MASSACHUSETTS

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Medical Policy

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

Table of Contents

Policy Number: 190

BCBSA Reference Number: 8.01.22
NCD/LCD: National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Related Policies

Hematopoietic Cell Transplantation for Autoimmune Diseases, #192

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Allogeneic hematopoietic stem cell transplantation (HCT) is considered **MEDICALLY NECESSARY** for select patients with the following disorders:

Hemoglobinopathies

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

Bone Marrow Failure Syndromes

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

Primary Immunodeficiencies*

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

*The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem cell transplantation (allo-HCT) (Gennery & Cant et al, 2008).

Lymphocyte Immunodeficiencies

- Adenosine deaminase deficiency
- Artemis deficiency
- Calcium channel deficiency
- CD 40 ligand deficiency
- Cernunnos/X-linked lymphoproliferative disease deficiency
- CHARGE syndrome with immune deficiency
- Common gamma chain deficiency
- Deficiencies in CD45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV deficiency syndrome
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 (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
- ICF syndrome
- IPEX syndrome
- NEMO deficiency
- NF-κB inhibitor, alpha (IκB-alpha) deficiency
- Nijmegen breakage syndrome

Inherited Metabolic Diseases**

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

****In the inherited metabolic disorders, allo-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, and aspartylglucosaminuria. Allogeneic HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM1 gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency,

Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HSCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes (Mehta, 2004).

Genetic Disorders Affecting Skeletal Tissue

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

Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

Medical necessity criteria and coding guidance can be found through the link below.

National Coverage Determinations (NCDs)

National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Note: To review the specific NCD, please remember to click "accept" on the CMS licensing agreement at the bottom of the CMS webpage.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	Prior authorization is **required**.
Commercial PPO and Indemnity	Prior authorization is **required**.
Medicare HMO Blue[SM]	Prior authorization is **required**.
Medicare PPO Blue[SM]	Prior authorization is **required**.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

CPT Codes

CPT codes:	Code Description
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38230	Bone marrow harvesting for transplantation; allogeneic
38240	Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic

HCPCS Codes

HCPCS codes:	Code Description
S2140	Cord blood harvesting for transplantation; allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

ICD-10 Procedure Codes

ICD-10-PCS procedure codes:	Code Description
30233G1	Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach
30233X1	Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach
30233Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach
30243G1	Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach
30243X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach
30243Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach
30263G1	Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach
30263X1	Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach
30263Y1	Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach
3E03305	Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach
3E04305	Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach
3E05305	Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach
3E06305	Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach

Description

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 b-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 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 allogeneic hematopoietic cell transplantation (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 myelodysplastic syndrome or acute myeloid leukemia. Most patients 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 patients developing aplastic anemia. As with other bone marrow failure syndromes, patients 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 patients also having a variety of physical anomalies.[3]

Treatment
In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of 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) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells.[4]

Treatment
Without treatment, patients with severe combined immunodeficiency 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 severe combined immunodeficiency 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 five 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.[6] The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells (eg, 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 Table 1.[6] 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	Mucopolysaccharidosis I H or H/S Mucopolysaccharidosis II Mucopolysaccharidosis III A-D Mucopolysaccharidosis IV A-B Mucopolysaccharidosis VI Mucopolysaccharidosis VII	Hurler syndrome or Hurler-Scheie syndrome Hunter syndrome Sanfilippo syndrome A-D Morquio syndrome A-B Maroteaux-Lamy syndrome Sly syndrome
Sphingolipidosis	Fabry disease Farber disease Gaucher disease types 1 and 3 GM_1 gangliosidosis Niemann-Pick disease A and B Tay-Sachs disease Sandhoff disease Globoid cell leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis Krabbe disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis Alpha-mannosidosis Beta-mannosidosis Mucolipidosis III and IV	 Sialidosis
Other lipidoses	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis type III	 Batten disease
Glycogen storage	Glycogen storage disease type II	Pompe disease
Multiple enzyme deficiency	Galactosialidosis Mucolipidosis type II	 I-cell disease
Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

Genetic Disorders Affecting Skeletal Tissue

Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow.[7] Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected 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 six months of age, and severe hematologic malfunction with bone marrow failure.[7] Seventy percent of these patients die before the age of six years, often of recurrent infections.[7]

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

Hematopoietic Cell Transplantation
HCT refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Allo-HCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Cord blood is discussed in greater detail in policy #285.

Immunologic compatibility between infused hematopoietic cells and the recipient is a critical factor in achieving a good outcome with allo-HCT. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (except umbilical cord blood).

Preparative Conditioning for Allo-HCT
The conventional practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. Reduced-intensity conditioning refers to chemotherapy regimens that seek to reduce adverse events secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo reduced-intensity conditioning with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for reduced-intensity conditioning allogeneic transplantation. They represent a continuum in their intensity, from almost totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition.

HCT for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis, is considered separately in policy #192.

Summary
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.

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, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. Allo-HCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

Policy History

Date	Action
3/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
1/2019	Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.
2/2018	New references added from BCBSA National medical policy.
12/2017	BCBSA National medical policy review. "Stem" removed from title and Policy. HSCT changed to HCT in policy text. Policy statement unchanged. 12/1/2017
12/2016	Coverage clarified for Medicare Advantage based on National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23). 12/14/2016
3/2016	New references added from BCBSA National medical policy.
9/2015	Clarified coding information.
6/2014	Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.
12/2013	New references from BCBSA National medical policy.
12/2012	Updated to add new CPT code 38243.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
7/2011	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
9/2010	Reviewed - Medical Policy Group - Hematology and Oncology. No changes to policy statements.
6/1/2010	New policy, effective 6/1/2010, describing covered and non-covered indications.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

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