Corporate Medical Policy

Allogeneic Hematopoietic Transplant for Genetic Diseases and Acquired Anemia

File Name:	allogeneic_hematopoietic_transplant_for_genetic_diseases
Origination:	2/2001
Last CAP Review:	4/2020
Next CAP Review:	4/2021
Last Review:	4/2020

Description of Procedure or Service

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) 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 radiation therapy. Allogeneic HSCT 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.

Immunologic compatibility between infused stem cells and the recipient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the Class I and Class II loci on chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Preparative Conditioning for Allogeneic Hematopoietic SCT

The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allogeneic HSCT 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 RIC allotransplantation. They represent a continuum in their intensity, from nearly totally myeloablative, to minimally myeloablative with lymphoablation.

Genetic Diseases and Acquired Anemias

Hemoglobinopathies

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, reducing oxygen delivery. The supportive treatment of beta-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. The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HSCT.

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. 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 males

and 48 for females. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea, and HSCT, the latter being the only possibility for cure.

Bone marrow failure syndromes

Aplastic anemia in children is rare, and is most often 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 myelogenous 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. In Fanconi anemia, HSCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allogeneic HSCT, with cure of the marrow failure and amelioration of the risk of leukemia.

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

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia. 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 with malignant transformation, especially acute myelogenous 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.

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 or SCID) cause an absence or dysfunction of T lymphocytes, and sometimes B lymphocytes and natural killer cells. Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the life span 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. Bone marrow transplant 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.

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. 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.

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. The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells, for example microglial cells in the brain and Kupffer cells in the liver.

Allogeneic HSCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders. 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 1,000 transplants have been performed worldwide.

Infantile malignant osteopetrosis

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. 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, often of recurrent infections. HSCT is the only curative therapy for this fatal disease.

Hematopoietic stem-cell transplantation for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis, is considered separately in policy, Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases.

Related Policies:
Hematopoietic Stem-Cell Transplantation for Autoimmune Diseases

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Allogeneic Hematopoietic Transplant for Genetic Diseases and Acquired Anemia when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Some health benefit plans may exclude benefits for transplantation.

When Allogeneic Hematopoietic Transplant for Genetic Diseases and Acquired Anemia is covered

Allogeneic hematopoietic transplant for genetic diseases and acquired anemias are considered medically necessary for selected 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 (e.g., 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)

(See policy guideline # 1)

Inherited metabolic disease

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

(See policy guideline # 2)

Genetic disorders affecting skeletal tissue

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

When Allogeneic Hematopoietic Transplant for Genetic Diseases and Acquired Anemia is not covered

Allogeneic hematopoietic transplant for genetic diseases and acquired anemia for diagnoses other than those listed above is considered not medically necessary.

Policy Guidelines

Refer to the individual member's benefit booklet for prior review requirements.

1. The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem-cell transplantation (HSCT)

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 CD 45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV
- Interleuken-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

- Chediak-Higashi syndrome
- Chronic granulomatous disease
- Hemophagocytic lymphohistiocytosis
- Griscelli syndrome, type 2
- 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

2. In the inherited metabolic disorders, allogeneic HSCT 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 HSCT 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.

There are numerous inherited and acquired conditions that are potentially severe and/or progressive, for which allogeneic HSCT has been used to alter the natural history of the disease or potentially offer a cure for the disease.

For individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome disease (specifically those other than Hunter, Sanfilippo, or Morquio syndromes), or a genetic disorder affecting skeletal tissue who receive allo-HCT, the evidence includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. 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. 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.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: 38205, 38230, 38240, 38242,38243, S2150

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual, 12/1/1999; 8.01.22

BCBSA Medical Policy Reference Manual, 7/12/2002; 8.01.22

Specialty Matched Consultant Advisory Panel - 11/2002

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 4/16/2004

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 4/1/2005

Specialty Matched Consultant Advisory Panel - 3/2006

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/10/2009

Specialty Matched Consultant Advisory Panel – 5/2010

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/16/2010

Specialty Matched Consultant Advisory Panel – 4/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/1/2011

