## MEDICAL POLICY – 8.01.22

### Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

**BCBSA Ref. Policy:** 8.01.22

<table>
<thead>
<tr>
<th>RELATED MEDICAL POLICIES:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>7.01.50</td>
<td>Placental and Umbilical Cord Blood as a Source of Stem Cells</td>
</tr>
<tr>
<td>8.01.15</td>
<td>Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma</td>
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<tr>
<td>8.01.21</td>
<td>Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms</td>
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<td>8.01.24</td>
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</tr>
<tr>
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<td>Hematopoietic Cell Transplantation for Primary Amyloidosis</td>
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<td>8.01.532</td>
<td>Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors</td>
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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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Medical Necessity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemoglobinopathies</strong></td>
<td>Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with hemoglobinopathies:</td>
</tr>
<tr>
<td></td>
<td>• 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</td>
</tr>
<tr>
<td></td>
<td>• Homozygous $\beta$-thalassemia (ie, thalassemia major)</td>
</tr>
<tr>
<td><strong>Bone marrow failure syndromes</strong></td>
<td>Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with bone marrow failure syndromes:</td>
</tr>
<tr>
<td></td>
<td>• Aplastic anemia including hereditary (including Fanconi anemia, dyskeratosis congenita, Shwachman-Diamond, Diamond-Blackfan) or acquired (eg, secondary to drug or toxin exposure) forms</td>
</tr>
<tr>
<td><strong>Primary immunodeficiencies</strong></td>
<td>Allogeneic hematopoietic cell transplantation is considered medically necessary for selected patients with primary immunodeficiencies:</td>
</tr>
<tr>
<td></td>
<td>• Absent or defective T cell function (eg, severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)</td>
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<tr>
<td></td>
<td>• Absent or defective natural killer function (eg, Chédiak-Higashi syndrome)</td>
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<tr>
<td></td>
<td>• Absent or defective neutrophil function (eg, Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)</td>
</tr>
<tr>
<td></td>
<td>The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic cell transplantation (allo-HCT) (Gennery &amp; Cant et al, 2008).</td>
</tr>
<tr>
<td></td>
<td>• Lymphocyte Immunodeficiencies</td>
</tr>
<tr>
<td></td>
<td>o Adenosine deaminase deficiency</td>
</tr>
<tr>
<td></td>
<td>o Artemis deficiency</td>
</tr>
<tr>
<td></td>
<td>o Calcium channel deficiency</td>
</tr>
<tr>
<td>Condition</td>
<td>Medical Necessity</td>
</tr>
<tr>
<td>-----------</td>
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</tr>
<tr>
<td>o CD 40 ligand deficiency</td>
<td></td>
</tr>
<tr>
<td>o Cernunnos/X-linked lymphoproliferative disease deficiency</td>
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</tr>
<tr>
<td>o CHARGE syndrome with immune deficiency</td>
<td></td>
</tr>
<tr>
<td>o Common gamma chain deficiency</td>
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<tr>
<td>o Deficiencies in CD45, CD3, CD8</td>
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</tr>
<tr>
<td>o DiGeorge syndrome</td>
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<tr>
<td>o DNA ligase IV deficiency syndrome</td>
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<td>o Interleukin-7 receptor alpha deficiency</td>
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</tr>
<tr>
<td>o Janus-associated kinase 3 (JAK3) deficiency</td>
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<tr>
<td>o Major histocompatibility class II deficiency</td>
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<tr>
<td>o Omenn syndrome</td>
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<tr>
<td>o Purine nucleoside phosphorylase deficiency</td>
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</tr>
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<td>o Recombinase-activating gene (RAG) 1/2 deficiency</td>
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<td>o Reticular dysgenesis</td>
<td></td>
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<tr>
<td>o Winged helix deficiency</td>
<td></td>
</tr>
<tr>
<td>o Wiskott-Aldrich syndrome</td>
<td></td>
</tr>
<tr>
<td>o X-linked lymphoproliferative disease</td>
<td></td>
</tr>
<tr>
<td>o Zeta-chain-associated protein-70 (ZAP-70) deficiency</td>
<td></td>
</tr>
</tbody>
</table>

