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Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

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Coverage

Allogeneic hematopoietic cell transplantation (HCT; allo-HCT) **may be considered medically necessary** for select individuals with the following disorders:

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

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

Primary Immunodeficiencies:

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

NOTE 1: Refer to the Description for a listing of immunodeficiencies that have been treated successfully with allo-HCT.

Inherited Metabolic Diseases:
Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes.

NOTE 2: Refer to the Description for a discussion of inherited metabolic disorders that have been proven effective when treated with allo-HCT.

Genetic Disorders Affecting Skeletal Tissue:
Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease).

Allo-HCT **is considered experimental, investigational and/or unproven** for any condition or disorder not included above.

Autologous HCT (auto-HCT) **is considered experimental, investigational and/or unproven** for any genetic disease or acquired anemia.

NOTE 3: This policy does not apply to the autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia. Coverage of autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia is dependent upon meeting the coverage criteria in the specific gene therapy policy (i.e., RX501.166 and RX501.167).

Policy Guidelines

None.

Description

Hematopoietic Cell Transplantation (HCT)
HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow function and immune function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT; auto-HCT) or a donor

(allogeneic HCT; allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is an allogeneic source; the stem-cells in it are antigenically "naive" and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in auto-HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

<u>Conditioning for Hematopoietic Cell Transplantation</u>

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD disease.

Reduced-Intensity Conditioning (RIC) Allogeneic Hematopoietic Cell Transplantation

RIC refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

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 ß-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 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 allo-HCT. Three major therapeutic options are available: chronic blood transfusions, chelation therapy, and allo-HCT, the latter being the only possibility for cure. (1)

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 (FA), 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 (MDS) or acute myeloid leukemia (AML). Most patients with FA succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age. (2)

Dyskeratosis congenita is characterized by marked telomere dysregulation with clinical features of reticulated skin hyperpigmentation, nail dystrophy, and oral leukoplakia. (3) 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. (3) Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of MDS and malignant transformation, especially AML. Diamond-Blackfan anemia is characterized by a failure in red blood cell production, with 30% of patients also having a variety of physical anomalies. (3)

Treatment
In FA, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

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 [SCID]) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells (NKC). (4)

Treatment
Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood. (4) Bone marrow transplantation is the only definitive cure, and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function. (5)

Other conditions that have been successfully treated by allo-HCT include the following (4):
1. *Lymphocyte Immunodeficiencies*:
    - Adenosine deaminase deficiency,
    - Artemis deficiency,
    - Calcium channel deficiency,
    - CD (cluster of differentiation) 40 ligand deficiency,
    - Cernunnos/X-linked lymphoproliferative disease deficiency,
    - CHARGE (coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities) syndrome with immune deficiency,
    - Common gamma chain deficiency,
    - Deficiencies in CD 45, CD 3, CD 8,
    - DiGeorge syndrome,
    - DNA ligase IV deficiency syndrome,
    - 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.

2. *Phagocytic deficiencies:*
   - Chediak-Higashi syndrome,
   - Chronic granulomatous disease,
   - Griscelli syndrome type 2,
   - Hemophagocytic lymphohistiocytosis,
   - Interferon-gamma receptor deficiencies,
   - Leukocyte adhesion deficiency,
   - Severe congenital neutropenias,
   - Shwachman-Diamond syndrome.
3. *Other immunodeficiencies:*
   - Autoimmune lymphoproliferative syndrome,
   - Cartilage hair hypoplasia,
   - CD25 deficiency,
   - Hyper IgD and IgE syndromes,
   - ICF (immunodeficiency, centromere instability and facial anomalies syndrome) syndrome,
   - IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome,
   - NEMO (nuclear factor-kappa-B essential modulator) deficiency,
   - NF (nuclear factor)-κB inhibitor, alpha (IκB-alpha) essential modulator deficiency,
   - Nijmegen breakage syndrome.

<u>Inherited Metabolic Diseases</u>:
Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait. (6) Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic substrate and a deficiency of the product of the enzyme reaction. (6) Hurler syndrome usually leads to premature death by 5 years of age.

