Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 9/1/24**

Title: Bone Marrow Transplant - Hematopoietic Cell Transplant for Genetic Diseases and Acquired Anemias, Allogeneic

Description/Background

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.

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is a procedure in which healthy hematopoietic stem cells are intravenously infused into a recipient to restore bone marrow and immune function in individuals. Bone marrow transplants have several benefits which vary depending on the disease being treated. In individuals with immune deficiency syndromes, hemoglobinopathies, and acquired anemias, bone marrow transplants can boost bone marrow function and help to generate functional cells to replace the dysfunctional or depleted cells. In individuals with malignancies, bone marrow transplant allows for the destruction and replacement of malignant cells with healthy cells. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

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

CONDITIONING FOR HEMATOPOIETIC CELL TRANSPLANTATION

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with 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 initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the 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 ability of cytotoxic chemotherapy with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC), sometimes referred to as non-myloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA 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. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

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 β-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.(1) Sickle cell disease typically

manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for individuals 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 for sickle cell disease: chronic blood transfusions, hydroxyurea 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, a rare, autosomal recessive disease, characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently, this disease terminates in a myelodysplastic syndrome or acute myeloid leukemia. Most individuals with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia or solid tumors, with a median survival of 30 years of age.(2)

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 cytopenia's, with some individuals developing aplastic anemia. As with other bone marrow failure syndromes, individuals 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 individuals also having a variety of physical anomalies.(3)

Treatment
In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic 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.(4) The most severe defects (collectively known as severe combined immunodeficiency, or SCID) cause an absence or dysfunction of T-lymphocytes and sometimes B-lymphocytes and natural killer cells.(4)

Treatment
Without treatment, individuals with severe combined immunodeficiency (SCID) usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these individuals 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)

Inherited Metabolic Diseases

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

Treatment

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don't cross the blood-brain barrier, which results in 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.(6) 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)

Allogeneic HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in the Table 1.(6) The first stem-cell transplant for an inherited metabolic disease was performed in 1980 in an individual with Hurler syndrome. Since that time, more than 1,000 transplants have been performed worldwide.(6)

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis	Mucopolysaccharidosis I H or H/S Mucopolysaccharidosis II Mucopolysaccharidosis III A-D Mucopolysaccharidosis IV A-B Mucopolysaccharidosis VI Mucopolysaccharidosis VII	Hurler syndrome or Hurler-Scheie syndrome Hunter syndrome Sanfilippo syndrome A-D Morquio syndrome A-B Maroteaux-Lamy syndrome Sly syndrome
Sphingolipidosis	Fabry disease Farber disease Gaucher disease types 1 and 3 GM1 gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff disease Globoid cell leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis Krabbe disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis	Sialidosis

	Alpha-mannosidosis Beta-mannosidosis Mucolipidosis III and IV	
Other lipidoses	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis type III	Batten disease
Glycogen storage	Glycogen storage disease type II	Pompe disease
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

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.(7) Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected individuals are those with infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease). Individuals with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately 6 months of age, and severe hematologic malfunction with bone marrow failure.(7) Seventy percent of these individuals die before the age of 6 years, often of recurrent infections.(7) HCT is the only curative therapy for this fatal disease.

Treatment

HCT is the only curative therapy for this fatal disease.

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.

Medical Policy Statement

The safety and effectiveness of allogeneic hematopoietic cell transplantation for specified genetic diseases and acquired anemias have been established. It may be considered a useful therapeutic or diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Clinical documentation supplied to the health plan *must* demonstrate that attending staff at the transplant center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Inclusions:
Allogeneic hematopoietic cell transplantation is considered established for selected individuals as listed below.

The conditioning regimens for the following diseases may include myeloablative conditioning, reduced intensity conditioning, or non-myeloablative conditioning as determined by the treating provider/transplant center.

Hemoglobinopathies:
- Sickle cell anemia for children or young adults
- Homozygous beta-thalassemia (i.e., thalassemia major)

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

Primary Immunodeficiencies
- Absent or defective T-cell function
- Absent or defective natural killer function
- Absent or defective neutrophil function

The following diseases are examples of the above:
- Lymphocyte Immunodeficiencies
  - Adenosine deaminase deficiency
  - Artemis deficiency
  - Calcium channel deficiency
  - CD 40 ligand deficiency
  - Cernunnos/X-linked lymphoproliferative disease deficiency
  - CHARGE syndrome with immune deficiency
  - Common gamma chain deficiency
  - Deficiencies in CD45, CD3, CD8
  - DiGeorge syndrome
  - DNA ligase IV deficiency syndrome
  - Interleukin-7 receptor alpha deficiency
  - Janus-associated kinase 3 deficiency
  - Major histocompatibility class II deficiency
  - Omenn syndrome
  - Purine nucleoside phosphorylase deficiency
  - Recombinase-activating gene 1/2 deficiency
  - Reticular dysgenesis
  - Severe combined immunodeficiency
  - Winged helix deficiency
  - Wiskott-Aldrich syndrome
  - X-linked lymphoproliferative disease
  - Zeta-chain-associated protein-70 deficiency
- Phagocytic Deficiencies
  - Chédiak-Higashi syndrome
  - Chronic granulomatous disease

    - Griscelli syndrome, type 2
    - Hemophagocytic lymphohistiocytosis
    - Interferon-gamma receptor deficiencies
    - Kostmann syndrome
    - Leukocyte adhesion deficiency
    - Severe congenital neutropenias
    - Shwachman-Diamond syndrome
- Other Immunodeficiencies
    - Autoimmune lymphoproliferative syndrome
    - Cartilage hair hypoplasia
    - CD25 deficiency
    - Hyper IgD and IgE syndromes
    - Immunodeficiency, centromeric instability, and facial dysmorphism syndrome
    - Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
    - Nuclear factor-κ B (NF-κB) essential modulator deficiency
    - NF-κB inhibitor, NF-κB-α deficiency
    - Nijmegen breakage syndrome

Inherited Metabolic Disease

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

The following diseases are examples of the above:

- Hurler
- Maroteaux-Lamy
- Sly syndromes
- Childhood onset cerebral X-linked adrenoleukodystrophy
- Globoid-cell leukodystrophy
- Metachromatic leukodystrophy
- Alpha-mannosidosis
- Aspartylglucosaminuria
- 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
- Wolman disease

Genetic Disorders Affecting Skeletal Tissue

- Infantile malignant osteopetrosis (Albers-Schönberg disease or marble bone disease)

Exclusions:
Allogeneic HCT has not been effective in:

- Hunter syndrome
- Sanfilippo syndrome
- Morquio syndrome

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38230
38240	38242	38243	81267	81268	81370
81371	81372	81373	81374	81375	81376
81377	81378	81379	81380	81381	81382
81383	86812	86813	86816	86817	86821
S2140	S2142	S2150			

Other codes (investigational, not medically necessary, etc.):

N/A

Potential contraindications for transplant:

Note: Final individual eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each individual. Therefore, potential contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that ***attending staff at the transplant center have considered all contraindications*** as part of their overall evaluation of potential organ transplant recipient ***and have decided to proceed.***

Rationale

For the purpose of this policy, the following PICO and study selection criteria will be used.

