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MEDICAL POLICY – 8.01.538

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

BCBSA Ref. Policy: 8.01.22

Effective Date:	Dec. 1, 2023
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RELATED MEDICAL POLICIES:

8.01.15	Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
8.01.24	Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
8.01.25	Hematopoietic Cell Transplantation for Autoimmune Diseases
8.01.29	Hematopoietic Cell Transplantation for Hodgkin Lymphoma
8.01.42	Hematopoietic Cell Transplantation for Primary Amyloidosis
8.01.511	Hematopoietic Cell Transplantation for Solid Tumors of Childhood
8.01.529	Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
8.01.532	Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors
8.01.539	Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms

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Introduction

Stem cells are like basic building blocks. They can develop into different types of cells, including cells that stimulate the production of new blood cells. This policy describes when donor (allogeneic) stem cells may be medically necessary for certain anemias and genetic diseases.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Condition	Medical Necessity
Hemoglobinopathies	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected individuals with hemoglobinopathies:** • Sickle cell anemia for children or young adults with either a history of prior stroke or at increased risk of stroke or end-organ damage • Homozygous β-thalassemia (i.e., thalassemia major)
Bone marrow failure syndromes	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected individual with 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	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected individual with primary immunodeficiencies:** • Absent or defective T cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome) **OR** • Absent or defective natural killer function (e.g., Chédiak-Higashi syndrome) **OR** • Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect) **The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic cell transplantation (allo-HCT) (Gennery & Cant et al, 2008).** • Lymphocyte Immunodeficiencies ○ Adenosine deaminase deficiency

Condition	Medical Necessity
	○ 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 (JAK3) deficiency ○ Major histocompatibility class II deficiency ○ Omenn syndrome ○ Purine nucleoside phosphorylase deficiency ○ Recombinase-activating gene (RAG) 1/2 deficiency ○ Reticular dysgenesis ○ Winged helix deficiency ○ Wiskott-Aldrich syndrome ○ X-linked lymphoproliferative disease ○ Zeta-chain-associated protein-70 (ZAP-70) deficiency • Phagocytic Deficiencies ○ Chédiak-Higashi syndrome ○ Chronic granulomatous disease ○ Griscelli syndrome, type 2 ○ Hemophagocytic lymphohistiocytosis ○ Interferon-gamma receptor deficiencies ○ Leukocyte adhesion deficiency ○ Severe congenital neutropenias ○ Shwachman-Diamond syndrome • Other Immunodeficiencies ○ Autoimmune lymphoproliferative syndrome ○ Cartilage hair hypoplasia ○ CD25 deficiency ○ Hyper IgD and IgE syndromes ○ Immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome

Condition	Medical Necessity
	○ Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome ○ Nuclear factor-κ B (NF-κB) essential modulator (NEMO) deficiency ○ NF-κB inhibitor, NF-κB-α deficiency ○ Nijmegen breakage syndrome
Inherited metabolic disease	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected individuals with the following inherited metabolic diseases:** • Lysosomal and peroxisomal storage disorders **except** for Hunter, Sanfilippo, and Morquio syndromes ○ Allogeneic HCT has been proven effective in some cases of: ▪ Hurler, Maroteaux-Lamy, and Sly syndromes ▪ Childhood onset cerebral X-linked adrenoleukodystrophy ▪ Globoid-cell leukodystrophy ▪ Metachromatic leukodystrophy ▪ Alpha-mannosidosis ▪ Aspartylglucosaminuria ○ Allogeneic HCT is possibly effective for: ▪ Fucosidosis ▪ Gaucher types 1 and 3 ▪ Farber lipogranulomatosis ▪ Galactosialidosis ▪ GM_1 gangliosidosis ▪ Mucolipidosis II (I-cell disease) ▪ Multiple sulfatase deficiency ▪ Niemann-Pick disease ▪ Neuronal ceroid lipofuscinosis ▪ Sialidosis ▪ Wolman disease **Allogeneic HCT is considered not medically necessary for individuals with the following inherited metabolic diseases:** • Hunter • Sanfilippo