- Phagocytic Deficiencies
  - o Chédiak-Higashi syndrome
  - o Chronic granulomatous disease
  - o Griscelli syndrome, type 2
  - o Hemophagocytic lymphohistiocytosis
  - o Interferon-gamma receptor deficiencies
  - o Leukocyte adhesion deficiency
  - o Severe congenital neutropenias
  - o Shwachman-Diamond syndrome

- Other Immunodeficiencies
  - o Autoimmune lymphoproliferative syndrome
  - o Cartilage hair hypoplasia
  - o CD25 deficiency
  - o Hyper IgD and IgE syndromes
  - o Immunodeficiency, centromeric instability, and facial dysmorphism (ICF) syndrome
  - o Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome
  - o Nuclear factor-κ B (NF-κB) essential modulator (NEMO)
### Condition | Medical Necessity
---|---
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 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  
    - GM₁  
    - Gangliosidosis  
    - Mucolipidosis II (Ii-cell disease)  
    - Multiple sulfatase deficiency  
    - Niemann-pick disease  
    - Neuronal ceroid lipofuscinosis  
    - Sialidosis  
    - Wolman disease  

### Genetic disorders affecting | *Allogeneic hematopoietic cell transplantation is considered*
### Condition | Medical Necessity
--- | ---
skeletal tissue | medically 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 policy 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.

### Documentation Requirements
The patient’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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
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<td>38242</td>
<td>Allogeneic lymphocyte infusions</td>
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<tr>
<td><strong>HCPCS</strong></td>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>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</td>
</tr>
</tbody>
</table>

**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. 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 for sickle cell disease: chronic blood transfusions, hydroxyurea, and allo-HCT, the latter being the only possibility for cure.

**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.

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.
Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan syndrome. 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.

**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. 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.

**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. 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.
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.

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. 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).

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. 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.

Table 1. Lysosomal and Peroxisomal Storage Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Other Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucopolysaccharidosis (MPS)</td>
<td>MPS I H or H/S</td>
<td>Hurler syndrome or Hurler-Scheie, syndrome</td>
</tr>
<tr>
<td></td>
<td>MPS II</td>
<td>Hunter syndrome</td>
</tr>
<tr>
<td></td>
<td>MPS III A-D</td>
<td>Sanfilippo syndrome A-D</td>
</tr>
<tr>
<td></td>
<td>MPS IV A-B</td>
<td>Morquio syndrome A-B</td>
</tr>
<tr>
<td>Category</td>
<td>Diagnosis</td>
<td>Other Names</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td></td>
<td>MPS VI</td>
<td>Maroteaux-Lamy syndrome</td>
</tr>
<tr>
<td></td>
<td>MPS VII</td>
<td>Sly syndrome</td>
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<td>Sphingolipidosis</td>
<td>Fabry disease</td>
<td>Lipogranuomatosis</td>
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<tr>
<td></td>
<td>Farber disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gaucher disease types 1 and 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GM$_1$ gangliosidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Niemann-Pick disease A and B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tay-Sachs disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sandhoff disease</td>
<td></td>
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<tr>
<td></td>
<td>Globoid leukodystrophy</td>
<td></td>
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<tr>
<td></td>
<td>Metachromatic leukodystrophy</td>
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<tr>
<td>Glycoproteinosis</td>
<td>Aspartylglucosaminuria</td>
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<td></td>
<td>Fucosidosis</td>
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<td></td>
<td>Alpha-Mannosidosis</td>
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<tr>
<td></td>
<td>Beta-Mannosidosis</td>
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<tr>
<td></td>
<td>Mucolipidosis III and IV</td>
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<td>Other lipidoses</td>
<td>Niemann-Pick disease C</td>
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</tr>
<tr>
<td></td>
<td>Wolman disease</td>
<td>Batten disease</td>
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<td></td>
<td>Ceroid lipofuscinosis</td>
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<td>Glycogen storage</td>
<td>Glycogen storage disease type II</td>
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<td>Multiple enzyme deficiency</td>
<td>Galactosialidosis</td>
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<td></td>
<td>Mucolipidosis type II</td>
<td>I-cell disease</td>
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<td>Lysosomal transport defects</td>
<td>Cystinosis</td>
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<td>Sialic acid storage disease</td>
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<td>Salla disease</td>
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<td>Peroxisomal storage disorders</td>
<td>Adrenoleukodystrophy</td>
<td>ALD</td>
</tr>
<tr>
<td></td>
<td>Adrenomyeloneuropathy</td>
<td>AMN</td>
</tr>
</tbody>
</table>
**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**