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 (e.g., microglial cells in the brain and Kupffer cells in the liver). (6)

Allo-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. (6)

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis	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 I-III GM_1 gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff's disease Globoid cell 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 Wolman disease Ceroid lipofuscinosis type III	Batten disease
Glycogen storage	Glycogen storage disease type II	Pompe
Multiple enzyme deficiency	Galactosialidosis Mucolipidosis type II	 I-cell disease
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

H/S: Hurler-Scheie syndrome; MPS: Mucopolysaccharidoses; GM_1: Monosialotetrahexosylganglioside; MLD: Metachromatic leukodystrophy; ALD: Adrenoleukodystrophy; AMN: Adrenomyeloneuropathy.

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 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. (7)

Treatment
HCT is the only curative therapy for this fatal disease.

NOTE 4: For additional information regarding autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, please see Medical Policy SUR703.036, “Hematopoietic Cell Transplantation for Autoimmune Diseases.”

Regulatory Status
The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation Title 21, parts 1270 and 1271. (8) Hematopoietic stem cells are included in these regulations.

Rationale

The medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life (QOL), 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, 2 domains are examined: the relevance and the 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.

Hemoglobinopathies
Review articles summarize the experience to date with HCT and the hemoglobinopathies. (9-12)

<u>β-Thalassemia</u>
More than 3000 patients worldwide have been treated for β-thalassemia with allo-HCT. (11) OS rates have ranged from 65% to 98% at 5 years, up to 87% at 15 years, up to 89% at 20 years, and thalassemia-free survival has been reported to be as high as 86% at 6 years. (13) The Pesaro risk stratification system classifies patients with thalassemia who plan to undergo allo-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 2 risk factors, and class 3 with all 3 risk factors). (14) 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. (15) Mean age at transplantation was 5.7 years (range, 1.1-23 years). At the time of transplantation, 26 (17%) patients had Pesaro class 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. (16) 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, 1 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. (17) Seventy-six of patients less than 10 years of age received a conventional myeloablative conditioning (MAC) regimen (cyclophosphamide, busulfan [BU], 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 BU). 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 MAC. Furthermore, graft failures occurred in 6 patients in the myeloablated group (8%), although none occurred in the RIC group.

<u>Sickle Cell Disease (SCD)</u>
A Cochrane systematic review published in 2013 (18) and updated in 2020 (19) identified no RCTs that assessed risk or benefit of any method of HCT in patients with SCD.

Approximately 500 to 600 patients with SCD have undergone allo-HCT, and most of the experience with allo-HCT and SCD comes from 3 major clinical series. (11) The largest series to date consists of 87 symptomatic patients, most of whom received donor allografts from siblings who are HLA-identical. (20) The results from that series and the 2 others (21, 22) 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 RIC preparative regimens (RIC and the allo-HCT for the hemoglobinopathies) is limited to a small number of patients. Challenges have included high rates of graft rejection (10%-30%) (9) and, in adult patients, severe GVHD, which has been observed with the use of RIC regimens. (10)

Hsieh et al. (2014) reported on results from 30 patients aged 16 to 65 years with severe sickle cell phenotype who were enrolled in an RIC allo-HCT study, consisting of alemtuzumab (1 mg/kg in divided doses), total body irradiation (300 centigray; cGy), sirolimus, and infusion of unmanipulated filgrastim-mobilized peripheral blood stem cells from HLA-matched siblings. (23) 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 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 3.4 years (range, 1-8.6 years), with no non-relapse 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.

