p=0.047 \)) over HCT post-IST failure.

A 2015 study (discussed earlier), which examined 489 patients with nonmalignant hematologic disorders who underwent allo-HCT, including 273 patients with severe aplastic anemia. Of these subjects, 212 were men, and 61 were women, 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, III, or 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 rates 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 regarding mean time to neutrophil engraftment (\( p=0.136 \)) or incidence of extensive chronic GVHD (\( p=0.651 \)). Mean time to platelet engraftment was significantly longer in the cyclophosphamide plus ATG group (\( p=0.016 \)). The incidence of transplant-related mortality in the fludarabine plus cyclophosphamide group was 17%, which was significantly lower than in the cyclophosphamide plus ATG group (33%; \( p=0.002 \)). After a median follow-up of 8 years, the OS rate was statistically significantly better in the fludarabine plus cyclophosphamide group (80%) than in the cyclophosphamide plus ATG group of patients (64%; \( p=0.021 \)).
Section Summary: Bone Marrow Failure Syndromes
Use of allo-HCT to treat patients with Fanconi anemia, dyskeratosis congenital, Shwachman-Diamond syndrome, Diamond-Blackfan syndrome, and aplastic anemia have been shown to improve OS or DFS.

PRIMARY IMMUNODEFICIENCIES
Clinical Context and Test Purpose
The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a primary immunodeficiency.
The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with a primary immunodeficiency?
The following PICOTS were used to select literature to inform this review.

- Patients
  The relevant population of interest are individuals with a primary immunodeficiency.
- Interventions
  The therapy being considered is allo-HCT.
- Comparators
  Comparators of interest include standard of care.
- Outcomes
  The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity.
- Timing
  Follow-up at 6- and 21-months is of interest for allo-HCT to monitor relevant outcomes.
- Setting
  Patients with a primary immunodeficiency are actively managed by hematologists and primary care providers in an outpatient clinical setting. Patients with primary immunodeficiency syndrome undergoing HCT are actively managed in the inpatient clinical setting.
- Study Selection Criteria
  Methodologically credible studies were selected using the following principles:
  To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
  In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
  To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
  Studies with duplicative or overlapping populations were excluded.

Review articles summarize experience the use of HCT to treat primary immunodeficiencies. Additional individual studies are reported next.

Chronic Granulomatous Disease
HCT outcomes 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 (age range, 1-35 years) underwent HCT 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 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 2014 prospective study in 16 centers across 10 countries worldwide enrolled CGD patients ages 0 to 40 years to examine the effects of an RIC regimen before HCT, 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 endpoints were OS and EFS, probabilities of OS and EFS at 2 years, the 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 auto-inflammation) 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 a median follow-up of 21 months, the OS rate was 93%, and the EFS rate was 89%. The 2-year probability of OS was 96% (95% confidence interval [CI], 86.46% to 99.09%) and of EFS was 91% (95% CI, 79.78% to 96.17%). Graft failure occurred in 5% of patients. The cumulative incidence of acute GVHD grade III or IV was 4% and of chronic GVHD was 7%. Stable (≥90%) myeloid donor chimerism was documented in 52 (93%) surviving patients.

Severe Combined Immunodeficiency

HCT 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. According to a 2008 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. Another 2008 report found an OS rate for patients with SCID who have undergone HCT to be 71%.

Hassan et al (2012) reported on a multicenter retrospective study, which analyzed HCT outcomes in 106 patients with adenosine deaminase deficient-SCID who received a total of 119 transplants. HCT using matched sibling and family donors had significantly better OS (86% and 81%, respectively) compared with HCT using matched unrelated (66%; p<0.05) and haploidentical donors (43%; p<0.001). Superior OS was also seen in patients who received unconditioned transplants compared with myeloablative procedures (81% vs 54%; p<0.003), although in unconditioned haploidentical donor HCT, nonengraftment was a major problem. Long-term immune recovery showed that, regardless of transplant type, overall T-cell counts were similar, although a faster rate of T-cell recovery was observed following matched sibling and family donor HCT. Humoral immunity and donor B-cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HCT.