Specialty Matched Consultant Advisory Panel – 4/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/13/2012

Specialty Matched Consultant Advisory Panel – 4/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/12/2013

Specialty Matched Consultant Advisory Panel – 4/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 9/11/2014

Specialty Matched Consultant Advisory Panel- 4/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 2/11/2016

Specialty Matched Consultant Advisory Panel- 4/2016

Specialty Matched Consultant Advisory Panel- 4/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 10/12/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 1/11/2018

Specialty Matched Consultant Advisory Panel 4/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 1/17/2019

Specialty Matched Consultant Advisory Panel 4/2019

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.22, 1/16/2020

Sanfilippo: JIMD Reports. DOI 10.1007/8904_2014_350.

Specialty Matched Consultant Advisory Panel 4/2020

Medical Director review 4/2020

Policy Implementation/Update Information

1/01	Specialty Matched Consultant Advisory Group.
2/01	Original policy issued.
2/03	Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242 and 38205 added to the Billing/Coding section. System coding changes.
1/04	Benefits Application and Billing/Coding sections updated for consistency.
7/29/04	Added HCPCS code S2150 to the Billing/Coding section of the policy.
12/9/04	Specialty Matched Consultant Advisory Group review 11/29/04. No changes to criteria. Description of Procedure or Service updated. References added.
4/10/06	Specialty Matched Consultant Advisory Panel review 3/15/2006. No changes to policy. References added. Active Archive, policy no longer scheduled for routine literature review.
7/6/10	Policy reactivated from "Policy Active, No .Longer Scheduled for Routine Review." Title changed from "Bone Marrow Transplant Allogeneic for Genetic Diseases and Acquired Anemias". Specialty Matched Consultant Advisory Panel review 5/24/2010. Revised "Description" section. Updated the "When Covered" and "Policy Guidelines" section. Clarified that treatment of Hunter, Sanfilippo, and Morquio syndromes are not included in

	the list of lysosomal and peroxisomal storage diseases for which allo-HSCT may be considered medically necessary. References added. Notice given 7/6/2010. Policy effective 10/12/2010. (btw)
5/24/11	Specialty Matched Consultant Advisory Panel review 4/27/2011. "Description" section revised and "Policy Guidelines" section updated. No change to policy intent. References added. (btw)
1/24/12	Reference added. (btw)
5/15/12	Specialty Matched Consultant Advisory Panel review 4/18/2012. No change to policy intent. (btw)
11/13/12	Reference added. (btw)
1/15/13	Add new 2013 CPT code, 38243 to Billing/Coding section. (btw)
4/30/13	Specialty Matched Consultant Advisory Panel review 4/17/2013. Removed the last statement under Policy Guidelines that indicated "as outlined in the clinical trial section under each disease type." No other changes to policy. (btw)
10/29/13	Reference added. (btw)
5/13/14	Specialty Matched Consultant Advisory Panel review 4/29/2014. No change to policy. (btw)
10/28/14	Reference added. (lpr)
5/26/15	Specialty Matched Consultant Advisory Panel review 4/29/2015. No change to policy. (lpr)
5/31/16	Updated Policy Guidelines section. Reference added. Specialty Matched Consultant Advisory Panel review 4/27/2016. No change to policy statement. (lpr)
5/26/17	Specialty Matched Consultant Advisory Panel review 4/26/2017. No change to policy statement. (lpr)
11/10/17	Reference added. (lpr)
5/11/18	Specialty Matched Consultant Advisory Panel review 4/25/2018. Updated Policy Guidelines section. No change to policy statement. Reference added. (lpr)
4/16/19	Specialty Matched Consultant Advisory Panel review 3/20/2019. Reference added. No change to policy statement. (lpr)
5/26/20	Specialty Matched Consultant Advisory Panel review 4/15/2020. References added. No change to policy statement. (lpr)