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 allogenic 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 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 currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT00176852</td>
<td>Allogeneic Hematopoietic Stem Cell Transplant for Patients With High Risk Hemoglobinopathy Using a</td>
<td>22</td>
<td>Jan 2019</td>
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<td></td>
<td>Preparative Regimen to Achieve Stable Mixed Chimerism</td>
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<td>NCT00358657</td>
<td>HLA-Haploidentical Related Marrow Grafts for the Treatment of Primary Immunodeficiencies and Other</td>
<td>20</td>
<td>Dec 2018 (estimated)</td>
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<td></td>
<td>Nonmalignant Disorders Using Conditioning With Low-Dose Cyclophosphamide, TBI and Fludarabine and</td>
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<td>Postgrafting Cyclophosphamide</td>
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<tr>
<td>NCT02356653</td>
<td>Processing of stem cells using the CliniMACs device to selectively deplete specific T cells to decrease</td>
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<td></td>
<td>risk of graft versus host disease when using donor stem cells which are not fully matched.</td>
<td>100</td>
<td>Jan 2020 (estimated)</td>
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<tr>
<td>NCT02986698</td>
<td>A Single-Center, Non-Randomized Study of the Safety and Efficacy of In Utero Hematopoietic Stem Cell</td>
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<td>Feb 2024 (estimated)</td>
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<td></td>
<td>Transplantation for the Treatment of Fetuses With Alpha Thalassemia Major</td>
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<td><strong>Unpublished</strong></td>
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<td>NCT00176826</td>
<td>In-vivo T-cell Depletion and Hematopoietic Stem Cell Transplantation for Life-Threatening Immune</td>
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<td>Deficiencies and Histiocytic Disorders</td>
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<td>Allogeneic Hematopoietic Stem Cell Transplantation For Severe Osteopetrosis</td>
<td>23</td>
<td>Oct 2015 (unknown)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00553098</td>
<td>Hematopoietic Cell Transplantation for Treatment of Patients With Primary Immunodeficiencies and Other</td>
<td>25</td>
<td>Mar 2015 (actual</td>
</tr>
<tr>
<td></td>
<td>Nonmalignant Inherited Disorders Using Low-Dose TBI and Fludarabine With or Without Campath®</td>
<td></td>
<td>completion)</td>
</tr>
</tbody>
</table>

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

The American Society for Blood and Marrow Transplantation (2015) published consensus guidelines on the use of hematopoietic cell transplantation (HCT) to treat specific conditions in and out of the clinical trial settings. 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