Wiskott-Aldrich Syndrome

For Wiskott-Aldrich syndrome, a 2001 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 survival probability of 87% (95% CI, 74% to 93%); 48 were from other relatives, with a 5-year survival probability of 52% (95% CI, 37% to 65%); and 67 were from unrelated donors with a 5-year survival probability of 71% (95% CI, 58% to 80%; p<0.001). Moratto et al (2011) retrospectively reported on the long-term outcome and donor cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HCT from 1980 to 2009. The OS rate was 84.0% and was even higher (89.1% 5-year survival) for those who had received HCT since the year 2000, reflecting the recent improvement in outcome after transplantation from mismatched family donors and for patients who received HCT from an unrelated donor older than 5 years of age. Also, patients who proceeded to transplantation in better clinical condition had a lower rate of post-HCT 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 HCT. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte counts and post-HCT autoimmunity, and myeloid donor cell chimerism less than 50% was associated with persistent thrombocytopenia.

**X-Linked Lymphoproliferative Disease**

XLP1 is a rare, deadly immune deficiency caused by variants in the SH2D1A gene. Allo-HCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. One study (2014) reported on an 8-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allo-HCT between 2006 and 2013 after a RIC regimen consisting of alemtuzumab, fludarabine, and melphalan. Fourteen of 16 patients received fully HLA-matched (8/8) unrelated or related bone marrow grafts, whereas 2 patients received mismatched unrelated grafts. All patients had hematopoietic recovery. No cases of hepatic venoocclusive disease or pulmonary hemorrhage were reported. One (6%) patient developed acute GVHD and later also developed chronic GVHD. Five (31%) patients 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 HCT.

**Other Immunodeficiencies**

For patients with genetic immune or inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the 5-year DFS rates with allo-HCT ranged from 60% to 70%.

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

To date, studies have indicated that RIC regimens 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 the superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae (e.g., infertility, growth retardation) may be avoided or reduced. Currently, RIC HCT using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (patients >5 years of age), and CGD with ongoing inflammatory or infective complications. Minimal-intensity conditioning HCT may be particularly suited to unrelated donor HCT in young SCID patients with significant comorbidities.

**Clinical Context and Test Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with inherited metabolic diseases including Hunter, Sanfilippo, or Morquio syndromes.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with an inherited metabolic disease?

The following PICOTS were used to select literature to inform this review.

- **Patients**
  The relevant population of interest are individuals with inherited metabolic diseases including Hunter, Sanfilippo, or Morquio syndromes.

- **Interventions**
  The therapy being considered is allo-HCT.

- **Comparators**
  Comparators of interest include standard of care.
Allogeneic HCT Genetic Diseases and Acquired Anemias

Outcomes
The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity.

Timing
Follow-up at 7- to 17- years is of interest for allo-HCT to monitor relevant outcomes.

Setting
Patients with inherited metabolic diseases including Hunter, Sanfilippo, or Morquio syndromes are actively managed by metabolic specialists and primary care providers in an outpatient clinical setting. Patients with Hunter, Sanfilippo, or Morquio syndromes undergoing HCT are actively managed in the inpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

Studies with duplicative or overlapping populations were excluded.

Hunter Syndrome
Hunter syndrome is composed of two distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged lifespan, minimal to no central nervous system involvement, and a slow progression.43 Experience with allo-HCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly. Some have suggested that HCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits.

Eight patients with Hunter syndrome received an allo-HCT between the ages of 3 and 16 years. In six cases, the donor was an HLA-identical sibling; in one case, an HLA-compatible unrelated donor was used, and in another, a mismatched unrelated donor was used. The severity of disease before the transplant was rated by assessing the age at diagnosis, behavior, and IQs at the time of graft and genotype. Five patients were considered to have severe central nervous system involvement (ie, diagnosis before the age of 4 years and an IQ <80), two were considered to have the attenuated form (ie, diagnosis at 5 years of age and normal IQ), and one as intermediate (ie, 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 except 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. The 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 their 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 of age, respectively, and 2 developed epilepsy. The remaining two patients with the severe form required special schooling and had poor social and language skills.

Sanfilippo Syndrome
Experience with allo-HCT in patients with Sanfilippo syndrome (MPS III) has shown no alteration in the course of neuropsychologic deterioration seen in these patients. The literature addressing the use of HCT in Sanfilippo syndrome consists of two older case reports. Vellodi et al (1992) reported on the outcomes of twin girls diagnosed with Sanfilippo syndrome who underwent allo-HCT and were followed for 9 years. At the time of transplant, both girls were functioning in the low-average range of intellectual development. Over the next eight years, both girls had a steady decline in cognitive development, and both functioned in the area of significant developmental delay. The authors postulated that the 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 Sanfilippo syndrome who had received allo-HCT was 5.3 years old at the time of the transplant and continued to deteriorate posttransplant.

