Medical Policy
Allogeneic Hematopoietic Stem Cell Transplantation for Genetic Diseases and Acquired Anemias

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Policy Number: 190
BCBSA Reference Number: 8.01.22
NCD/LCD: National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23)

Related Policies
None

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

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

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

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

Primary Immunodeficiencies*
- Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
- Absent or defective natural killer function (e.g. Chediak-Higashi syndrome)
- Absent or defective neutrophil function (e.g. Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)
The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem cell transplantation (allo-HSCT) (Gennery & Cant et al, 2008).

**Lymphocyte Immunodeficiencies**
- Adenosine deaminase deficiency
- Artemis deficiency
- Calcium channel deficiency
- CD 40 ligand deficiency
- Cernunnos/X-linked lymphoproliferative disease deficiency
- CHARGE syndrome with immune deficiency
- Common gamma chain deficiency
- Deficiencies in CD45, CD3, CD8
- DiGeorge syndrome
- DNA ligase IV deficiency syndrome
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 (JAK3) deficiency
- Major histocompatibility class II deficiency
- Omenn syndrome
- Purine nucleoside phosphorylase deficiency
- Recombinase-activating gene (RAG) 1/2 deficiency
- Reticular dysgenesis
- Winged helix deficiency
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative disease
- Zeta-chain-associated protein-70 (ZAP-70) deficiency

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

**Other Immunodeficiencies**
- Autoimmune lymphoproliferative syndrome
- Cartilage hair hypoplasia
- CD25 deficiency
- Hyper IgD and IgE syndromes
- ICF syndrome
- IPEX syndrome
- NEMO deficiency
- NF-κB inhibitor, alpha (IκB-alpha) deficiency
- Nijmegen breakage syndrome

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

**In the inherited metabolic disorders, allo-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 (Mehta, 2004).

Genetic Disorders Affecting Skeletal Tissue
- Infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease).

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Allogeneic HSCT for sickle cell disease (SCD)

Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study.

A prospective clinical study seeking Medicare coverage for allogeneic HSCT for sickle cell disease pursuant to Coverage with Evidence Development (CED) must address the following question:

Compared to patients who do not receive allogeneic HSCT, do Medicare beneficiaries with SCD who receive allogeneic HSCT have improved outcomes as indicated by:
- Graft vs. host disease (acute and chronic),
- Other transplant-related adverse events;
- Overall survival; and
- (optional) Quality of life?

All CMS-approved clinical studies and registries must adhere to the below listed standards of scientific integrity and relevance to the Medicare population:

a. The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.
b. The rationale for the study is well supported by available scientific and medical evidence.
c. The study results are not anticipated to unjustifiably duplicate existing knowledge.
d. The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination.
e. The study is sponsored by an organization or individual capable of completing it successfully.
f. The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.
g. All aspects of the study are conducted according to appropriate standards of scientific integrity.
h. The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.
i. The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.
j. The clinical research studies and registries are registered on the www.ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the Agency for Healthcare Quality (AHRQ) Registry of Patient Registries (RoPR).
k. The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study’s primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the
trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessible manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as ClinicalTrials.gov, or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).

I. The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.

m. The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.

Facilities must submit the required transplant essential data to the Stem Cell Therapeutics Outcomes Database.

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

**Prior Authorization Information**
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tr>
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<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
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<tr>
<td>Medicare PPO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
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</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

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

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

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

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

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per</td>
</tr>
<tr>
<td></td>
<td>collection; allogeneic</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
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### HCPCS Codes

<table>
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<th>HCPCS codes</th>
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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 peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose</td>
</tr>
<tr>
<td></td>
<td>chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical,</td>
</tr>
<tr>
<td></td>
<td>diagnostic and emergency services)</td>
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### ICD-9 Procedure Codes

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<th>ICD-9-CM procedure codes</th>
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<tr>
<td>41.02</td>
<td>Allogeneic bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.03</td>
<td>Allogeneic bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.05</td>
<td>Allogeneic hematopoietic stem cell transplant without purging</td>
</tr>
<tr>
<td>41.06</td>
<td>Cord blood stem cell transplant</td>
</tr>
<tr>
<td>41.08</td>
<td>Allogeneic hematopoietic stem cell transplant with purging</td>
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### ICD-10 Procedure Codes