Clinical Context and Test Purpose
The purpose of allogeneic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with genetic diseases and/or acquired anemias.

The question addressed in this evidence review is: Does the use of allogeneic hematopoietic cell transplantation improve the net health outcome in individuals with genetic diseases and/or acquired anemias?

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

Populations
The relevant population of interest are individuals with genetic diseases and/or acquired anemias..

Interventions
The therapy being considered is allogeneic hematopoietic cell transplantation.

Comparators
Comparators of interest include standard of care.

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

Follow-up to monitor relevant outcomes of allogeneic hematopoietic cell transplantation is as follows:
- Hemoglobinopathy: at 3- and 12- years
- Bone marrow failure syndrome: at 1.1- and 8-years
- Primary immunodeficiencies: at 6- and 21-months
- Inherited metabolic diseases including Hunter, Sanfilippo, or Morquio syndromes: at 7- to 17-years
- Inherited metabolic diseases excluding Hunter, Sanfilippo, or Morquio syndromes: at 5.5- and 9.2 years
- Genetic disorders affecting skeletal tissue: Not completely standardized, but would typically occur in the months to years after starting treatment

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 longer 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.

HEMOGLOBINOPATHIES

Systemic Review

Review articles summarize the experience to date with HCT and the hemoglobinopathies.(8-11)

The thalassaemias are a group of genetic disorders which are endemic in the tropics but are also found worldwide due to migration. Basic standard of care includes regular transfusions to maintain a hemoglobin level of 10 g/dL and to prevent iron overload.

β-Thalassemia

More than 3,000 individuals worldwide have been treated for beta-thalassemia with allogeneic HCT.(10) Overall survival (OS) rates have ranged from 65% to 98% at 5 years, up to 87% at 15 years, up to 89% at 20 years, and thalassemia-free survival has been reported to be as high as 86% at 6 years.(12) The Pesaro risk stratification system classifies individuals with thalassemia who plan to undergo allo-HCT into risk groups I through III based on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with 2 risk factors, and III with all 3 risk factors).(13) The outcome of allo-HCT in more than 800 individuals with thalassemia according to risk stratification has shown overall and event-free survival (EFS) of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III.

A 2015 study of 489 individuals with non-malignant hematologic disorders who underwent allo-HCT between 1997 and 2012 included 152 individuals with β-thalassemia.(14) Mean age at transplantation was 5.7 years (range 1.1–23 years). At the time of transplantation, 26 individuals (17%) had Pesaro class I, 103 (68%) had class II and 23 (15%) had class III; 132 individuals received peripheral blood stem cells and 20 received bone marrow grafts. Mean times to neutrophil and platelet engraftment were 21.4 days (8–69) and 32.8 days (7–134), respectively. The incidence of graft rejection was significantly lower in individuals 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 individuals with β-thalassemia , 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 individuals was 82.4%. The disease-free survival (DFS) rate for the whole group of individuals with β-thalassemia was 72.4% (74% in the peripheral blood stem 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 individuals with thalassemia (median age, 7 years; range, 1-37) who underwent allo-HCT after a reduced-intensity conditioning (RIC) regimen based on treosulfan.(15) Before the transplant, 27 children were assigned to class 1 of the Pesaro risk stratification system, 17 to class II, and IV to class III; 12 individuals were adults. Twenty individuals were transplanted from an HLA-identical sibling and 40 from an unrelated donor. The cumulative incidence of graft failure and transplantation-related mortality was 9% and 7%, respectively. Eight individuals experienced grade II-IV acute GVHD, the cumulative incidence being 14%. Among 56 individuals at risk, 1 developed limited chronic GVHD. With a median follow-up of 36 months (range, 4-72), the 5-year probability of survival and thalassemia-

free survival were 93% and 84%, respectively. Neither the class of risk nor the donor used influenced outcomes.

In a 2014 report on RIC HCT, 98 individuals with class III thalassemia were transplanted with related or unrelated donor stem cells.(16) Seventy-six of individuals less than 10 years of age received a conventional myeloablative conditioning regimen (cyclophosphamide [Cy], busulfan, with or without fludarabine). The remaining 22 individuals were 10 years of age or older with hepatomegaly and, in several instances, additional comorbidity problems, 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 6 individuals in the myeloablated group (8%), although none occurred in the RIC group.

Sickle Cell Disease

A Cochrane systematic review published in 2013,(17) updated in 2016,(18) and again in 2020,(19) identified no completed randomized controlled trials that assessed a risk or benefit of any method of HCT in individuals with sickle cell disease.

Approximately 500 to 600 individuals 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.(1,10) The largest series to date consisted of 87 symptomatic individuals, 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 0.9–17.9 years.(1)

Experience with reduced-intensity preparative regimens (RIC and allo-HCT for the hemoglobinopathies) is limited to a small number of individuals. Challenges have included high rates of graft rejection (10–30%) (8) and, in adult subjects, severe GVHD, which has been observed with the use of RIC regimens.(9)

Hsieh et al (2014) reported on results from 30 subjects 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.(23) The primary end point was treatment success at 1 year after the transplant, defined as a full donor-type hemoglobin for individuals with sickle cell disease and transfusion independence for individuals with thalassemia. Secondary end points included the level of donor leukocyte chimerism; incidence of acute and chronic GVHD; and sickle cell-thalassemia disease-free survival (DFS), immunologic recovery, and changes in organ function. Twenty-nine individuals survived a median 3.4 years (range, 1-8.6), with no non-relapse mortality. One individual died from intracranial bleeding after relapse. The normalized hemoglobin and resolution of hemolysis among engrafted individuals 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.