**Morquio Syndrome**

Allogeneic HCT has not been effective in Morquio syndromes.

**Section Summary: Inherited Metabolic Diseases Including Hunter, Sanfilippo, or Morquio Syndromes**

The use of allo-HCT to treat patients with Hunter, Sanfilippo or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function.

**Inherited Metabolic Diseases Excluding Hunter, Sanfilippo, or Morquio syndromes**

**Clinical Context and Test Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with an inherited metabolic disease?

The following PICOTS were used to select literature to inform this review.

- **Patients**
  The relevant population of interest are individuals with inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes.

- **Interventions**
  The therapy being considered is allo-HCT.

- **Comparators**
  Comparators of interest include standard of care.

- **Outcomes**
  The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity.

- **Timing**
  Follow-up at 5.5- and 9.2-year intervals is of interest for allo-HCT to monitor relevant outcomes.

- **Setting**
  Patients with inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes are actively managed by metabolic specialists and primary care providers in an outpatient clinical setting. Patients with inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes undergoing HCT are actively managed in the inpatient clinical setting.

- **Study Selection Criteria**
  Methodologically credible studies were selected using the following principles: To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
Studies with duplicative or overlapping populations were excluded.

**Review articles summarize the experience using HCT to treat inherited metabolic diseases.**

**Lysosomal Storage Disorders**

HCT has been performed in approximately 20 of the estimated 40 known lysosomal storage disorders and peroxisomal storage disorders. Most instances (>80%) have been in patients with Hurler syndrome (mucopolysaccharidosis I [MPS I]) or other MPS syndromes (Hunter syndrome [MPS II], Sanfilippo syndrome types A [MPS IIIA] and B [MPS IIIB], Maroteaux-Lamy syndrome [MPS VI]), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid cell leukodystrophy.6, Except for Hurler syndrome and globoid cell leukodystrophy, most published data are from single-case reports or small series with short follow-up. The benefit of allo-HCT appears to be 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 neuro-developmental deterioration, severe orthopedic manifestations, and cardiopulmonary complications leading to death in early childhood. Although enzyme replacement therapy is available, HCT remains the only treatment that delivers the deficient enzyme to the central nervous system. Impressive results have been observed with allo-HCT 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 2007 analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%.

In 2015, an international retrospective analysis reported on long-term results of 217 patients with Hurler syndrome who successfully underwent allo-HCT between 1985 and 2011.50 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 endpoints were neurodevelopmental outcomes and growth; secondary endpoints included outcomes involving several different organ systems. Pre-HCT, 56.9% of patients showed normal neurodevelopment, and 26.6% showed only mildly impaired neurodevelopment. At last follow-up post-HCT, normal or only mildly impaired neurodevelopment was observed in 26.9% and 28.3% of the patients, respectively, and 44.9% suffered from moderately to severely impaired neurodevelopment. Predictors of better outcomes posttransplant were higher baseline developmental and IQ pretransplant, younger age at transplant, and a normal α-L-iduronidase enzyme level posttransplant.

Experience with allo-HCT and a RIC regimen was reported in 2008 for 7 patients with Hurler syndrome. 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 7 children were alive at a median of 1014 days (range, 726-2222 days) posttransplant. Mynarek et al (2012) reported on the results of a retrospective, multicenter analysis of 17 patients with α-mannosidosis who underwent allo-HCT.53, Patients were diagnosed with the disease at a median age of 2.5 years (range, 1.1-23 years) and underwent allo-HCT at a median age of 3.6 years (1.3-23.1 years). After a median follow-up of 5.5 years (range, 2.1-12.6 years), the OS rate was 88%. One patient died 76 days after transplantation from sepsis, GVHD, and pulmonary hemorrhage, and another patient died on
day 135 posttransplant due to viral infections and multi-organ failure. Before allo-HCT, the extent of developmental delay in the 17 patients varied over a wide range. After allo-HCT, patients made some developmental progress; however, normal development was not achieved. Hearing ability improved in some but not all patients.

Fewer than 40 patients with globoid cell leukodystrophy have undergone allo-HCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function. Many patients with metachromatic leukodystrophy who have undergone allo-HCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival. The few patients with Maroteaux-Lamy syndrome (MPS VI) or Sly syndrome (MPS VII) who have received transplants have shown promising results, with clinical improvement posttransplant.

