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Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

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

Hemoglobinopathies:
- Sickle cell anemia for individuals with severe clinical disease (see Policy Guidelines); or
- Transfusion-dependent thalassemias.

Bone Marrow Failure Syndromes:

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

Primary Immunodeficiencies, including but not limited to the following:

- Severe combined immunodeficiency;
- Wiskott-Aldrich syndrome;
- X-linked lymphoproliferative syndrome;
- Chediak-Higashi syndrome;
- Kostmann syndrome;
- Chronic granulomatous disease;
- Leukocyte adhesion defect.

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

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

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

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

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

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

Policy Guidelines

Manifestations of severe clinical disease in sickle cell anemia may include and of the following:

- Overt stroke;
- Abnormal transcranial Doppler ultrasound;
- Frequent pain that is unresponsive to or with an inadequate response to standard of care, such as hydroxyurea (HU), new targeted therapies, or chronic transfusion therapies; or

- Recurrent acute chest syndrome despite optimal standard of care (e.g., HU, L-glutamine, crizanlizumab, and chronic transfusion therapy). (9)

Description

Hematopoietic Cell Transplantation
HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow function and immune function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT; auto-HCT) or a donor (allogeneic HCT; allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood is an allogeneic source; the stem-cells in it are antigenically "naive" and thus, are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

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

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

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with

presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD disease.

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

Genetic Diseases and Acquired Anemias
Hemoglobinopathies
Thalassemias result from variants in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of ß-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function. Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for men and 48 for women.

Treatment
The only definitive cure for thalassemia is to correct the genetic defect with allo-HCT. Three major therapeutic options are available: chronic blood transfusions, chelation therapy, and allo-HCT, the latter being the only possibility for cure. (1)

Bone Marrow Failure Syndromes
Aplastic anemia in children is rare; most often, it is idiopathic and, less commonly, due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading

to pancytopenia and severe aplastic anemia. Frequently, this disease terminates in myelodysplastic syndrome or acute myeloid leukemia. Most patients with FA succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age. (2)

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

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome. (3) Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of MDS and malignant transformation, especially AML. Diamond-Blackfan anemia is characterized by a failure in red blood cell production, with 30% of patients also having a variety of physical anomalies. (3)

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

Primary Immunodeficiencies
The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes. The most severe defects (collectively known as severe combined immunodeficiency [SCID]) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells. (4)

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

Other conditions that have been successfully treated by allo-HCT include the following (4):
1. *Lymphocyte Immunodeficiencies*:
    - Adenosine deaminase deficiency,
    - Artemis deficiency,

- Calcium channel deficiency,
- CD (cluster of differentiation) 40 ligand deficiency,
- Cernunnos/X-linked lymphoproliferative disease deficiency,
- CHARGE (coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities) syndrome with immune deficiency,
- Common gamma chain deficiency,
- Deficiencies in CD 45, CD 3, CD 8,
- DiGeorge syndrome,
- DNA ligase IV deficiency syndrome,
- Interleukin-7 receptor alpha deficiency,
- Janus-associated kinase 3 (JAK3) deficiency,
- Major histocompatibility class II deficiency,
- Omenn syndrome,
- Purine nucleoside phosphorylase deficiency,
- Recombinase-activating gene (RAG) 1/2 deficiency,
- Reticular dysgenesis,
- Winged helix deficiency,
- Wiskott-Aldrich syndrome,
- X-linked lymphoproliferative disease,
- Zeta-chain-associated protein-70 (ZAP-70) deficiency.

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

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 do not cross the blood-brain barrier, which results in the ineffective treatment of the central nervous system. Stem cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier. The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells (e.g., microglial cells in the brain and Kupffer cells in the liver). (6)

Allo-HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1. The first stem cell transplant for an inherited metabolic disease was performed in 1980 in a patient with Hurler syndrome. Since that time, more than 1000 transplants have been performed worldwide. (6)

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler, Scheie, H/S Hunter Sanfilippo A-D Morquio A-B Maroteaux-Lamy Sly
Sphingolipidosis	Fabry's Farber's Gaucher I-III GM_1 gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff's disease	Lipogranulomatosis

	Globoid cell leukodystrophy Metachromatic leukodystrophy	Krabbe disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis Alpha-mannosidosis Beta-mannosidosis Mucolipidosis III and IV	 Sialidosis
Other lipidoses	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis type III	Batten disease
Glycogen storage	Glycogen storage disease type II	Pompe
Multiple enzyme deficiency	Galactosialidosis Mucolipidosis type II	 I-cell disease
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

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

Genetic Disorders Affecting Skeletal Tissue:
Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow. Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease). Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately 6 months of age, and severe hematologic malfunction with bone marrow failure. Seventy percent of these patients die before the age of 6 years, often of recurrent infections. (7)

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

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

Rationale

This policy is based on a review of relevant professional association guidelines and recommendations.

