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MEDICAL POLICY – 8.01.22

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

BCBSA Ref. Policy: 8.01.22

Effective Date:	May 1, 2018
Last Revised:	April 3, 2018
Replaces:	8.01.109

RELATED MEDICAL POLICIES:

7.01.50	Placental and Umbilical Cord Blood as a Source of Stem Cells
8.01.15	Hematopoietic Cell Support for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
8.01.21	Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
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
8.01.511	Hematopoietic Cell Transplantation for Solid Tumors of Childhood
8.01.529	Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
8.01.530	Hematopoietic Cell Transplantation for Primary Amyloidosis
8.01.532	Hematopoietic Cell Transplantation in the Treatment of Germ Cell Tumors

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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 patients 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 (ie, thalassemia major)
Bone marrow failure syndromes	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with bone marrow failure syndromes:** • Aplastic anemia including hereditary (including Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond, Diamond-Blackfan) or acquired (eg, secondary to drug or toxin exposure) forms

Primary immunodeficiencies	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with primary immunodeficiencies:**
	• Absent or defective T cell function (eg, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
	• Absent or defective natural killer function (eg, Chédiak-Higashi syndrome)
	• Absent or defective neutrophil function (eg, 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

Condition	Medical Necessity
	○ 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 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 ○ Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome ○ Nuclear factor-κ B (NF-κB) essential modulator (NEMO)

Condition	Medical Necessity
	deficiency ○ NF-κB inhibitor, alpha (IκB- α) deficiency ○ Nijmegen breakage syndrome
Inherited metabolic disease	**Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with the following inherited metabolic diseases:** • Lysosomal and peroxisomal storage disorders **except** 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 ▪ Neuronal ceroid lipofuscinosis ▪ Sialidosis ▪ Wolman disease **Allogeneic HCT is considered not medically necessary for patients with the following inherited metabolic diseases :** • Hunter • Sanfilippo • Morquio transplantation syndromes (Mehta, 2004)
Genetic disorders affecting	**Allogeneic hematopoietic cell is considered medically**

Condition	Medical Necessity
skeletal tissue	**necessary for selected patients 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 evidence review has been limited to small numbers of patients 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.

Coding

Code	Description
CPT	
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38242	Allogeneic lymphocyte infusions
HCPCS	
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic

Code	Description
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

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

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 patients with sickle cell disease has been demonstrated as 42 years for males and 48 for females.

Treatment

The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HCT (allo-HCT). Three major therapeutic options are available: 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 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.[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 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.[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 HLA-matched sibling allogeneic 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, 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] 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. Allo-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 the **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 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 MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler syndrome or Hurler-Scheie, syndrome Hunter syndrome Sanfilippo syndrome A-D Morquio syndrome A-B Maroteaux-Lamy syndrome Sly sundrome
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 leukodystrophy	 Lipogranuomatosis Krabbe disease

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

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 6 months of age, and severe hematologic malfunction with bone marrow failure.[7] Seventy percent of these patients die before the age of 6 years, often of recurrent infections.[7]

Treatment

Allo-HCT is the only curative therapy for this fatal disease.

Hematopoietic Cell Transplantation

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. Allogeneic HCT (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 addressed in a separate policy (see **Related Policies**).

Immunologic compatibility between infused stem cells and the recipient is a critical factor for achieving a good outcome of 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 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 Allogeneic 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 (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 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 RIC allotransplantation. 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 addressed in a separate policy (see **Related Policies**).

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. 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 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.

Ongoing and Unpublished Clinical Trials

Some current trials are listed in **Table 2**.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT00176852	Allogeneic Hematopoietic Stem Cell Transplant for Patients With High Risk Hemoglobinopathy Using a Preparative Regimen to Achieve Stable Mixed Chimerism	30	Jun 2016
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT00176826	In-vivo T-cell Depletion and Hematopoietic Stem Cell Transplantation for Life-Threatening Immune Deficiencies and Histiocytic Disorders	22	Jul 2015
NCT00775931	Allogeneic Hematopoietic Stem Cell Transplantation For Severe Osteopetrosis	23	Oct 2015

NCT: national clinical trial.

Clinical Input Received 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 1 physician specialty society (3 reviewers) and 3 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 address the issue of the use of HCT in the inherited metabolic diseases, except for Hunter, Sanfilippo, and Morquio syndromes; 4 reviewers agreed with the current policy statement, 1 disagreed, and 1 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 hematopoietic cell transplantation (HCT) to treat specific conditions in and out of the clinical trial settings.57 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
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.[58] The following key recommendations on HCT were included in the guidelines:

- Matched sibling donor (allogeneic) HCT is the treatment of choice for severe aplastic anemia; however, for patients aged 35 to 50 years, patients need to be assessed for comorbidities before being considered for HCT.
- For adults, unrelated donor HCT should be considered if patients fail to respond to a single course of immunosuppressive therapy.

- Although there have been improvements in outcomes after alternative donor HCT, these transplants are still experimental, and expert consultation should be sought before considering their use.

European Blood and Marrow Transplantation

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.[59]

U.S. Preventive Services Task Force Recommendations

Allogeneic HCT is not a preventive service.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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.
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

Date	Comments
	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.
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.

Date	Comments
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.

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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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
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Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በእከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

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Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

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ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).