**Peroxisomal Disorders**

Outcomes with allo-HCT have varied but 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 presented.

Miller et al (2011) reported on the results of 60 boys who underwent allo-HCT for cerebral adrenoleukodystrophy between 2000 and 2009. Median age at transplantation was 8.7 years; conditioning regimens and allograft sources varied. At HCT, 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) were alive at a median 3.7 years after allo-HCT. The 5-year survival estimate for boys with a Loes score less than 10 at HCT was 89%, whereas that for boys with a Loes score of 10 or more was 60% (p=0.03). The 5-year survival estimate for boys without clinical cerebral disease at HCT 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%. Posttransplantation progression of neurologic dysfunction depended significantly on the pre-HCT Loes score and clinical neurologic status.

Section Summary: Inherited Metabolic Diseases Excluding Hunter, Sanfilippo, or Morquio Syndromes Use of allo-HCT to treat select subsets of patients without overt neurologic symptoms or without aggressive infantile forms with lysosomal and peroxisomal storage disorders results in improvements in neurologic, neuropsychologic, and neurophysiologic function.

**Genetic Disorders Affecting Skeletal Tissue**

**Clinical Context and Test Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with a genetic disorder affecting skeletal tissue.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcome in individuals with a genetic disorder affecting skeletal tissue?

The following PICOTS were used to select literature to inform this review.

- **Patients**
  - The relevant population of interest are individuals with a genetic disorder affecting skeletal tissue.

- **Interventions**
  - The therapy being considered is allo-HCT.

- **Comparators**
  - Comparators of interest include standard of care.

- **Outcomes**
The general outcomes of interest are OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity.

- **Timing**
  Though not completely standardized, follow-up for a genetic disorder affecting skeletal tissue symptoms would typically occur in the months to years after starting treatment.

- **Setting**
  Patients with a genetic disorder affecting skeletal tissue are actively managed by orthopedists and primary care providers in an outpatient clinical setting.

- **Study Selection Criteria**
  Methodologically credible studies were selected using the following principles:
  - To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
  - In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
  - To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
  - Studies with duplicative or overlapping populations were excluded.

A 2010 review article has summarized the experience using HCT to treat osteopetrosis. The success of allo-HCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having 5-year DFS rates of 73% to 79% vs 13% to 45% for those requiring transplantation from an unrelated or mismatched donor.

A 2003 retrospective analysis of 122 children who received an allo-HCT for autosomal recessive osteopetrosis between 1980 and 2001 reported 5-year DFS rates of 73% for recipients of a genotype HLA-identical HCT (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).

**Summary of Evidence**

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

For individuals who have an inherited metabolic syndrome disease (specifically those including Hunter, Sanfilippo, and Morquio syndromes) who receive allo-HCT, the evidence includes case reports. The relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. Use of allo-HCT to treat patients with Hunter, Sanfilippo, or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function. The evidence is insufficient to determine the effects of the technology on health outcomes.
VI. SUPPLEMENTAL INFORMATION

Clinical Input 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 comment on the use of hematopoietic cell transplant in the inherited metabolic diseases, except for Hunter, Sanfilippo, and Morquio syndromes; four reviewers agreed with the current policy statement, one disagreed, and one did not address this specific question.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

The American Society for Blood and Marrow Transplantation (2015) published consensus guidelines on the use of hematopoietic cell transplantation (HCT) to treat specific conditions in and out of the clinical trial settings. Specific to this review Table 2 provides the allogeneic guidelines for specific indications.