Eapen et al (2024) discussed long-term outcomes of a phase II, Blood and Marrow Transplant Clinical Trial that enrolled subjects 3-19 years of age. The median age of this cohort at transplant was 13 years (range: 6–18); 5 were 6–9 years old, 10 were 10–15 years old, and 6 were 16–19 years old. Median donor age was 34 years (range: 21–53). HLA-matched unrelated donor bone marrow transplantation (URD BMT) was conducted for severe sickle cell disease (SCD) between 2008 and 2014. Eighteen (86%) had ≥5 years of follow-up. Three patients died beyond 2 years post-transplant. Two deaths were secondary to complications of chronic GVHD at 2.6 and 3.9 years. A third patient who had primary GR (reported in the initial report), underwent a second myeloablative URD umbilical cord blood transplant 27 months after the first and died at 2.5 years after the first transplant of grade IV acute GVHD that developed following the second transplant. Consequently, the 5- and 8-year probabilities of OS were 68% (95% CI: 48%–82%). With a single secondary GR 5 years after transplantation, the 5- and 8-year probabilities of EFS were 61% (95% CI: 41%–76%) and 57% (95% CI: 37%–73%), respectively. Extended follow-up demonstrated that engraftment and cure were achievable with a RIC regimen following unrelated donor transplantation. The GVHD prophylaxis, however, was inadequate especially in recipients over 13 years of age, compromising outcomes and increasing mortality. Since completion of BMT CTN 0601 and the recognition of the GVHD-related complications, successful application of novel GVHD prophylaxis, including extended duration abatacept, has been reported with this conditioning regimen in HLA matched and minimally mismatched unrelated transplants. Authors determined it is encouraging that the results from these collective curative efforts are now approaching those previously described only after HLA-matched sibling donor transplantation and serve to expand curative options for SCD individuals over a wide age and therapeutic range. Importantly, these curative therapies require long-term follow-up via registries as described here to ensure that short-term success is sustained and pros and cons are tracked.

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

BONE MARROW FAILURE SYNDROMES
Aplastic anemia is a rare and serious hematologic disorder caused by hematopoietic stem cell failure in maintaining hematopoiesis. Aplastic anemia is virtually fatal if not treated, and diagnosis and therapy require extensive hematologic infrastructure.

Review articles summarize the experience to date on the use of HCT to treat bone marrow failure syndromes.(8, 24-26)

Fanconi Anemia
According to the Fanconi Anemia Research Fund (2024) at the present time, bone marrow transplantation remains the only cure for the hematologic manifestations of Faconi Anenia (FA). Individuals who have had a successful bone marrow transplant and, thus, are cured of the blood problems associated with FA, still must have regular exams for cancer.(27)

Yabe et al (2020) analyzed nationwide records of 163 individuals with Fanconi anemia who received an allo-HCT in Japan between 1987and 2015.(28) The 5-year OS rate was 81%. The 10-year and 15-year OS rates were 77% and 72%. Of the 163 individuals, 154 had a stable engraftment. Among evaluable individuals (n=154), 17% and 5.8% developed grade II-IV and grade III-IV GVHD, respectively.

Zanis-Neto et al (2005) reported the results of 30 individuals with Fanconi anemia treated with RIC regimens, consisting of low-dose cyclophosphamide.(29) Seven individuals 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 individuals who received the higher and lower doses, respectively (p=0.001). Four of the 7 individuals 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 this retrospective analysis of allogeneic UCBT for FA performed between 1988 and 2021 in European Society for Blood and Marrow Transplantation (EBMT)-affiliated centers, Rafii et al (2023) described the outcomes, with a special focus on late complications, of FA individuals who underwent umbilical cord blood transplantation (UCBT).(30) A total of 205 FA individuals underwent UCBT (55 related and 150 unrelated) across 77 transplant centers. Indications for UCBT were bone marrow failure in 190 patients and acute leukemia/myelodysplasia in 15 patients. The median age at transplantation was 9 years (range, 1.2 to 43 years), with only 20 patients age >18 years. Among the donor-recipient pairs, 56% (n = 116) had a 0 to 1/6 HLA mismatch. Limited-field radiotherapy was administered to 28% (n = 58), and 78% (n = 160) received a fludarabine (Flu)-based conditioning regimen. Serotherapy consisted of antithymocyte globulin (n = 159; 78%) or alemtuzumab (n = 12; 6%). The median follow-up was 10 years for related UCBT and 7 years for unrelated UCBT. Excellent outcomes were observed in the setting of related UCBT, including a 60-day cumulative incidence (CuI) of neutrophil recovery of 98.1% (95% confidence interval [CI], 93.9% to 100%), a 100-day CuI of grade II-IV acute graft-versus-host disease (GVHD) of 17.3% (95% CI, 9.5% to 31.6%), and a 5-year CuI of chronic GVHD (cGVHD) of 22.7% (95% CI, 13.3% to 38.7%; 13% extensive). Five-year overall survival (OS) was 88%. In multivariate analysis, none of the factors included in the model predicted a better OS. In unrelated UCBT, the 60-day CuI of neutrophil recovery was 78.7% (95% CI, 71.9% to 86.3%), the 100-day CuI of grade II-IV aGVHD was 31.4% (95% CI, 24.6% to 40.2%), and the 5-year CuI of cGVHD was 24.3% (95% CI, 17.8% to 32.2%; 12% extensive). Five-year OS was 44%. In multivariate analysis, negative recipient cytomegalovirus serology, Flu-based conditioning, age <9 years at UCBT, and 0 to 1/6 HLA mismatch were associated with improved OS. A total of 106 individuals, including 5 with acute leukemia/myelodysplasia, survived for >2 years after UCBT. Nine of these individuals developed subsequent neoplasms (SNs), including 1 donor-derived acute myelogenous leukemia and 8 solid tumors, at a median of 9.7 years (range, 2.3 to 21.8 years) post-UCBT (1 related and 8 unrelated UCBT). In a subset of 49 individuals with available data, late nonmalignant complications affecting various organ systems were observed at a median of 8.7 years (range, 2.7 to 28.8 years) post-UCBT. UCB is a valid source of stem cells for transplantation in individuals with FA, with the best results observed after related UCBT. After unrelated UCBT, improved survival was observed in individuals who underwent transplantation at a younger age, with Flu-based conditioning, and with better HLA parity. The incidence of organ-specific complications and SNs was relatively low. The incidence of SNs, mostly squamous cell carcinoma, increases with time. Rigorous follow-up and lifelong screening are crucial in survivors of UCBT for FA.

