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Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

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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.

Genetic Disorders Affecting Skeletal Tissue:

Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease).

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

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

NOTE 2: This policy does not apply to the autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia. Coverage of autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia is dependent upon meeting the coverage criteria in the specific gene therapy policy (i.e., RX501.166 and RX501.167).

Policy Guidelines

Manifestations of severe clinical disease in sickle cell anemia may include any 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)

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.

Conditioning for Hematopoietic Cell Transplantation

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 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 typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for men and 48 for women.

Treatment

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

Bone Marrow Failure Syndromes

Aplastic anemia in children is rare; most often, it is idiopathic and, less commonly, due to a hereditary disorder. Inherited syndromes include Fanconi anemia (FA), a rare, autosomal recessive disease characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility, and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently, this disease terminates in myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). Most patients with FA succumb to the complications of severe aplastic anemia, leukemia, or solid tumors, with a median survival of 30 years of age. (2)

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

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome. (3) Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some

patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of MDS and malignant transformation, especially AML. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow, with 30% of patients also having a variety of physical anomalies. (3)

Treatment

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

Primary Immunodeficiencies

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

Treatment

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

Other conditions that have been successfully treated by allo-HCT include the following (4):

1. *Lymphocyte Immunodeficiencies:*

- Adenosine deaminase deficiency,
- Artemis deficiency,
- Calcium channel deficiency,
- CD (cluster of differentiation) 40 ligand deficiency,
- Cernunnos/X-linked lymphoproliferative disease deficiency,
- CHARGE (coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities) syndrome with immune deficiency,
- Common gamma chain deficiency,
- Deficiencies in CD 45, CD 3, CD 8,
- DiGeorge syndrome,
- DNA ligase IV deficiency syndrome,
- Interleukin-7 receptor alpha deficiency,
- Janus-associated kinase 3 (JAK3) deficiency,
- Major histocompatibility class II deficiency,
- Omenn syndrome,

- Purine nucleoside phosphorylase deficiency,
 - Recombinase-activating gene (RAG) 1/2 deficiency,
 - Reticular dysgenesis,
 - Winged helix deficiency,
 - Wiskott-Aldrich syndrome,
 - X-linked lymphoproliferative disease,
 - Zeta-chain-associated protein-70 (ZAP-70) deficiency.
2. *Phagocytic deficiencies:*
- Chediak-Higashi syndrome,
 - Chronic granulomatous disease,
 - Griscelli syndrome type 2,
 - Hemophagocytic lymphohistiocytosis,
 - Interferon-gamma receptor deficiencies,
 - Leukocyte adhesion deficiency,
 - Severe congenital neutropenias,
 - Shwachman-Diamond syndrome.
3. *Other immunodeficiencies:*
- Autoimmune lymphoproliferative syndrome,
 - Cartilage hair hypoplasia,
 - CD25 deficiency,
 - Hyper IgD and IgE syndromes,
 - ICF (immunodeficiency, centromere instability and facial anomalies syndrome) syndrome,
 - IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked) syndrome,
 - NEMO (nuclear factor-kappa-B essential modulator) deficiency,
 - NF (nuclear factor)- κ B inhibitor, alpha (I κ B-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. Hurler syndrome usually leads to premature death by 5 years of age.

Treatment

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in

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

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

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler, Scheie, H/S Hunter Sanfilippo A-D Morquio A-B Maroteaux-Lamy Sly
Sphingolipidosis	Fabry's Farber's Gaucher I-III GM ₁ gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff's disease Globoid cell leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis Krabbe disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis Alpha-mannosidosis Beta-mannosidosis Mucopolysaccharidosis 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 Mucopolysaccharidosis type II	I-cell disease
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	

Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN
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H/S: Hurler-Scheie syndrome; MPS: Mucopolysaccharidoses; GM₁: Monosialotetrahexosylganglioside; MLD: Metachromatic leukodystrophy; ALD: Adrenoleukodystrophy; AMN: Adrenomyeloneuropathy.

Genetic Disorders Affecting Skeletal Tissue

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

Treatment

HCT is the only curative therapy for this fatal disease.

NOTE 3: For additional information regarding autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, please see Medical Policy SUR703.036, “Hematopoietic Cell Transplantation for Autoimmune Diseases.”

Regulatory Status

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

Rationale

This policy is based on a review of relevant professional guidelines and/or position statements.