Condition	Medical Necessity
	• Morquio transplantation syndromes (Mehta, 2004)
Genetic disorders affecting skeletal tissue	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected individuals with genetic disorders affecting skeletal tissue:** • Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease)

Condition	Investigational
Hemoglobinopathies	**Reduced-intensity conditioning (RIC) and allogeneic HCT for hemoglobinopathies is considered investigational.**

Note: The experience with reduced-intensity conditioning and allo-HCT for the diseases listed in this policy has been limited to small numbers of individuals and has yielded mixed results, depending on the disease category. In general, the results have been most promising in the bone marrow failure syndromes and primary immunodeficiencies. In the hemoglobinopathies, success has been hampered by difficulties with high rates of graft rejection, and in adults, severe graft-versus-host-disease. Phase 2/3 trials are ongoing or completed examining the role of this type of transplant for these diseases, as outlined in the **Ongoing and Unpublished Clinical Trials** section.

Documentation Requirements
The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of: • Diagnosis/condition • History and physical examination documenting the severity of the condition

Coding

Code	Description
CPT	

Code	Description
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
HCPCS	
S2142	Cord blood-derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition

Related Information

N/A

Evidence Review

Description

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.

Background

Genetic Diseases and Acquired Anemias

Hemoglobinopathies

Thalassemias result from variants in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of 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 allogeneic 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 cytopenias, 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, allo-HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of human leukocyte antigen (HLA)-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

Primary Immunodeficiencies

The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes.[4] 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, individuals with 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] Allogeneic bone marrow transplantation is the only definitive cure at this time, 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 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 (MPS)	MPS I H or H/S	Hurler syndrome or Hurler-Scheie, syndrome
	MPS II	Hunter syndrome
	MPS III A-D	Sanfilippo syndrome A-D
	MPS IV A-B	Morquio syndrome A-B

Category	Diagnosis	Other Names
	MPS VI	Maroteaux-Lamy syndrome
	MPS VII	Sly sundrome
Sphingolipidosis	Fabry disease	Lipogranuomatosis
	Farber disease	Krabbe disease
	Gaucher disease types 1 and 3	MLD
	GM_1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff disease	
	Globoid leukodystrophy	
	Metachromatic leukodystrophy	
Glycoproteinosis	Aspartylglucosaminuria	Sialidosis
	Fucosidosis	
	Alpha-Mannosidosis	
	Beta-Mannosidosis	
	Mucolipidosis III and IV	
Other lipidoses	Niemann-Pick disease C	Batten disease
	Wolman disease	
	Ceroid lipofuscinosis type III	
Glycogen storage	Glycogen storage disease type II	Pompe disease
Multiple enzyme deficiency	Galactosialidosis	I-cell disease
	Mucolipidosis type II	
Lysosomal transport defects	Cystinosis	
	Sialic acid storage disease	
	Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy	ALD
	Adrenomyeloneuropathy	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]

Treatment

HCT is the only curative therapy for this fatal disease.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer individuals 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) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Cord blood is addressed in a separate policy (see **Related Policies**).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and individual is a critical factor for achieving a successful outcome. Compatibility is established by typing of 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 individual 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 individuals 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 (GVHD), 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 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 GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-Intensity Conditioning (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 individual condition. Individuals 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 review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Summary of Evidence

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

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

Ongoing and Unpublished Clinical Trials

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

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02766465	A Study to Compare Bone Marrow Transplantation to Standard Care in Adolescents and Young Adults With Severe Sickle Cell Disease	200	Mar 2023
NCT02356653	Expanded Access Protocol Using CD3+/CD19+ Depleted Unrelated Donor or Partially Matched Related Donor Peripheral Stem Cells	100	Jan 2021
NCT02986698	A Single-Center, Non-Randomized Study of the Safety and Efficacy of In Utero Hematopoietic Stem Cell Transplantation for the Treatment of Fetuses With Alpha Thalassemia Major	10	Feb 2024
Unpublished			
NCT00176826	In-vivo T-cell Depletion and Hematopoietic Stem Cell Transplantation for Life-Threatening Immune Deficiencies and Histiocytic Disorders	22	Aug 2015 (Terminated)

NCT: national clinical trial.