Dyskeratosis Congenita

Dyskeratosis congenita is a multisystem and ultra-rare hereditary disease characterized by somatic involvement, bone marrow failure, and predisposition to cancer. Results with allo-HCT in dyskeratosis congenita have been disappointing because of severe late effects, including diffuse vasculitis and lung fibrosis.(3) Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results have been published.(3)

Outcomes after allo-HCT were recently reported in 2013 for 34 individuals with dyskeratosis congenita who underwent transplantation between 1981 and 2009.(31) Median age at transplantation was 13 years (range, 2-35). Approximately 50% of transplantations were from related donors. The day-28 probability of neutrophil recovery was 73% and the day-100 platelet recovery was 72%. The day-100 probability of grade II, 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 individuals were alive at last follow-up. Ten deaths occurred within 4 months from transplantation because of graft failure (n=6) or other transplantation-related complications; 9 of these individuals had undergone transplantation from mismatched related or from unrelated donors. Another 10 deaths occurred after four months; 6 of which occurred more than 5 years after transplantation, and four 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 individuals have undergone allogeneic transplants for this disease.(3) Cesaro et al (2005) reported on 26 individuals with Shwachman-Diamond syndrome from the European Group for Blood and Bone Marrow Transplantation registry, who received HCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (n=9); or another diagnosis (n=1).(32) Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n= 6), mismatched related (n= 1), or unrelated graft (n=19). Graft failure occurred in 5 (19%) individuals, 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 myelodysplastic syndrome-acute myeloid leukemia or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

Myers et al (2020) evaluated outcomes in 52 individuals with Shwachman-Diamond syndrome who received a HCT between 2000 and2017 for bone marrow failure (n=39) or myelodysplastic syndrome-acute myeloid leukemia (n=13).(33) For individuals with bone marrow failure, preparative regimens were myeloablative in 13 individuals and reduced intensity in 26 individuals. The 5-year OS in this subgroup was 72%. For individuals with myelodysplastic syndrome-acute myeloid leukemia, preparative regimens were myeloablative in 8 individuals and reduced intensity in 5. At the time of the study report, only 2 of 13 (15%) were alive. Most deaths in this subgroup (8/11) occurred within 8 months after transplantation.

Cesaro et al (2020) reported on outcomes in 74 individuals with Shwachman-Diamond syndrome who received a HCT between 1988 and 2016 for bone marrow failure (n=61), myelodysplastic syndrome (n=7), or acute myeloid leukemia (n=6) in an updated report from the European Group for Blood and Marrow Transplantation registry.(34) The preparative regimens were myeloablative and reduced intensity in 54% and 46% of the cases, respectively. After a median follow-up of 7.3 years, the 5-year OS was 63.3%. The 5-year OS was significantly higher in individuals who received HCT due to bone marrow failure (70.7%) versus in individuals who received HCT due to myelodysplastic syndrome/acute myeloid leukemia (28.8%; p=0.005).The rate of graft failure was 15% and grades I-IV GVHD were reported in 55% of individuals.

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 individuals 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 between 1984 and 2000 for 61 individuals with Diamond-Blackfan syndrome who underwent HCT.(35) Sixty-seven percent of individuals were transplanted with an HLA-identical sibling donor. Probability of OS after transplantation for individuals transplanted from an HLA-identical sibling donor (vs an alternative donor) was 78% versus 45% (p=0.01) at 1 year and 76% vs 39% (p=0.01) at 3 years, respectively.

Aplastic Anemia
ElGohary et al (2020) performed a systematic review and meta-analysis on 15 prospective or retrospective studies (N=577) evaluating outcomes after HCT in individuals with idiopathic aplastic anemia.(36) Seven studies were retrospective in nature, deriving data from registries and records, while 8 studies had a prospective design. Across the studies, the pooled incidence of successful engraftment was 97.3% (95% confidence interval [CI], 95.9 to 98.7). Grade II-IV GVHD was reported in 26.6% of individuals. The pooled incidence of transplant-related mortality was 6.7% per year (95% CI, 4.0 to 9.4). Individuals who received reduced intensity conditioning regimens had lower rates of GVHD (18.7% vs 29.5%) and engraftment (91.7% vs 97.7%) compared to nonmyeloablative regimens.

A randomized Phase III trial (2012) compared 2 conditioning regimens in individuals (n=79) with high-risk aplastic anemia who underwent allo-HCT.(37) Individuals in the cyclophosphamide plus anti-thymocyte globulin (ATG) arm (n=39) received cyclophosphamide at 200 mg/kg; those in the cyclophosphamide-fludarabine 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 suggest an 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 individuals who, after having failed IST, underwent rescue HCT, and to compare their outcomes using front-line HCT and those who did not fail IST (IST with no subsequent transplant). Additional outcomes that were evaluated were the cumulative incidence of post-therapy 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 individuals 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 individuals. The 3-year probability of OS and EFS for the whole population was 90% and 86%, respectively. The 3-year OS 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 individuals with non-malignant hematologic disorders who underwent allo-HCT, including 273 individuals with severe aplastic anemia.(14) 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 individuals. Acute GVHD grade II, III, or IV occurred in 15% and chronic GVHD occurred in 28% of +individuals. The incidence of transplant related mortality was 22%. OS and DFS were both 74%. Conditioning regimens differed among the individuals, with 181 receiving fludarabine and cyclophosphamide and 92 received 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, OS rate was statistically significantly better in the fludarabine plus cyclophosphamide group (80%) than in the cyclophosphamide plus ATG group of individuals (64%; p =0.021).

Section Summary: Bone Marrow Failure Syndrome
Use of allo-HCT to treat individuals 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.(39,40) Additional individual studies are reported next.

Chronic Granulomatous Disease
HCT outcomes were compared with those of conventional treatment in a study of 41 individuals in Sweden who were diagnosed with chronic granulomatous disease (CGD) between 1990 and 2012.(41) From 1997 to 2012, 14 individuals (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 individuals 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 remaining individuals suffered life-threatening infections.

A 2014 prospective study in 16 centers across countries worldwide enrolled individuals with CGD 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.(42) Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related-donors or HLA-9/10 or HLA-10/10 matched unrelated-donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at 2 years, 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 individuals (median age 12.7 years) were included; 42 (75%) individuals had high-risk features (i.e., intractable infections and auto-inflammation), 25 (45%) were adolescents and young adults (age range, 14-39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At median follow-up of 21 months, 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 individuals. The cumulative incidence of acute GVHD of grade III or IV was 4% and of chronic GVHD was 7%. Stable ($\geq$90%) myeloid donor chimerism was documented in 52 (93%) surviving individuals.

Chiesa et al (2020) conducted a retrospective, multicenter evaluation of 712 individuals with CGD who received a HCT between 1993 and 2018.(43) The majority of individuals in the cohort were children (n=635) and the median age at transplantation was 7 years (range,0.1 to 48.6). Additionally, 87% of individuals underwent transplantation after 2006. The 3-year OS probability was 85.7% (95% CI, 82.8 to88.5) and the 3-year EFS probability was 75.8% (95% CI, 72.3 to 79.3). Donor engraftment was achieved in 88% of evaluable individuals. The cumulative incidence of grades II-IV and grades III-IV acute GVHD was 20.1% and 9%, respectively. The cumulative incidence of chronic GVHD at 3 years was 17.8%.