Practice Guidelines and Position Statements

American Society of Hematology (ASH)

In 2021, the ASH published guidelines on hematopoietic cell transplantation (HCT) for sickle cell disease (SCD), noting that “Hematopoietic stem cell transplantation (HSCT) is currently the only established curative intervention for SCD that can restore normal hematopoiesis.” (9)
Autologous HCT was not recommended as a treatment option. The guideline panel issued recommendations on how to apply allogeneic 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 (TCD) (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 [acute chest syndrome], 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 (ASTCT)

The ASTCT, formerly known as the American Society for Blood and Marrow Transplantation, (2020) published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings. (10) Specific to this policy, Table 3 provides guidelines for select 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 HCT to Treat Genetic Diseases and Acquired Anemias

Indications	Allogeneic HCT <18 Years	Autologous HCT <18 Years
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi anemia	R	N
Other bone marrow failure syndrome (includes dyskeratosis congenita, Shwachman-Diamond syndrome)	R	N
Sickle cell disease	C	N
Thalassemia	S	N
Congenital amegakaryocytic thrombocytopenia	R	N
Severe combined immunodeficiency	R	N
T-cell immunodeficiency, severe combined immunodeficiency variants	R	N
Wiskott-Aldrich syndrome	R	N
Hemophagocytic disorders	S	N
Severe congenital neutropenia	R	N
Chronic granulomatous disease	R	N
Other phagocytic cell disorders	R	N
Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome	R	N
Other autoimmune and immune dysregulation disorders	R	N
Mucopolysaccharidoses I (severe; Hurler syndrome)	R	N
Other mucopolysaccharidoses (II, IV, VI)	D	N

Other lysosomal metabolic diseases	D	N
Osteopetrosis (severe, recessive)	R	N
Osteopetrosis (intermediate)	D	N
Globoid cell leukodystrophy	R	N
Metachromatic leukodystrophy	R	N
Cerebral X-linked adrenoleukodystrophy	R	N
Indications	Allogeneic HCT ≥18 Years	Autologous HCT ≥18 Years
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi anemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	S	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	S	N
Common variable immunodeficiency	R	N
Wiskott-Aldrich syndrome	C	N
Chronic granulomatous disease	R	N
Osteopetrosis (intermediate)	D	N
Cerebral X-linked adrenoleukodystrophy	R	N

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. 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 Society for Haematology (BSH)

The BSH (2024) published guidelines on the diagnosis and management of adult aplastic anemia. (12) The publication states that outcomes following aplastic anemia treatment with HCT depend on age, with those from 30 to 50 years having a 70-90% overall survival rate and the possibility of a cure. The following key recommendations on allogeneic HCT were included in the guidelines:

- Potential HCT candidates should undergo human leucocyte antigen (HLA)-typing at diagnosis, followed by related or unrelated donor searches as appropriate to assess the availability of potential donors.
- Matched sibling donor (allogeneic) HCT is the treatment of choice for severe aplastic anemia for candidates less than 40 years of age. Patients aged 40 to 50 years should 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, and for young adults with severe infections and an available matched unrelated donor.

Cure Sanfilippo Foundation and Sanfilippo Children's Foundation

In 2022, the first ever global consensus guidelines for Sanfilippo syndrome clinical care were published. The Cure Sanfilippo Foundation (United States) and Sanfilippo Children's Foundation (Australia) worked in collaboration with clinicians specializing in the treatment of Sanfilippo syndrome (mucopolysaccharidosis type III). The guidelines indicate that HCT is one of multiple disease specific modalities being studied. However, there is no disease-modifying therapy currently available for the treatment of this disorder, and management focuses on supportive interventions. (13)

European Blood and Marrow Transplantation (EBMT)

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 haemoglobinopathies, 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 (TDT) 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." (14)

Concerning inherited conditions in adults, the document states "While allo-HCT in inherited diseases is predominantly performed in childhood, adult patients with inherited diseases, including haemoglobinopathies, constitutional BMF [bone marrow failure] syndromes and inborn errors of metabolism (IEM) and immunity (IEI) are increasingly considered for HCT." Treatment indications are the same for inherited diseases in pediatric and adult populations. However, the authors recommend enlisting guidance from experts in specialty treatment facilities, as presentation, course and prognosis in adults may differ. Fanconi anaemia, dyskeratosis congenita, Blackfan–Diamond anaemia and other inborn bone marrow failure syndromes are causes of constitutional severe aplastic anemia which may be treated with allogeneic HCT. Allo-HCT is the only treatment which will restore normal bone marrow function for those with constitutional BMF syndromes. It also offers curative options for adaptive immune defects and in specific IEIs. Gene therapy using gene-corrected autologous HCT was discussed as an option for individuals diagnosed with an IEM, however that indication is beyond scope of this policy. (14)

European Society for Immunodeficiencies (ESID) 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 receptor activator of nuclear factor kappa-B ligand (RANKL) mutations. (15) Autologous HCT was not discussed.