Clinical Input from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from one physician specialty society (three reviewers) and three academic medical centers while this policy was under review in 2009. There was general agreement with the policy statements. In particular, the reviewers were specifically asked to comment on the use of hematopoietic cell transplant in the inherited metabolic diseases, except for Hunter, Sanfilippo, and Morquio syndromes; four reviewers agreed with the current policy statement, one disagreed, and one did not address this specific question.

Practice Guidelines and Position Statements

American Society for Blood and Marrow Transplantation

In 2015, the American Society for Blood and Marrow Transplantation published consensus guidelines on the use of HCT to treat specific conditions in and out of the clinical trial settings.[64] Specific to this review **Table 3** provides the allogeneic guidelines for specific indications.

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

Indications	Allo-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

Indications	Allo-HCT <18 Years
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	Allo-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

In 2015, the British Committee for Standards in Haematology 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

In 2014, the European Blood and Marrow Transplantation provided consensus-based recommendations on indications for HCT and transplant management in the hemoglobinopathies.[10]

Pediatric Haemato-Oncology Italian Association

In 2015, the Pediatric Haemato-Oncology Italian Association issued guidelines on the diagnosis and treatment of acquired aplastic anemia in childhood.[66]

Medicare National Coverage

There is no national coverage determination.

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. Hematopoietic stem cells are included in these regulations.

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History

Date	Comments
02/01/00	Add to Therapy Section - New policy. Policy represents revision of original 7.03.10. Myelofibrosis and myelodysplasia, originally included in that policy, are now addressed in policy CP.MP.BC.8.01.21. Policy replaced CP.MP.BC.8.01.22, with policy statement on remaining indications unchanged.

Date	Comments
11/12/02	Replace policy - Policy reviewed without literature review; new review date only. Replaces CP.MP.PR.8.01.109.
12/10/02	Replace policy - Policy reviewed by OAP; no criteria changes.
05/13/03	Replace policy - Update CPT codes only.
07/13/04	Replace policy - Policy reviewed; no change to policy statement.
07/12/05	Replace policy - Policy reviewed with literature search; no change to policy statement. No further review scheduled; status changed from BC to AR.
06/09/06	Update Scope and Disclaimer - No other changes.
03/13/07	Replace policy - Policy updated with literature search; no change in policy statement. Policy status updated to annual review with literature search (AR to BC). Reviewed and recommended by OAP on February 22, 2007.
10/09/07	Cross References Updated - No other changes.
11/12/07	Code updated - CPT code 86817 deleted as directed by RPIW.
04/08/08	Replace policy - Policy updated with literature search; no change to the policy statement. Reviewed and recommended by OAP on February 21, 2008.
05/13/08	Cross Reference Update - No other changes
12/08/09	Replace policy - Policy updated and extensively edited based on literature search. Except for one change, the intent of the policy statements is unchanged. The change in the policy statement is that treatment of Hunter, Sanfilippo, and Morquio syndromes are not included in the list of lysosomal and peroxisomal storage diseases where allo-HSCT may be considered medically necessary and are now considered not medically necessary. References added. On hold for notification, release to publish on May 10, 2010.
12/14/10	Replace policy - Policy updated and extensively edited with information on use of reduced-intensity conditioning based upon literature search. References 9, 10, 15, 18, 19, 21, 22, 25, 26, 30 and 33 have been added; the policy statements remain unchanged. Reviewed and approved by OAP on November 18, 2010.
10/11/11	Replace policy – Policy updated with literature search; reference 30 added; no change in policy statement. HCPCS and ICD-9 diagnosis codes updated; ICD-10 codes added. Codes 38220 and 38221 removed.
01/24/12	Code 38232 added.
02/09/12	The CPT codes 38204 and 38206 removed from the policy; they do not apply.
06/20/12	Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.
08/01/12	Update to Related Policies Titles: 8.01.17, 8.01.20, 8.01.21, 8.01.29, 8.01.30, 8.01.31, 8.01.35, and 8.01.520.