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.(44) According to a 2008 European series of 475 individuals 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.(44) Another 2008 report found an OS rate for individuals with SCID who have undergone HCT to be 71%.(4)

Hassan et al (2012) reported a multicenter retrospective study, which analyzed HCT outcomes in 106 individuals 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<0.0001). Superior OS was also seen in individuals 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 individuals and was seen even after unconditioned HCT.

Wiskott-Aldrich Syndrome
For Wiskott-Aldrich syndrome, a 2001 analysis of 170 individuals 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 probability of survival of 87% (95% CI, 74% to 93%); 48 were from other relatives, with a 5-year probability of survival 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 the long-term outcome and donor-cell engraftment in 194 individuals with Wiskott-Aldrich syndrome treated by HCT from 1980-2009.(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 individuals who received HCT from an unrelated donor at older than 5 years of age. Also, individuals 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 individuals 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.

Burroughs et al (2020) reported outcomes in individuals with Wiskott-Aldrich syndrome who received a HCT at a Primary Immune Deficiency Treatment Consortium center between 2005 through 2015.(48) The most common conditioning regimens were a myeloablative busulfan-based regimen (n=84) and a busulfan-based reduced intensity conditioning regimen (n=25). After a median follow-up of 4.5 years, the 5-year OS probability was 91% (95% CI, 85 to 95). Individuals who received the HCT prior to age 5 years had superior 5-year OS outcomes compared to older individuals (94% vs 66%). The cumulative incidence of grades II-IV and grades III-IV acute GVHD were 27% and 15%, respectively.

X-Linked Lymphoproliferative Disease
X-linked lymphoproliferative disease type 1 (XLP1) is a rare, deadly immune deficiency caused by variants in *SH2D1A*. Allo-HCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these individuals. One study (2014) reported an 8-year single-center experience.(49) Sixteen consecutive individuals diagnosed with XLP1 underwent allo-HCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, fludarabine, and melphalan. Fourteen of 16 individuals received fully HLA-matched (8/8) unrelated or related bone marrow grafts, whereas 2 individuals received mismatched unrelated grafts. All individuals had hematopoietic recovery. No cases of hepatic

veno-occlusive disease or pulmonary hemorrhage were reported. One (6%) individual developed acute GVHD and later also developed chronic GVHD. Five (31%) individuals 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 individuals with genetic immune/inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the 5-year DFS rates with allo-HCT ranged from 60% to 70%.

For individuals 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 individuals with primary immunodeficiency.(40) In the absence of prospective or larger registry studies, it is not possible to prove the superiority of RIC in more stable individuals with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae (e.g., infertility and growth retardation) may be avoided or reduced. Currently, RIC HCT using unrelated donors may offer a survival advantage in individuals with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (individuals >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 individuals with significant comorbidities.

Section Summary: Primary Immunodeficiencies
Use of allo-HCT to treat select individuals with primary immunodeficiencies results in improvements in OS or DFS.

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 life span, minimal to no central nervous system involvement, and a slow progression. Experience with allo-HCT in individuals 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.(50)

Eight individuals with Hunter syndrome received an allo-HCT between the ages of 3 and 16 years.(51) In 6 cases, the donor was an HLA-identical sibling; in 1 case, 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 individuals were considered to have severe central nervous system involvement (i.e., diagnosis before the age of 4 years and an IQ <80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years 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 individual who died of unrelated causes. Successful engraftment was achieved in all individuals, and cardiovascular abnormalities

stabilized in all individuals, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. The neuropsychological outcome was variable: the 2 individuals with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four individuals 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 individuals with the severe form, 3 lost the ability to walk in their early teens, 2 lost language at 9 and 11 years, and 2 developed epilepsy. The remaining 2 individuals with the severe form required special schooling and had poor social and language skills.

Sanfilippo Syndrome
Experience with allo-HCT in individuals with Sanfilippo syndrome (MPS III) has shown no alteration in the course of neuropsychologic deterioration seen in these individuals.(50) The literature addressing the use of HCT in Sanfilippo syndrome consists of 2 older case reports.(52,53) Vellodi et al (1992) reported on the outcomes of twin girls diagnosed with Sanfilippo syndrome who underwent allo-HCT and were followed up for 9 years.(52) 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 individual with Sanfilippo syndrome who had received allo-HCT was 5.3 years old at the time of the transplant and continued to deteriorate post-transplant.(53)

Morquio Syndrome
Allogeneic HCT has not been effective in Morquio syndromes.(50)

Section Summary: Inherited Metabolic Diseases Including Hunter, Sanfilippo, or Morquio Syndromes
Use of allo-HCT to treat individuals 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.(54,55)

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 individuals 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 IV]), 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.(56) The benefit of allo-HCT appears to be limited to select subsets of individuals with few types of lysosomal storage diseases and is not effective in individuals who have developed overt neurologic symptoms or in those with aggressive infantile forms.(56)

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.(57) Impressive results have been observed with allo-HCT in Hurler syndrome. The benefits that have been observed include improvement of neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others.(6) Survival of engrafted Hurler syndrome individuals has been radically changed from that of untransplanted individuals, with long-term survival data indicating that life span can be extended by many decades.(50) A 2007 analysis of nearly 150 transplanted individuals with Hurler syndrome showed an OS rate of more than 80%.(58)

In 2015, an international retrospective analysis reported on long-term results of 217 individuals with Hurler who successfully underwent allo-HCT between 1985 and 2011.(57) Median follow-up was 9.2 years (range, 3-23 years), median age at diagnosis was 9 months (range, 0-42 months), and median age at transplant was 16 months (range, 2-47 months). Primary study end points were neurodevelopmental outcomes and growth, and secondary end points included outcomes involving several different organ systems. Pre-HCT, 56.9% of individuals 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 individuals, respectively, and 44.9% suffered from moderately to severely impaired neurodevelopment. Predictors of better outcomes post-transplant were higher baseline developmental and IQ pre-transplant, younger age at transplant and a normal α-L-iduronidase enzyme level post-transplant.

Experience with allo-HCT and an RIC regimen was reported in 2008 for 7 individuals with Hurler syndrome.(59) Six of the individuals received transplants from unrelated donors and 1 received the transplant from a sibling. All individuals had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the 7 children were alive at a median of 1,014 days (range, 726–2,222 days) post-transplant.