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allogeneic HCT &lt;18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe aplastic anemia, relapse/refractory</td>
<td>S</td>
</tr>
<tr>
<td>Severe aplastic anemia, new diagnosis</td>
<td>S</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>R</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>R</td>
</tr>
<tr>
<td>Blackfan-Diamond anemia</td>
<td>R</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>C</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>S</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>R</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>R</td>
</tr>
<tr>
<td>T-cell immunodeficiency, severe combined</td>
<td>R</td>
</tr>
<tr>
<td>immunodeficiency variants</td>
<td></td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Hemophagocytic disorders</td>
<td>R</td>
</tr>
<tr>
<td>Lymphoproliferative disorders</td>
<td>R</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>R</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>R</td>
</tr>
<tr>
<td>Other phagocytic cell disorders</td>
<td>R</td>
</tr>
<tr>
<td>Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>D</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>D</td>
</tr>
<tr>
<td>Other autoimmune and immune dysregulation</td>
<td>R</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
</tr>
<tr>
<td>Mucopolysaccharidoses (MPS-I and MPS-VI)</td>
<td>R</td>
</tr>
<tr>
<td>Other metabolic diseases</td>
<td>R</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>R</td>
</tr>
<tr>
<td>Globoid cell leukodystrophy (Krabbe)</td>
<td>R</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>R</td>
</tr>
<tr>
<td>Indications</td>
<td>Cerebral X-linked adrenoleukodystrophy</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------</td>
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<tr>
<td>Allogeneic HCT &gt;18 Years</td>
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<td>C</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>D</td>
</tr>
<tr>
<td>Hemophagocytic syndromes, refractory</td>
<td>R</td>
</tr>
<tr>
<td>Mast cell diseases</td>
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<tr>
<td>Common variable immunodeficiency</td>
<td>R</td>
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<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>R</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>N</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>N</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>N</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>N</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>N</td>
</tr>
<tr>
<td>Polymyositis-dermatomyositis</td>
<td>N</td>
</tr>
</tbody>
</table>

C: clinical evidence available; D: developmental; HCT: hematopoietic cell transplantation; N: not generally recommended; R: standard of care, rare indication; S: standard of care.

**British Committee for Standards in Haematology**
The British Committee for Standards in Haematology (2015) published guidelines on the diagnosis and management of adult aplastic anemia. The following key recommendations on HCT were included in the guidelines:

- Matched sibling donor (allogeneic) HCT is the treatment of choice for severe aplastic anemia; however, for patients aged 35 to 50 years, patients need to be assessed for comorbidities before being considered for HCT.
- For adults, unrelated donor HCT should be considered if patients fail to respond to a single course of immunosuppressive therapy.
- Although there have been improvements in outcomes after alternative donor HCT, these transplants are still experimental, and expert consultation should be sought before considering their use.

**European Blood and Marrow Transplantation**
The European Blood and Marrow Transplantation (2014) provided consensus-based recommendations on indications for HCT and transplant management in the hemoglobinopathies.

**Pediatric Haemato-Oncology Italian Association**
The Pediatric Haemato-Oncology Italian Association (2015) issued guidelines on the diagnosis and treatment of acquired aplastic anemia in childhood.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.
Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<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>
<td>22</td>
<td>Jan 2019</td>
</tr>
<tr>
<td>NCT00358657</td>
<td>HLA-Haploidentical Related Marrow Grafts for the Treatment of Primary Immunodeficiencies and Other Nonmalignant Disorders Using Conditioning With Low-Dose Cyclophosphamide, TBI and Fludarabine and Postgrafting Cyclophosphamide</td>
<td>20</td>
<td>Dec 2018 (estimated)</td>
</tr>
<tr>
<td>NCT02356653</td>
<td>Processing of stem cells using the CliniMACs device to selectively deplete specific T cells to decrease risk of graft versus host disease when using donor stem cells which are not fully matched.</td>
<td>100</td>
<td>Jan 2020 (estimated)</td>
</tr>
<tr>
<td>NCT02986698</td>
<td>A Single-Center, Non-Randomized Study of the Safety and Efficacy of In Utero Hematopoietic Stem Cell Transplantation for the Treatment of Fetuses With Alpha Thalassemia Major</td>
<td>10</td>
<td>Feb 2024 (estimated)</td>
</tr>
<tr>
<td>NCT00176826</td>
<td>In-vivo T-cell Depletion and Hematopoietic Stem Cell Transplantation for Life-Threatening Immune Deficiencies and Histiocytic Disorders</td>
<td>22</td>
<td>Terminated</td>
</tr>
<tr>
<td>NCT00775931</td>
<td>Allogeneic Hematopoietic Stem Cell Transplantation For Severe Osteopetrosis</td>
<td>23</td>
<td>Oct 2015 (unknown)</td>
</tr>
<tr>
<td>NCT00553098</td>
<td>Hematopoietic Cell Transplantation for Treatment of Patients With Primary Immunodeficiencies and Other Nonmalignant Inherited Disorders Using Low-Dose TBI and Fludarabine With or Without Campath</td>
<td>25</td>
<td>Mar 2015 (actual completion)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

VII. References