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allo-HCT &lt;18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe aplastic anemia, new diagnosis</td>
<td>S</td>
</tr>
<tr>
<td>Severe aplastic anemia, relapse/refractory</td>
<td>S</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>R</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>R</td>
</tr>
<tr>
<td>Blackfan-Diamond anemia</td>
<td>R</td>
</tr>
<tr>
<td>Indications</td>
<td>Allo-HCT &lt;18 Years</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>C</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>S</td>
</tr>
<tr>
<td>Congenital amegakaryocytic thrombocytopenia</td>
<td>R</td>
</tr>
<tr>
<td>Severe combined immunodeficiency</td>
<td>R</td>
</tr>
<tr>
<td>T-cell immunodeficiency, severe combined immunodeficiency variants</td>
<td>R</td>
</tr>
<tr>
<td>Wiskott-Aldrich syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Hemophagocytic disorders</td>
<td>R</td>
</tr>
<tr>
<td>Lymphoproliferative disorders</td>
<td>R</td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>R</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>R</td>
</tr>
<tr>
<td>Other phagocytic cell disorders</td>
<td>R</td>
</tr>
<tr>
<td>Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome</td>
<td>R</td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>D</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>D</td>
</tr>
<tr>
<td>Other autoimmune and immune dysregulation disorders</td>
<td>R</td>
</tr>
<tr>
<td>Mucopolysaccharidoses (MPS-I and MPS-VI)</td>
<td>R</td>
</tr>
<tr>
<td>Other metabolic diseases</td>
<td>R</td>
</tr>
<tr>
<td>Osteopetrosis</td>
<td>R</td>
</tr>
<tr>
<td>Globoid cell leukodystrophy (Krabbe)</td>
<td>R</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>R</td>
</tr>
<tr>
<td>Cerebral X-linked adrenoleukodystrophy</td>
<td>R</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications</th>
<th>Allo-HCT &gt;18 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe aplastic anemia, new diagnosis</td>
<td>S</td>
</tr>
<tr>
<td>Severe aplastic anemia, relapse/refractory</td>
<td>S</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>R</td>
</tr>
<tr>
<td>Dyskeratosis congenita</td>
<td>R</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>C</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>D</td>
</tr>
<tr>
<td>Hemophagocytic syndromes, refractory</td>
<td>R</td>
</tr>
</tbody>
</table>
**Indications** | **Allo-HCT >18 Years**
---|---
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**

The British Committee for Standards in Haematology (2015) published guidelines on the diagnosis and management of adult aplastic anemia. 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**
The European Blood and Marrow Transplantation (2014) provided consensus-based recommendations on indications for HCT and transplant management in the hemoglobinopathies.10

_Pediatric Haemato-Oncology Italian Association_

The Pediatric Haemato-Oncology Italian Association (2015) 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.