Mynarek et al (2012) reported on the results of a retrospective, multicenter analysis of 17 individuals with α-mannosidosis who underwent allo-HCT.(60) Individuals 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 individual died 76 days after transplantation from sepsis, GVHD and pulmonary hemorrhage, and another individual died on day 135 post-transplant due to viral infections and multi-organ failure. Before allo-HCT, the extent of developmental delay in the 17 individuals varied over a wide range. After allo-HCT, individuals made some developmental progress; however normal development was not achieved. Hearing ability improved in some but not all individuals.

Fewer than 40 individuals with globoid cell leukodystrophy have undergone allo-HCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.(50)

Many individuals 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.(50)

The few individuals with Maroteaux-Lamy syndrome (MPS VI) or Sly syndrome (MPS VII) who have received transplants have shown promising results, with clinical improvement post-transplant.(50)

Peroxisomal Disorders
Outcomes with allo-HCT have been varied but promising. In boys and men with X-linked adrenoleukodystrophy, outcomes have depended on disease status at transplant and transplant-related complications,(50) but reports of preservation of neuropsychologic and neurologic function have been presented.

Miller et al (2011) reported the results of 60 boys who underwent allo-HCT for cerebral adrenoleukodystrophy between 2000 to 2009.(61) 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 HCT. The 5-year survival estimate for boys with Loes score less than 10 at HCT was 89%, whereas that for boys with Loes score 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%. Post-transplantation 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 individuals 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.(62)

The success of allo-HCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with individuals receiving grafts from HLA-identical siblings having a 5-year DFS rates of 73% to 79% vs 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 individuals who received an HLA-haplotype-mismatch graft from a related donor (n=41).(63)

Section Summary: Genetic Disorders Affecting Skeletal Tissues
Use of allo-HCT to treat individuals with osteopetrosis results in improvements in DFS.

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. 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. Use of allo-HCT to treat select subsets of individuals without overt neurologic symptoms or without aggressive infantile forms with lysosomal and peroxisomal storage disorders results in improvements in neurologic, neuropsychologic, and neurophysiologic function. Allo-HCT is likely to improve health outcomes in select individuals with certain inherited and acquired diseases. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. Use of allo-HCT to treat individuals with Hunter, Sanfilippo, or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Supplemental Information

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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

PRACTICE GUIDELINES AND POSITION STATEMENTS

American Society for Blood and Marrow Transplantation
In 2015 the American Society for Blood and Marrow Transplantation published consensus guidelines on the use of hematopoietic cell transplantation (HCT) to treat specific conditions in,

and out, of the clinical trial settings.(64) Specific to this review, Table 2 provides the allogeneic guidelines for specific indications.

Table 2. 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
Dyskeratosis congenita	R
Blackfan-Diamond anemia	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	R
Lymphoproliferative disorders	R
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 (MPS-I and MPS-VI)	R
Other metabolic diseases	R
Osteopetrosis	R
Globoid cell leukodystrophy (Krabbe)	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	C
Thalassemia	D
Hemophagocytic syndromes, refractory	R
Mast cell diseases	R
Common variable immunodeficiency	R
Wiskott-Aldrich syndrome	R
Chronic granulomatous disease	R
Multiple sclerosis	N
Systemic sclerosis	N
Rheumatoid arthritis	N
Systemic lupus erythematosus	N
Crohn's disease	N
Polymyositis-dermatomyositis	N

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

British Committee for Standards in Haematology (2015) 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 individuals aged 35 to 50 years, individuals need to be assessed for comorbidities before being considered for HCT.
- For adults, unrelated donor HCT should be considered if individuals 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.(10)

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.(66)

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03240731	HLA Haploidentical Bone Marrow Transplant in Patients With Severe Sickle Cell Disease (DREPHAPLO)	18	Sep 2025
NCT02171104	MT2013-31: Allo HCT for Metabolic Disorders and Severe Osteopetrosis	100	Jul 2028
NCT05392894	RElated Haplo-DonoR Haematopoietic stEm Cell Transplantation for Adults With Severe Sickle Cell Disease (REDRESS)	120	Mar 2027

NCT: national clinical trial

Government Regulations

National:
There are numerous autoimmune diseases and the Centers for Medicare and Medicaid Services have not issued a national coverage determination (NCD) for stem cell transplantation for each disease. CMS has a general NCD for stem cell transplantation.

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16

A. General
Stem cell transplantation is a process in which stem cells are harvested from either an individual's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the individual's own previously stored cells. AuSCT must be used to effect hematopoietic

reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage
Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)

a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
b) Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
c) Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood **CELL**s. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. The abnormal production of blood **CELL**s in the bone marrow leads to low blood **CELL** counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow

Medicare payment for these beneficiaries will be restricted to individuals enrolled in an approved clinical study. In accordance with the **STEM CELL** Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic **TRANSPLANT** patients in the United States by the Center for International Blood and Marrow **TRANSPLANT** Research. The elements in this dataset, comprised of 2 mandatory forms plus 1 additional form, encompass the information we require for a study under CED. (see guideline for more information)

II. **Allogeneic Hematopoietic STEM CELL transplantation (HSCT)**

Effective for claims with dates of service on or after May 24, 1996, through January 26, 2016, allogeneic HSCT is not covered as treatment for multiple myeloma.

All other indications for STEM CELL transplantation not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2016.)

Local:

Refer to NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

1. Bhatia M, Walters MC. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. *Bone Marrow Transplant*. Jan 2008;41(2):109-117. PMID 18059330
2. Mehta P. Hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. In: Mehta P (ed). *Pediatric Stem Cell Transplantation*. Sudbury, MA: Jones and Bartlett; 2004;281-316.
3. Gluckman E, Wagner JE. Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome. *Bone Marrow Transplant.* Jan 2008;41(2):127-132. PMID 18084332
4. Gennery AR, Cant AJ. Advances in hematopoietic stem cell transplantation for primary immunodeficiency. *Immunol Allergy Clin North Am*. May 2008;28(2):439-456, x-xi. PMID 18424341
5. Porta F, Forino C, De Martiis D et al. Stem cell transplantation for primary immunodeficiencies. *Bone Marrow Transplant*. Jun 2008;41(suppl 2):S83-86. PMID 18545252
6. Prasad VK, Kurtzberg J. Emerging trends in transplantation of inherited metabolic diseases. *Bone Marrow Transplant.* Jan 2008;41(2):99-108. PMID 18176609
7. Askmyr MK, Fasth A, Richter J. Towards a better understanding and new therapeutics of osteopetrosis. *Br J Haematol*. Mar 2008;140(6):597-609. PMID 18241253
8. MacMillan ML, Walters MC, Gluckman E. Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies. *Semin Hematol.* Jan 2010;47(1):37-45. PMID 20109610
9. Smiers F, Krishnamurti L, Lucarelli G. Hematopoietic stem cell transplantation for hemoglobinopathies: current practice and emerging trends. *Pediatr Clin N Am*. Feb 2010; 57(1):181-205. PMID 20307718
10. Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. *Haematologica.* May 2014;99(5):811-820. PMID 24790059
11. Mathews V, Srivastava A, Chandy M. Allogeneic stem cell transplantation for thalassemia major. *Hematol Oncol Clin North Am.* Dec 2014;28(6):1187-1200. PMID 25459187
12. Locatelli F, Kabbara N, Ruggeri A, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. *Blood.* Aug 8 2013;122(6):1072-1078. PMID 23692854
13. Mehta P. Hematopoietic stem cell transplantation for hemoglobinopathies. In: Mehta P (ed). *Pediatric Stem Cell Transplantation*. Sudbury, MA: Jones and Bartlett; 2004;259-279.
14. Mahmoud HK, Elhaddad AM, Fahmy OA, et al. Allogeneic hematopoietic stem cell transplantation for non-malignant hematological disorders. *J Adv Res.* May 2015;6(3):449-458. PMID 26257943
15. Bernardo ME, Piras E, Vacca A et al. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. *Blood*. Jul 12 2012;120(2):473-476. PMID 22645178
16. Anurathapan U, Pakakasama S, Mekjaruskul P, et al. Outcomes of thalassemia patients undergoing hematopoietic stem cell transplantation by using a standard myeloablative versus a novel reduced-toxicity conditioning regimen according to a new risk stratification. *Biol Blood Marrow Transplant.* Dec 2014;20(12):2066-2071. PMID 25064743

17. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. *Cochrane Database Syst Rev*. May 31 2013(5):CD007001. PMID 23728664
18. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. *Cochrane Database Syst Rev*. May 19 2016(5):CD007001. PMID 27194464
19. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev. Jul 03 2020; 7: CD007001. PMID 32617981
20. Bernaudin F, Socie G, Kuentz M et al. Long-term results of related, myeloablative stem cell transplantation to cure sickle cell disease. Blood. Oct 1 2007;110(7):2749-2756. PMID 17606762
21. Walters MC, Patience M, Leisenring W et al. Bone marrow transplantation for sickle cell disease. *N Engl J Med*. Aug 8 1996;335(6):369-376. PMID 8663884
22. Walters MC, Storb R, Patience M et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. *Blood*. Mar 15 2000;95(6):1918-1924. PMID 10706855
23. Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. *JAMA*. Jul 2 2014;312(1):48-56. PMID 25058217
24. Mehta P, Locatelli F, Stary J et al. Bone marrow transplantation for inherited bone marrow failure syndromes. *Pediatr Clin N Am*. Feb 2010;57(1):147-170. PMID 20307716
25. Miano M, Dufour C. The diagnosis and treatment of aplastic anemia: a review. *Int J Hematol.* Jun 2015;101(6):527-535. PMID 25837779
26. Bacigalupo A. Bone marrow transplantation for acquired severe aplastic anemia. *Hematol Oncol Clin North Am.* Dec 2014;28(6):1145-1155. PMID 25459184
27. Fanconi Anemia Research Fund. “Treatment.” 2024. https://www.fanconi.org/explore/treatment#:~:text=At%20the%20present%20time%2C%20bone,watch%20for%20signs%20of%20cancer. Accessed March 20, 2024.
28. Yabe M, Morio T, Tabuchi K, et al. Long-term outcome in patients with Fanconi anemia who received hematopoietic stem cell transplantation: a retrospective nationwide analysis. Int J Hematol. Jan 2021; 113(1): 134-144. PMID 32949371
29. Zanis-Neto J, Flowers ME, Medeiros CR et al. Low-dose cyclophosphamide conditioning for haematopoietic cell transplantation from HLA-matched related donors in patients with Fanconi anaemia. *Br J Haematol*. Jul 2005; 130(1):99-106. PMID 15982351
30. Rafii, H., Fernanda V., Bierings, M., et al. “Umbilical Cord Blood Transplantation for Fanconi Anemia With a Special Focus on Late Complications: a Study on Behalf of Eurocord and SAAWP-EBMT.” *The American Society for Transplantation and Cellular Therapy*. 2024. 3:1-15. PMID: 38452872
31. Gadalla SM, Sales-Bonfim C, Carreras J, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. *Biol Blood Marrow Transplant*. Aug 2013;19(8):1238-1243. PMID 23751955
32. Cesaro S, Oneto R, Messina C et al. Haematopoietic stem cell transplantation for Shwachman-Diamond disease: a study from the European Group for Blood and Marrow Transplantation. *Br J Haematol*. Oct 2005;131(2):231-236. PMID 16197455
33. Myers K, Hebert K, Antin J, et al. Hematopoietic Stem Cell Transplantation for Shwachman-Diamond Syndrome. Biol Blood Marrow Transplant. Aug 2020; 26(8): 1446-1451. PMID 32428734

34. Cesaro S, Pillon M, Sauer M, et al. Long-term outcome after allogeneic hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: a retrospective analysis and a review of the literature by the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (SAAWP-EBMT). Bone Marrow Transplant. Sep 2020; 55(9): 1796-1809. PMID 32203264
35. Roy V, Perez WS, Eapen M et al. Bone marrow transplantation for Diamond-Blackfan anemia. *Biol Blood Marrow Transplant*. Aug 2005;11(8):600-608. PMID 16041310
36. ElGohary G, El Fakih R, de Latour R, et al. Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT). Bone Marrow Transplant. Oct 2020; 55(10): 1906-1917. PMID 32346079
37. Kim H, Lee JH, Joo YD et al. A randomized comparison of cyclophosphamide vs. reduced dose cyclophosphamide plus fludarabine for allogeneic hematopoietic cell transplantation in patients with aplastic anemia and hypoplastic myelodysplastic syndrome. *Ann Hematol*. Sep 2012;91(9):1459-1469. PMID 22526363
38. Dufour C, Pillon M, Socie G, et al. Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. *Br J Haematol.* May 2015;169(4):565-573. PMID 25683884
39. Smith AR, Gross TG, Baker KS. Transplant outcomes for primary immunodeficiency disease. *Semin Hematol*. Jan 2010;47(1):79-85. PMID 20109615
40. Szabolcs P, Cavazzana-Calvo M, Fischer A et al. Bone marrow transplantation for primary immunodeficiency diseases. *Pediatr Clin N Am*. Feb 2010;57(1):207-237. PMID 20307719
41. Ahlin A, Fugelang J, de Boer M, et al. Chronic granulomatous disease-haematopoietic stem cell transplantation versus conventional treatment. Acta Paediatr. Nov 2013;102(11):1087-1094. PMID 23937637
42. Gungor T, Teira P, Slatter M, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet. Feb 1 2014;383(9915):436-448. PMID 24161820
43. Chiesa R, Wang J, Blok HJ, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood. Sep 03 2020; 136(10): 1201-1211. PMID 32614953
44. Filipovich AH. Hematopoietic cell transplantation for correction of primary immunodeficiencies. Bone Marrow Transplant. Aug 2008;42(Suppl 1):S49-S52. PMID 18724301
45. Hassan A, Booth C, Brightwell A et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase deficient severe combined immunodeficiency. Blood. Oct 25 2012;120(17):3615-3624; quiz 3626. PMID 22791287
46. Filipovich AH, Stone J, Tomany SC et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. *Blood*. Mar 15 2001; 97(6):1598-1603. PMID 11238097
47. Moratto D, Giliani S, Bonfim C et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. *Blood*. Aug 11 2011; 118(6):1675-1684. PMID 21659547