Allo-HCT is the sole established curative treatment option for patients with SCD. However, a lack of HLA-identical sibling donors is a limiting factor. (24) Haploidentical related donors are a promising donor pool, potentially extending SCT as a curative treatment option to a larger group of patients with no other meaningful treatment options for their severe SCD. In the present study, Aydin et al. (2021) aimed to systematically review the results of haploidentical SCT in patients with SCD. A comprehensive search was performed in MEDLINE/PubMed and Embase up to May 2021. Data were extracted by 2 reviewers independently, and the Newcastle-Ottawa Quality Assessment Scale was used to assess the quality of the studies. Fourteen studies met inclusion criteria. To provide an overview of the results of haploidentical SCT, studies were grouped into myeloablative conditioning versus nonmyeloablative conditioning as well as into in vitro versus in vivo (i.e., with post-transplantation cyclophosphamide) T cell depletion with a subgroup meta-analysis of proportions. All the included studies were observational cohort studies. Only 3 of these studies reported data for both matched sibling donor (MSD) SCT and haploidentical SCT. Based on a comparative meta-analysis of the 3 studies that included both haploidentical and MSD transplantation, graft failure was significantly higher in the haploidentical group than in the MSD group (odds ratio, 5.3; 95% CI, 1.0 to 27.6). Overall survival was not significantly different between the groups. A subgroup meta-analysis of the results of haploidentical SCT showed relatively low overall pooled proportions of graft failure (7%; 95% CI, 2% to 20%), acute GVHD (4%; 95% CI, 2% to 12%), and chronic GVHD (11%; 95% CI, 7% to 16%). Overall survival was high in all the included studies (91%; 95% CI, 85% to 94%). Adjustments to the conditioning regimens, robust pretransplantation and post-transplantation T cell depletion, and improved supportive care have resulted in reduced graft failure and improved OS following haploidentical SCT in patients with SCD. Investigators concluded that the safety of haploidentical SCT in SCD patients has improved significantly, and that this should be considered as a curative option in patients with severe SCD.

Section Summary: Hemoglobinopathies
Use of allo-HCT to treat patients with β-thalassemia or SCD has been shown to improve OS, EFS, or DFS.

Bone Marrow Failure Syndromes
Review articles summarize the experience to date on the use of HCT to treat bone marrow failure syndromes. (8, 25-27)

Fanconi Anemia (FA)
In a 2008 summary of patients with FA 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%. (28)

The outcomes in patients with FA 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 FA. Median 2-year survival was 28%. (3) Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. (3) The Center for International Blood and Marrow Transplant Research (CIBMTR) 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. (3)

Zanis-Neto et al. (2005) reported on the results of 30 patients with FA treated with RIC regimens, consisting of low-dose cyclophosphamide. (29) 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 FA reported to the CIBMTR, 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% versus 13%, respectively; p<0.001) compared with non-fludarabine-based regimens. (30)

Doval and co-workers (2020) noted that HSCT is the only therapeutic option for the hematological manifestations of FA. (31) Fludarabine-based RIC regimens have helped in improving outcomes significantly in FA patients. These investigators retrospectively analyzed the outcomes of FA patients who underwent allogeneic-HCT at BLK Super-Specialty Hospital, New Delhi from June 2011 to September 2019. A total of 20 FA patients underwent 23 transplants at the authors' center; OS and DFS were 65 % and 50 %, respectively at a median of 23 months; overall mortality was 30 %. The authors concluded that HCT for FA is a feasible option even in developing countries although children presented late to transplant centers after multiple transfusions and infections.

Furthermore, an UpToDate review on "HCT for inherited bone marrow failure syndromes" states that "Management of children with FA consists of supportive modalities, androgens, and hematopoietic growth factors, which can achieve a transient improvement in hematopoietic function. For those who cannot tolerate this approach, or who have developed severe bone marrow failure, myelodysplasia, or acute myeloid leukemia, allogeneic HCT is the only treatment option that can restore normal hematopoiesis. If an HLA-identical sibling donor (the best choice) is not available, children receiving HCT from an HLA-matched unrelated donor may do well when fludarabine is part of the conditioning regimen." (32)

Dyskeratosis Congenita

Results with allo-HCT in dyskeratosis congenita have been disappointing because of severe late effects, including diffuse vasculitis and lung fibrosis. (3) Currently, non-MAC 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. (33) 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 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; six of which occurred more than 5 years after transplantation, and 4 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 non-radiation 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 (MDS)-acute myeloid leukemia (n=9); or another diagnosis (n=1). (34) Various preparative regimens were used; most included BU (54%) or total body irradiation (TBI) (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 presence of MDS- acute myeloid leukemia (AML) or use of TBI-based conditioning regimens were factors associated with a poorer outcome.