Date	Comments
11/27/12	Replace policy - Policy updated with literature search; references 15, 25 and 27 added; no change in policy statements. HCPCS codes G0265 – G0267 removed as these are deleted codes as of 2008.
02/01/13	Update Related Policies, change title of policy 8.01.21.
03/20/13	The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.
09/30/13	Update Related Policies. Change title to 8.01.31.
12/04/13	Replace policy. Rationale updated based on a literature search through July 15, 2013; references 16 and 23 added; others renumbered/removed. Removed CPT 38231-code deleted in 2003. Policy statements unchanged.
02/27/14	Update Related Policies. Change title to 8.01.30.
03/11/14	Coding Update. Codes 41.02, 41.03, and 41.05 were removed per ICD-10 mapping project; these codes are not utilized for adjudication of policy.
03/21/14	Update Related Policies. Add 8.01.15 and delete 8.01.514.
04/18/14	Update Related Policies. Remove 8.01.20 and add 8.01.529.
06/24/14	Update Related Policies. Delete 8.01.35 and 8.01.42 and add 8.01.530 and 8.01.532
11/10/14	Annual Review. Policy updated with literature review through July 31, 2014; references 15, 17, 23, 29-30, and 35 added; no change in policy statements. ICD-9 and ICD-10 diagnosis and procedure codes removed; they do not relate to adjudication.
02/03/15	Update Related Policies. Remove 8.01.23, 8.01.28 and 8.01.30.
11/10/15	Annual Review. Policy updated with literature search; reference 48 added; no change in policy statement.
05/01/16	Annual Review, approved April 12, 2016. Policy updated with literature review through October 27, 2015; references 11-13, 15, 24-25, 33, 46, and 57 added. Policy statements unchanged.
08/09/16	Update Related Policies. Remove 8.01.27 as it was archived.
09/30/16	Coding Update. Remove CPT 86817 from coding section.
11/04/16	Coding update. Removed codes that are transplant benefit related.
04/01/17	Update Related Policies; updated some of the titles. Minor formatting update.
08/01/17	Updated title of Related Policy 8.01.511.
12/01/17	Annual Review, approved November 9, 2017. Policy statements reorganized for clarity, intent remains unchanged.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; reference 57 added. Policy statement unchanged.

Date	Comments
04/01/19	Annual Review, approved March 5, 2019. Policy updated with literature review through November 2018; no references added. Policy statement unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020. Approved March 19, 2020, policy updated with literature review through November 2019; no references added. Policy statement unchanged. Removed CPT code 38242 effective April 1, 2020; code does not match criteria.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.
11/01/20	Annual Review, approved October 22, 2020. Policy updated with literature review; no references added, Policy statement unchanged.
04/01/21	New policy, approved March 9, 2021. Policy replaces 8.01.22 that was archived by BCBSA. Policy updated with literature review through December 7, 2020; references added. Policy statements remain unchanged; this is effectively a policy renumber.
05/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
10/01/22	Coding update. Removed HCPC code S2140.
01/01/23	Annual Review, approved December 12, 2022. No changes to policy statement. Changed the wording from "patient" to "individual" throughout the policy for standardization.
12/01/23	Annual Review, approved November 6, 2023. No changes to policy statement.
04/11/24	Minor update to related policies. 8.01.21 was replaced by 8.01.539 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

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Washington residents: You can also file a civil rights complaint with the Washington State Office of the Insurance Commissioner, electronically through the Office of the Insurance Commissioner Complaint Portal available at https://www.insurance.wa.gov/file-complaint-or-check-your-complaint-status, or by phone at 800-562-6900, 360-586-0241 (TDD). Complaint forms are available at https://fortress.wa.gov/oic/onlineservices/cc/pub/complaintinformation.aspx.

Alaska residents: Contact the Alaska Division of Insurance via email at insurance@alaska.gov, or by phone at 907-269-7900 or 1-800-INSURAK (in-state, outside Anchorage).

Language Assistance

ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al 800-722-1471 (TTY: 711).

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เรียน: ถ้าคุณพูดภาษาไทยคุณสามารถใช้บริการช่วยเหลือทางภาษาได้ฟรี โทร 800-722-1471 (TTY: 711).

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