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<tr>
<td>30233G1</td>
<td>Transfusion of Nontautologous Bone Marrow into Peripheral Vein, Percutaneous</td>
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<tr>
<td></td>
<td>Approach</td>
</tr>
<tr>
<td>30233X1</td>
<td>Transfusion of Nontautologous Cord Blood Stem Cells into Peripheral Vein,</td>
</tr>
<tr>
<td></td>
<td>Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y1</td>
<td>Transfusion of Nontautologous Hematopoietic Stem Cells into Peripheral Vein,</td>
</tr>
<tr>
<td></td>
<td>Percutaneous Approach</td>
</tr>
<tr>
<td>30243G1</td>
<td>Transfusion of Nontautologous Bone Marrow into Central Vein, Percutaneous</td>
</tr>
<tr>
<td></td>
<td>Approach</td>
</tr>
<tr>
<td>30243X1</td>
<td>Transfusion of Nontautologous Cord Blood Stem Cells into Central Vein,</td>
</tr>
<tr>
<td></td>
<td>Percutaneous Approach</td>
</tr>
<tr>
<td>30243Y1</td>
<td>Transfusion of Nontautologous Hematopoietic Stem Cells into Central Vein,</td>
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<tr>
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<td>Percutaneous Approach</td>
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<tr>
<td>30263G1</td>
<td>Transfusion of Nontautologous Bone Marrow into Central Artery, Percutaneous</td>
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<td>Transfusion of Nontautologous Cord Blood Stem Cells into Central Artery,</td>
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<td>30263Y1</td>
<td>Transfusion of Nontautologous Hematopoietic Stem Cells into Central Artery,</td>
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<td>Percutaneous Approach</td>
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<td>3E03305</td>
<td>Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach</td>
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<tr>
<td>3E04305</td>
<td>Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach</td>
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</table>
Description
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 radiotherapy. Allogeneic HSCT (allo-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. Cord blood is discussed in greater detail in policy #285.

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

Preparative Conditioning for Allogeneic HSCT
The conventional practice of allo-HSCT 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-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 almost totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition.

Genetic Diseases and Acquired Anemias
Hemoglobinopathies
The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of -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 allo-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 men and 48 for women. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea, and allo-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 myeloid leukemia (AML). 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.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.³

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan anemia.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 AML. 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

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 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 Bone marrow transplantation 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.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.⁸ 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 do not cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier.⁶ The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells (eg, microglial cells in the brain and Kupffer cells in the liver).⁶

Allogeneic HSCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1.⁶ The first stem cell transplant for an inherited metabolic disease was performed in 1980 in a patient with Hurler syndrome. Since that time, more than 1000 transplants have been performed worldwide.⁶

Table 1. Lysosomal and Peroxisomal Storage Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Diagnosis</th>
<th>Other Names</th>
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</thead>
<tbody>
<tr>
<td>Mucopolysaccharidosis (MPS)</td>
<td>MPS I</td>
<td>Hurler, Scheie, H-S</td>
</tr>
<tr>
<td></td>
<td>MPS II</td>
<td>Hunter</td>
</tr>
</tbody>
</table>
**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 (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. Seventy percent of these patients die before the age of 6 years, often of recurrent infections. HSCT is the only curative therapy for this fatal disease.

**Summary**
A number of inherited and acquired conditions have the potential for severe and/or progressive disease. For some conditions, allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been used to alter the natural history of the disease or potentially offer a cure.

The evidence for allo-HSCT in select individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome diseases, or a genetic disorder affecting skeletal tissue includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, change in disease status, morbid events, functional outcomes, quality of life, hospitalizations, medication use, resource utilization, and treatment.
related mortality and morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. The exception has been with the use of allo-HSCT in the inherited metabolic diseases Hunter, Sanfilippo, and Morquio syndromes. Allo-HSCT is likely to improve health outcomes in select patients with certain inherited and acquired diseases.

**Policy History**

<table>
<thead>
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<th>Date</th>
<th>Action</th>
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<tr>
<td>12/2016</td>
<td>Coverage clarified for Medicare Advantage based on National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23). 12/14/2016</td>
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<tr>
<td>9/2015</td>
<td>Clarified coding information.</td>
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<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>12/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<tr>
<td>12/2012</td>
<td>Updated to add new CPT code 38243.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

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

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

**References**