In 2022, Cesaro and colleagues published recommendations from the European Society for Blood and Marrow Transplantation Severe Aplastic Anaemia Working Party regarding HSCT in individuals affected by SDS. (35) In general, about 10% to 20% of individuals with SDS require treatment with HSCT, an option that is effective in improving survival for this otherwise incurable condition. A 5-year OS of 70.7% has been reported in individuals with bone marrow failure due to SDS who received HSCT, with graft failure and transplant-related mortality being the main factors affecting success of the procedure. Among the key recommendations for improving survival were early recognition of an indication for HSCT, the importance of regular and structured hematologic follow-up and the potential reduction of transplant related mortality by using reduced-intensity conditioning regimens.

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. (3) Another team of investigators (2005) examined outcomes reported to the International Bone Marrow Transplant Registry (IBMTR) between 1984 and 2000 for 61 patients with Diamond-Blackfan syndrome who underwent HCT. (36) Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of OS after transplantation for patients transplanted from an HLA-identical sibling donor (vs. an alternative donor) was 78% versus 45% (p=0.01) at 1 year and 76% versus 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. (37) Patients in the cyclophosphamide plus antithymocyte 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/m^2. 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. (38) 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. (15) 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).

UpToDate

A 2024 UpToDate article on HCT for aplastic anemia in adults states: ‘For most patients under age 50 years with severe or very severe aplastic anemia who have an available matched related or unrelated donor, we suggest proceeding directly to allogeneic HCT rather than pursuing a course of immunosuppressive therapy. The rationale for early transplantation includes improved outcomes with HCT, especially in younger patients, and concerns about the risks of severe infections, excessive blood product transfusions, and late clonal disorders such as myelodysplasia and/or acute leukemia with immunosuppressive therapy.” (39)

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 has been shown to improve OS or DFS.

Primary Immunodeficiencies

Review articles summarize experience the use of HCT to treat primary immunodeficiencies. (40, 41) Additional individual studies are reported next.

Chronic Granulomatous Disease (CGD)

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. (42) 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 a 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 BU administration. (43) 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 (i.e., 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 (SCID)

HCT using HLA-identical sibling donors can correct underlying primary immunodeficiencies, such as SCID, Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies, in approximately 90% of cases. (44) 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. (39) Another 2008 report found an OS rate for patients with SCID who have undergone HCT to be 71%. (4)

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. (45) 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, non-engraftment 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. (46) 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. (47) 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 (XLP) Disease

XLP type 1 (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. (48) 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 a hematopoietic recovery. No cases of hepatic veno-occlusive 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. (4)

To date, studies have indicated that RIC regimens have an important role in treating patients with primary immunodeficiency. (42) 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.

Inherited Metabolic Diseases Including Hunter, Sanfilippo, or Morquio Syndromes

Hunter Syndrome

Hunter syndrome is composed of 2 distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged lifespan, minimal to no central nervous system (CNS) involvement, and a slow progression. 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. (49)

Eight patients with Hunter syndrome received an allo-HCT between the ages of 3 and 16 years. (50) In 6 cases, the donor was an HLA-identical sibling; in 1 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 CNS involvement (i.e., diagnosis before the age of 4 years and an IQ <80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years of age 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 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 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 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 2 patients with the severe form required special schooling and had poor social and language skills.

Sanfilippo Syndrome (MPS III)

Experience with allo-HCT in patients with MPS III has shown no alteration in the course of neuropsychologic deterioration seen in these patients. (49) The literature addressing the use of HCT in Sanfilippo syndrome consists of 2 older case reports. Vellodi et al. (1992) reported on the outcomes of twin girls diagnosed with MPS III who underwent allo-HCT and were followed for 9 years. (51) 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 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 MPS III who had received allo-HCT was 5.3 years old at the time of the transplant and continued to deteriorate posttransplant. (52)

Morquio Syndrome

Allo-HCT has not been effective in Morquio syndromes. (49)