Thalassaemia International Federation (TIF)

The 2021 TIF Guidelines Taskforce publication discussed the phenotypic classification of thalassemia syndromes based on clinical severity and transfusion requirement. (16) These guidelines focused on the management of TDT, consisting of non-deleotional 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. The TIF reaffirmed these existing recommendations for HCT in TDT in 2025. Additional recommendations for HCT required special attention for adult patients and the utilization of thalassemia-expert transplant centers working with thalassemia reference centers. (17) Autologous HCT outside of gene therapy was not discussed.

Coding

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

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

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

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

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Centers for Medicare and Medicaid Services (CMS)

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

The Centers for Medicare and Medicaid Services (CMS) does 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 <<https://www.cms.hhs.gov>>.

Policy History/Revision	
Date	Description of Change
06/15/2026	Document updated. The following change was made to Coverage: Removed "NOTE 2: Refer to the Description for a discussion of inherited metabolic disorders that have been proven effective when treated with allo-HCT". Added references 13 and 17.
01/01/2026	Document updated. The following change was made to Coverage: 1) Hemoglobinopathies section: Bullets revised to "Sickle cell anemia for individuals with severe clinical disease (see Policy Guidelines)" and "Transfusion-dependent thalassemias"; 2) Primary immunodeficiencies section added statement "but not limited to the following", previously listed conditions bulleted, removed criteria discussing specific types of cell function. References 9 and 13-15 added; others removed/updated.
03/15/2025	Document updated. The following change was made to Coverage: Added the following NOTE: "This policy does not apply to the autologous stem cell infusion of genetically modified cells associated with the administration of

	Casevy or Lyfgenia. Coverage of autologous stem cell infusion of genetically modified cells associated with the administration of Casevy or Lyfgenia is dependent upon meeting the coverage criteria in the specific gene therapy policy (i.e., RX501.166 and RX501.167).” No new references added.
02/01/2025	Document updated with literature review. Coverage unchanged. Added references 1, 24, 31-32, 35, 39, and 64-65.
07/15/2023	Reviewed. No changes.
01/01/2023	Document updated with literature review. Coverage unchanged. References revised and one removed.
08/01/2021	Reviewed. No changes.
10/01/2020	Document updated with literature review. Coverage unchanged. No new references added.
06/15/2019	Reviewed. No changes.
05/15/2018	Document updated with literature review. Coverage unchanged. References reorganized and 19, 58-59 were added; none removed.
06/01/2017	Reviewed. No changes.
06/01/2016	Document updated with literature review. Coverage unchanged. Rationale significantly revised.
07/15/2015	Document updated with literature review. Coverage unchanged. Title changed from Stem-Cell Transplant for Genetic Diseases and Acquired Anemias.
06/01/2014	Document updated with literature review. The following was changed: reorganized and expanded multiple coverage indications/conditions, including: 1) hemoglobinopathies (adding history of prior stroke or at increased risk of stroke or end-organ damage for sickle cell anemia and homozygous for beta-thalassemia with example); 2) bone marrow failure syndromes (adding examples of hereditary or acquired forms); 3) primary immunodeficiencies (including absent or defective T-cell function, natural killer function, neutrophil function); 4) inherited metabolic disease (adding lysosomal and peroxisomal storage disorders with examples); and 5) genetic disorders affecting skeletal tissue (adding examples of infantile malignant osteopetrosis). The following coverage statements were added: 1) hematopoietic progenitor cell boost is considered experimental, investigational and/or unproven. and 2) expanded coverage to consider a) short tandem repeat (STR) markers medically necessary when used in pre- or post-stem-cell support testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment following allogeneic SCS for specific genetic diseases and acquired anemias listed; b) all other uses of STR markers experimental, investigational and/or unproven, if not listed in the coverage section. Description and Rationale significantly revised.
04/01/2010	New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem-cell Transplantation (PSCT/BMT)

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