**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.

**References**


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>02/01/00</td>
<td>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.</td>
</tr>
<tr>
<td>11/12/02</td>
<td>Replace policy - Policy reviewed without literature review; new review date only. Replaces CP.MP.PR.8.01.109.</td>
</tr>
<tr>
<td>12/10/02</td>
<td>Replace policy - Policy reviewed by OAP; no criteria changes.</td>
</tr>
<tr>
<td>05/13/03</td>
<td>Replace policy - Update CPT codes only.</td>
</tr>
<tr>
<td>07/13/04</td>
<td>Replace policy - Policy reviewed; no change to policy statement.</td>
</tr>
<tr>
<td>07/12/05</td>
<td>Replace policy - Policy reviewed with literature search; no change to policy statement. No further review scheduled; status changed from BC to AR.</td>
</tr>
<tr>
<td>06/09/06</td>
<td>Update Scope and Disclaimer - No other changes.</td>
</tr>
<tr>
<td>03/13/07</td>
<td>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.</td>
</tr>
<tr>
<td>10/09/07</td>
<td>Cross References Updated - No other changes.</td>
</tr>
<tr>
<td>11/12/07</td>
<td>Code updated - CPT code 86817 deleted as directed by RPIW.</td>
</tr>
<tr>
<td>04/08/08</td>
<td>Replace policy - Policy updated with literature search; no change to the policy statement. Reviewed and recommended by OAP on February 21, 2008.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>Cross Reference Update - No other changes</td>
</tr>
<tr>
<td>12/08/09</td>
<td>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.</td>
</tr>
<tr>
<td>12/14/10</td>
<td>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.</td>
</tr>
<tr>
<td>10/11/11</td>
<td>Replace policy – Policy updated with literature search; reference 30 added; no change in policy statement. HCPSCS and ICD-9 diagnosis codes updated; ICD-10 codes added. Codes 38220 and 38221 removed.</td>
</tr>
<tr>
<td>01/24/12</td>
<td>Code 38232 added.</td>
</tr>
<tr>
<td>02/09/12</td>
<td>The CPT codes 38204 and 38206 removed from the policy; they do not apply.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>06/20/12</td>
<td>Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.</td>
</tr>
<tr>
<td>08/01/12</td>
<td>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.</td>
</tr>
<tr>
<td>11/27/12</td>
<td>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.</td>
</tr>
<tr>
<td>02/01/13</td>
<td>Update Related Policies, change title of policy 8.01.21.</td>
</tr>
<tr>
<td>03/20/13</td>
<td>The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.</td>
</tr>
<tr>
<td>09/30/13</td>
<td>Update Related Policies. Change title to 8.01.31.</td>
</tr>
<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.30.</td>
</tr>
<tr>
<td>03/11/14</td>
<td>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.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Add 8.01.15 and delete 8.01.514.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Remove 8.01.20 and add 8.01.529.</td>
</tr>
<tr>
<td>06/24/14</td>
<td>Update Related Policies. Delete 8.01.35 and 8.01.42 and add 8.01.530 and 8.01.532</td>
</tr>
<tr>
<td>11/10/14</td>
<td>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.</td>
</tr>
<tr>
<td>02/03/15</td>
<td>Update Related Policies. Remove 8.01.23, 8.01.28 and 8.01.30.</td>
</tr>
<tr>
<td>11/10/15</td>
<td>Annual Review. Policy updated with literature search; reference 48 added; no change in policy statement.</td>
</tr>
<tr>
<td>05/01/16</td>
<td>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.</td>
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<tr>
<td>08/09/16</td>
<td>Update Related Policies. Remove 8.01.27 as it was archived.</td>
</tr>
<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding section.</td>
</tr>
<tr>
<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
</tr>
<tr>
<td>04/01/17</td>
<td>Update Related Policies; updated some of the titles. Minor formatting update.</td>
</tr>
<tr>
<td>08/01/17</td>
<td>Updated title of Related Policy 8.01.511.</td>
</tr>
<tr>
<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Policy statements reorganized for clarity,</td>
</tr>
</tbody>
</table>
### Date | Comments
--- | ---
| | intent remains unchanged.
| 04/01/19 | Annual Review, approved March 5, 2019. Policy updated with literature review through November 2018; no references added. Policy statement unchanged.

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

**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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Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at: https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
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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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 and/or keep your health insurance or benefits. It is important for you to take action to maintain your health insurance coverage and benefits. You have the right to free language assistance and information in your primary language.

Oromo (Cushite):

French (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon yon lan oswa konvèt ki kouvèt 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 kelbe kouvèt asirans sante w la oswa pou yo ka ede w avek depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou paile a, san ou pa gen pou peye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoo (Hmong):

Illoko (Ilocano):
Daytoy a Pakdaa ket naglao iti Napateg nga Impormasion. Daytoy a pakdaa mabalini nga adda ket naglao iti napateg nga impormasion maianggape i aplikasyon wo coverage babaen i Premera Blue Cross. Daytoy ket mabalini dagiti importante a petsa iti daytoy a pakdaak. Mabalini nga adda rumbeng nga aramideng nga adda sakuay dagiti partikular a naituding nga adaw tapon mapagyadagdy nga coverage ti salun-atyo nga tulong kadayit nga gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukyddy nga pagasasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italian (Italian):
Premera Blue Cross. 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 dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de tempo limitado para a manutenção da 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)

Polskie (Polish): To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie polityki ubezpieczeniowej lub pomocy związanej z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwonij pod 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 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)

Español (Spanish): Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas claves 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).

Тагальский (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 may mga petsa kahit pa sa paunawa. Maaring mangailanigan ka na magsagawa ng kabahayan sa ilang mga tawag non gaanupan unang mapanianat ang iyong pagsakop sa kalsugan o tulong na walang gastos. May karapatan ka na makuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Turnawag sa 800-722-1471 (TTY: 800-842-5357).