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

Review articles summarize the experience using HCT to treat inherited metabolic diseases. (53, 54)

Lysosomal Storage Disorders

HCT has been performed in approximately 20 of the estimated 40 known lysosomal storage disorders and peroxisomal storage disorders. (6) 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. (55) 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. (55)

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 CNS. (56) 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. (6) Survival of engrafted Hurler syndrome patients has been radically changed from that of un-transplanted patients, with long-term survival data indicating that lifespan can be extended by many decades. (49) A 2007 analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%. (57)

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. (56) 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. (58) 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. (59) 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 multiorgan 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. (49)

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. (49)

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. (49)

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, (49) 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. (60) 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

A 2010 review article has summarized the experience using HCT to treat osteopetrosis. (61)

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 a 5-year DFS rates of 73% to 79% versus 13% to 45% for those requiring a transplantation from an unrelated or mismatched donor. (7)

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). (62)

Genetic Diseases and Acquired Anemias Treated with Autologous HCT (Auto-HCT)

There were no peer-reviewed clinical studies addressing the treatment of any genetic disease or acquired anemia by auto-HCT.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 2.

Table 2. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02356653	Expanded Access Protocol Using CD3+/CD19+ Depleted PBSC (ExpMACs)	100	Jan 2027
NCT02986698	In Utero Hematopoietic Stem Cell Transplantation for Alpha-Thalassemia Major (ATM)	10	Feb 2026
NCT03653247	A Study to Assess the Safety, Tolerability, and Efficacy of BIVV003 for Autologous Hematopoietic Stem Cell Transplantation in Patients With Severe Sickle Cell Disease	8	July 2025
NCT06065189	Base-edited Autologous Hematopoietic Stem Cell Transplantation in Treating Patients With β-thalassemia Major	5	Dec 2024
Unpublished			
NCT00553098	Alemtuzumab, Fludarabine Phosphate, and Total-Body Irradiation Followed by a Donor Stem Cell Transplant in Treating Patients With Immunodeficiency or Other Nonmalignant Inherited Disorders	29	Mar 2015
NCT00176852	Stem Cell Transplant for Hemoglobinopathy	22	Jan 2020
NCT00358657	Fludarabine Phosphate, Cyclophosphamide, and Total-Body Irradiation Followed by Donor Bone Marrow Transplant and Cyclophosphamide, Mycophenolate Mofetil, Tacrolimus, and Sirolimus in Treating Patients With Primary Immunodeficiency Disorders or Noncancerous Inherited Disorders	14	May 2019 (terminated)

NCT: National Clinical Trial.

Practice Guidelines and Position Statements

American Society for Transplantation and Cellular Therapy (ASTCT)

The ASTCT, formerly known as the American Society for Blood and Marrow Transplantation, (2020) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings. (63) Specific to this policy, Table 3 provides the allogeneic guidelines for specific indications. This guideline was updated in 2024 noting that indications for autologous and allogeneic HCT have no new updates. (64)

Table 3. Recommendations for Use of Allogeneic-HCT to Treat Genetic Diseases and Acquired Anemias

Indications	**Allogeneic HCT ≤18 Years**
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S
Fanconi anemia	R
Other bone marrow failure syndrome (includes dyskeratosis congenita, Shwachman-Diamond syndrome)	R
Sickle cell disease	C
Thalassemia	S
Congenital amegakaryocytic thrombocytopenia	R
Severe combined immunodeficiency	R
T-cell immunodeficiency, severe combined immunodeficiency variants	R
Wiskott-Aldrich syndrome	R
Hemophagocytic disorders	S
Severe congenital neutropenia	R
Chronic granulomatous disease	R
Other phagocytic cell disorders	R
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome	R
Juvenile rheumatoid arthritis	D
Systemic sclerosis	D
Other autoimmune and immune dysregulation disorders	R
Mucopolysaccharidoses (severe; Hurler syndrome)	R
Other mucopolysaccharidoses (II, IV, VI)	D
Other lysosomal metabolic diseases	D
Osteopetrosis (severe, recessive)	R
Osteopetrosis (intermediate)	D
Globoid cell leukodystrophy	R
Metachromatic leukodystrophy	R
Cerebral X-linked adrenoleukodystrophy	R
Indications	**Allogeneic HCT >18 Years**
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S