48. Burroughs LM, Petrovic A, Brazauskas R, et al. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. Blood. Jun 04 2020; 135(23): 2094-2105. PMID 32268350
49. Marsh RA, Bleesing JJ, Chandrakasan S, et al. Reduced-Intensity Conditioning Hematopoietic Cell Transplantation Is an Effective Treatment for Patients with SLAM-Associated Protein Deficiency/X-linked Lymphoproliferative Disease Type 1. *Biol Blood Marrow Transplant*. Jun 9 2014. PMID 24923536
50. Mehta P. Metabolic diseases. In: Mehta P, ed. *Pediatric Stem Cell Transplantation*. Sudbury, MA: Jones and Bartlett; 2004:233-258.
51. Guffon N, Bertrand Y, Forest I et al. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. *J Pediatr*. May 2009;154(5):733-737. PMID 19167723
52. Vellodi A, Young E, New M et al. Bone marrow transplantation for Sanfilippo disease type B. *J Inherit Metab Dis*. 1992;15(6):911-918. PMID 1293388
53. Bordigoni P, Vidailbet M, Lena M et al. Bone marrow transplantation for Sanfilippo syndrome. In Hobbs JR, ed. *Correction of Certain Genetic Diseases by Transplantation*. London: Cogent; 1989:114-119.
54. Boelens JJ, Prasad VK, Tolar J et al. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. *Pediatr Clin North Am*. Feb 2010; 57(1):123-145. PMID 20307715
55. Prasad VK, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. Semin Hematol. Jan 2010;47(1):59-69. PMID 20109613
56. Rovelli AM. The controversial and changing role of haematopoietic cell transplantation for lysosomal storage disorders: an update. *Bone Marrow Transplant*. Jun 2008;41(suppl 2):S87-89. PMID 18545253
57. Aldenhoven M, Wynn RF, Orchard PJ, et al. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. *Blood.* Mar 26 2015;125(13):2164-2172. PMID 25624320
58. Boelens JJ, Wynn RF, O'Meara A et al. Outcomes of haematopoietic cell transplantation for MPS-1 in Europe: a risk factor analysis for graft failure. *Bone Marrow Transplant*. Aug 2007; 40(3):225-33. PMID 17529997
59. Hansen MD, Filipovich AH, Davies SM et al. Allogeneic hematopoietic cell transplantation (HCT) in Hurler's syndrome using a reduced intensity preparative regimen. *Bone Marrow Transplant*. Feb 2008;41(4):349-353. PMID 18026148
60. Mynarek M, Tolar J, Albert MH et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. Mar 2012;47(3):352-359. PMID 21552297
61. Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. *Blood.* Aug 18, 2011; 118(7):1971-1978. PMID 21586746
62. Steward CG. Hematopoietic stem cell transplantation for osteopetrosis. Pediatr Clin N Am. Feb 2010;57(1):171-180. PMID20307717
63. Driessen GJ, Gerritsen EJ, Fischer A et al. Long-term outcome of hematopoietic stem cell transplantation in autosomal recessive osteopetrosis: an EBMT report. *Bone Marrow Transplant.* Oct 2003;32(7):657-63. PMID 13130312
64. Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation; guidelines from the American Society for Blood and

Marrow Transplantation. *Biol blood Marrow Transplant.* Nov 2015;21(11):1863-1869. PMID 26256941
65. Killick SB, Bown N, Cavenagh J, et al. guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol.* Jan 2016:172(2):187-207. PMID 26568159
66. Barone A, Lucarelli A, Onofrillo D, et al. Diagnosis and management of acquired aplastic anemia in childhood. Guidelines from the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association (AIEOP). *Blood Cells Mol Dis.* Jun 2015;55(1):40-47. PMID 25976466
67. National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23) Effective 1/27/2016; retrieved May 6, 2021 from: https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&bc=AgAAgAAAAAAAAA%3d%3d&.
68. Kanter J, Liem RI, Bernaudin F, et al. American Society of Hematology 2021 guidelines for sickle cell disease: stem cell transplantation. Blood Adv. 2021 Sep 28;5(18):3668-3689. PMID: 34581773
69. Calado, R.T. “The future of aplastic anemia treatment in Brazil: Lessons learned for global hematology.” *Seminars in Hematology.* 2023; Sep;60(4):200-203. PMID: 37806793.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 3/12/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/14/11	1/31/12	Joint policy established. **Note: This policy was generated from former combined policies on established allogeneic bone marrow transplants*
3/1/13	12/11/12	12/31/12	Policy updated with literature search; references 15, 25 and 27 added; no change in policy statements. Added CPT code 38243 effective 1/1/13. Updated CPT verbiage as needed. Added definition of progenitor cell infusions. Added relative contraindications to policy.
3/1/14	12/10/13	1/6/14	Routine update. No substantive changes. No change in status. CPT codes 38207, 38230 and 38243 added to policy.
11/1/15	8/24/15	9/14/15	Routine maintenance. Added rationale and references. No change to policy status. Added “potential contraindications” to policy.
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance Changed “Hematopoietic Stem Cell Transplant” to “hematopoietic cell transplant” throughout policy.
11/1/18	8/21/18	8/21/18	Routine Maintenance Changed “allogeneic HCT” to “allo-HCT” throughout the policy. CPT code 86822 is no longer active and removed; codes 38220 and 38221 were removed as they are for diagnostic purposes only.
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor Managed: N/A
9/1/24	6/11/24		Routine maintenance (slp) Vendor Managed: N/A

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MARROW TRANSPLANT - HEMATOPOIETIC CELL TRANSPLANT, ALLOGENEIC FOR GENETIC DISEASES AND ACQUIRED ANEMIAS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of the policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.