Practice Guidelines and Position Statements
American Society of Hematology
In 2021, the ASH published guidelines on hematopoietic cell transplantation for sickle cell disease, noting that "Hematopoietic stem cell transplantation is currently the only established curative intervention for SCD that can restore normal hematopoiesis." (9) The guideline panel issued recommendations on how to apply HCT in clinical practice. Select recommendations follow:

- "The ASH guideline panel *suggests* HLA-matched related HSCT rather than standard of care (hydroxyurea (HU)/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (conditional recommendation, very low certainty in the evidence)
- For patients with frequent pain, the ASH guideline panel *suggests* using related matched allogeneic transplantation rather than standard of care (conditional recommendation, very low certainty in the evidence about effects)
- For patients with recurrent episodes of ACS, the ASH guideline panel *suggests* using matched related allogeneic transplantation over standard of care (conditional recommendation, very low certainty in the evidence about effects)"

American Society for Transplantation and Cellular Therapy
The ASTCT, formerly known as the American Society for Blood and Marrow Transplantation, (2020) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings. (10) Specific to this policy, Table 3 provides the allogeneic guidelines for specific indications. This guideline was updated in 2023 noting that indications for autologous and allogeneic HCT have no new updates. (11)

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

Indications	Allogeneic HCT ≤18 Years
Severe aplastic anemia, new diagnosis	S
Severe aplastic anemia, relapse/refractory	S

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

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

The ASTCT guideline included information concerning specific considerations related to rare diseases, stating that nonanalytic studies were reviewed and recommendations based on expert opinion for rare diseases where prospective studies were neither available nor feasible. Rather than providing an exhaustive list of unique rare diseases, guideline tables show a concise list of selected diagnoses for which transplant may be offered. It is recognized that for many rare disorders, the appropriateness of HCT may depend on the severity of the phenotype and the degree of disease progression at the time transplant is considered. To address these scenarios in their entirety is beyond the scope of this report. For rare indications, physicians are advised to discuss with individual patients the risks and benefits of the HCT procedure while considering the available literature and clinical experience. When possible, referral to a center of expertise in the specific disease entity or enrollment in a clinical trial should be considered.

British Committee for Standards in Haematology

The BCS in Haematology (2024) published guidelines on the diagnosis and management of adult aplastic anemia. (12) The following key recommendations on HCT were included in the guidelines:

- Matched sibling donor (allogeneic) HCT is the treatment of choice for severe aplastic anemia; however, for patients aged 40 to 50 years, patients need to be assessed for comorbidities before being considered for HCT.
- For adults, unrelated donor HCT should be considered if patients fail to respond to a single course of immunosuppressive therapy.
- Although there have been improvements in outcomes after alternative donor HCT, these transplants are still experimental, and expert consultation should be sought before considering their use.

European Blood and Marrow Transplantation

The EBMT (2025) provided consensus-based recommendations on indications for HCT and transplant management for haematological diseases, solid tumours and immune disorders for adults, adolescents and children. Concerning the treatment of haemaglobinopathies, the authors discussed that allogeneic HCT should be performed early in life to reduce disease related complications, such as irreversible damage due to iron overload in patients with transfusion dependent thalassaemia and systemic vasculopathy in patients with SCD. They also stated "In SCD, the EBMT hemoglobinopathies registry data have recently demonstrated that age is no longer a factor determining adverse outcomes with success rates over 90% in adults as in children." (13)

European Society for Immunodeficiencies and European Blood and Marrow Transplantation

In 2015, the ESID and EBMT published joint consensus guidelines for the diagnosis, treatment and follow up of patients suffering from infantile (malignant) osteopetrosis. The publication states that that HCT is the treatment of choice in patients with severe forms

denominated “malignant infantile osteopetrosis”, except in patients with neurodegeneration and with RANKL mutations. (14)

Thalassaemia International Federation

The 2021 TIF Guidelines Taskforce publication discussed the phenotypic classification of thalassemia syndromes based on clinical severity and transfusion requirement. (15) These guidelines focused on the management of TDT, consisting of non-delectional HbH (hemoglobin H) β-thalassaemia major or severe HbE/β-thalassaemia. The authors stated that an improved understanding of the pathophysiology of β thalassemia has paved the way for the development of novel therapies, which include correction of the α/β globin chain imbalance by hematopoietic stem cell transplantation or gene therapy. Recommendations included offering HCT thalassemia patients and their parents at an early age, before complications due to iron overload have developed, if an HLA identical sibling is available. The authors also noted that HCT is cost-effective when compared to life-long supportive therapy.

Coding

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

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

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

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

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

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Centers for Medicare & Medicaid Services

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

The Centers for Medicare & Medicaid Services does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
TBD	New medical document. Allogeneic hematopoietic cell transplantation (HCT; allo-HCT) may be considered medically necessary for select individuals with the following disorders when specific criteria for each indication in Coverage are met: Hemoglobinopathies; Bone Marrow Failure Syndromes; Primary Immunodeficiencies; Inherited Metabolic Diseases; Genetic Disorders Affecting Skeletal Tissue. Allo-HCT is considered experimental, investigational and/or unproven for any condition or disorder not included above. Autologous HCT (auto-HCT) is considered experimental, investigational and/or unproven for any genetic disease or acquired anemia.