Fanconi anemia	R
Dyskeratosis congenita	R
Sickle cell disease	S
Thalassemia	D
Hemophagocytic syndromes, refractory	S
Common variable immunodeficiency	R
Wiskott-Aldrich syndrome	C
Chronic granulomatous disease	R
Multiple sclerosis	N
Systemic sclerosis	N
Rheumatoid arthritis	N
Systemic lupus erythematosus	N
Crohn's disease	N
Polymyositis-dermatomyositis	N
Osteopetrosis (intermediate)	D
Cerebral X-linked adrenoleukodystrophy	R

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

British Committee for Standards (BCS) in Haematology

The BCS in Haematology (2024) published guidelines on the diagnosis and management of adult aplastic anemia. (65) 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 40 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 (EBMT)

The EBMT (2022) provided consensus-based recommendations on indications for HCT and transplant management in the hemoglobinopathies. (11)

Pediatric Haemato-Oncology Italian Association

The Pediatric Haemato-Oncology Italian Association (2024) issued guidelines on the diagnosis and treatment of acquired aplastic anemia in childhood. (66)

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 allogeneic hematopoietic cell transplantation (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.

As of this update, no trials have been published that would alter the current coverage statement for autologous HCT, which is considered experimental, investigational and/or unproven to treat genetic diseases and acquired anemias.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
HCPCS Codes	S2140, S2142, S2150

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
03/15/2025	Document updated. The following change was made to Coverage: Added the following NOTE: “This policy does not apply to the autologous stem cell

	infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia. Coverage of autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia is dependent upon meeting the coverage criteria in the specific gene therapy policy (i.e., RX501.166 and RX501.167)." No new references added.
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 1, 24, 31-32, 35, 39, and 64-65.
07/15/2023	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. References revised and one removed.
08/01/2021	Reviewed. No changes.
10/01/2020	Document updated with literature review. Coverage unchanged. No new references added.
06/15/2019	Reviewed. No changes.
05/15/2018	Document updated with literature review. Coverage unchanged. References reorganized and 19, 58-59 were added; none removed.
06/01/2017	Reviewed. No changes.
06/01/2016	Document updated with literature review. Coverage unchanged. Rationale significantly revised.
07/15/2015	Document updated with literature review. Coverage unchanged. Title changed from Stem-Cell Transplant for Genetic Diseases and Acquired Anemias.
06/01/2014	Document updated with literature review. The following was changed: reorganized and expanded multiple coverage indications/conditions, including: 1) hemoglobulinopathies (adding history of prior stroke or at increased risk of stroke or end-organ damage for sickle cell anemia and homozygous for beta-thalassemia with example); 2) bone marrow failure syndromes (adding examples of hereditary or acquired forms); 3) primary immunodeficiencies (including absent or defective T-cell function, natural killer function, neutrophil function); 4) inherited metabolic disease (adding lysosomal and peroxisomal storage disorders with examples); and 5) genetic disorders affecting skeletal tissue (adding examples of infantile malignant osteopetrosis). The following coverage statements were added: 1) hematopoietic progenitor cell boost is considered experimental, investigational and/or unproven. and 2) expanded coverage to consider a) short tandem repeat (STR) markers medically necessary when used in pre- or post-stem-cell support testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment following allogeneic SCS for specific genetic diseases and acquired anemias listed; b) all other uses of STR markers experimental, investigational and/or unproven, if not listed in the coverage section. Description and Rationale significantly revised.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Non-Malignancies;

	SUR703.018, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem-cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem-cell Support for Malignancies. Stem-cell transplant continues to be medically necessary when stated criteria are met. [NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information): • Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Non-Malignancies; • Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Malignancies; • Cord Blood as a Source of Stem-cells; • Donor Leukocyte Infusion (DLI); and Tandem/Triple High-Dose Chemoradiotherapy with Stem-cell Support for Malignancies.