Medical Policy

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***Current Policy Effective Date: 3/1/13**

Title: Bone Marrow Transplant - Allogenic Hematopoietic Stem Cell, for Genetic Diseases and Acquired Anemias

Description / Background

Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in patients who receive bone marrow toxic doses of cytotoxic drugs with or without whole body radiation therapy. Allogeneic HSCT refers to the use of hematopoietic progenitor cells obtained from a donor. They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates.

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

Preparative Conditioning for Allogeneic HSCT

The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity **(i.e. progenitor cell infusion/boost, donor lymphocyte infusions, etc)**. These regimens partially eradicate the patient's hematopoietic ability, thereby allowing for relatively prompt hematopoietic recovery. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. A number of different cytotoxic regimens, with or without radiotherapy, may be used for RIC

allotransplantation. They represent a continuum in their intensity, from almost totally myeloablative, to minimally myeloablative with lymphoablation.

Genetic Diseases and Acquired Anemias

Hemoglobinopathies

The thalassemias result from mutations in the globin genes, resulting in reduced or absent hemoglobin production, reducing oxygen delivery. The supportive treatment of beta-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic and endocrine function. (1) The only definitive cure for thalassemia is to correct the genetic defect with allogeneic HSCT.

Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin and, unlike thalassemia major, has a variable course of clinical severity. (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. Three major therapeutic options are available: chronic blood transfusions, hydroxyurea and HSCT, the latter being the only possibility for cure. (1)

Bone marrow failure syndromes

Aplastic anemia in children is rare and is most often idiopathic and less commonly due to a hereditary disorder. Inherited syndromes include Fanconi anemia, a rare, autosomal recessive disease, characterized by genomic instability, with congenital abnormalities, chromosome breakage, cancer susceptibility and progressive bone marrow failure leading to pancytopenia and severe aplastic anemia. Frequently this disease terminates in a myelodysplastic syndrome or acute myelogenous leukemia. Most patients with Fanconi anemia succumb to the complications of severe aplastic anemia, leukemia or solid tumors, with a median survival of 30 years of age. (2) 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 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)

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, or 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 life span of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood. (4) Bone marrow transplant is the only definitive cure, and the treatment of choice for SCID and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function. (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.

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

Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS)	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler, Scheie, H-S Hunter Sanfilippo A-D Morquio A-B Maroteaux-Lamy Sly
Sphingolipidosis	Fabry's Farber's Gaucher's I-III GM_1 gangliosidosis Niemann-Pick disease A and B	Lipogranulomatosis

	Tay-Sachs disease Sandhoff's disease Globoid leukodystrophy Metachromatic leukodystrophy	Krabbe disease MLD
Glycoproteinosis	Aspartylglycosaminuria Fucosidosis alpha-Mannosidosis beta-Mannosidosis Mucolipidosis III and IV	Sialidosis
Other lipidoses	Niemann-Pick disease C Wolman disease Ceroid lipofuscinosis	Type III-Batten disease
Glycogen storage	GSD 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

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. (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. 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, often of recurrent infections. (7) HSCT is the only curative therapy for this fatal disease.

Medical Policy Statement

The safety and effectiveness of allogenic hematopoietic stem cell transplantation for specified genetic diseases and acquired anemias have been established. It may be considered a useful therapeutic or diagnostic option when indicated.

Contraindications

Absolute and relative contraindications represent situations where proceeding with transplant may not be advisable in the context of limited organ/tissue availability. Contraindications may evolve over time as transplant experience grows in the medical community. Clinical documentation supplied to the health plan *must* demonstrate that attending staff at the transplant

center have considered *all* contraindications as part of their overall evaluation of potential organ transplant recipients and have decided to proceed.

Relative contraindications:

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, relative contraindications to HSCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Inclusionary and Exclusionary Guidelines (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

Allogeneic hematopoietic stem cell transplantation is considered established for selected patients with the following disorders:

Hemoglobinopathies

- Sickle cell anemia for children or young adults with a history either 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 (HSCT):
  - Lymphocyte immunodeficiencies
    - Adenosine deaminase deficiency
    - Artemis deficiency
    - Calcium channel deficiency
    - CD 40 ligand deficiency
    - Cernunnos/X-linked lymphoproliferative disease deficiency
    - CHARGE syndrome with immune deficiency

    - Common gamma chain deficiency
    - Deficiencies in CD 45, CD3, CD8
    - DiGeorge syndrome
    - DNA ligase IV
    - 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
  - <u>Phagocytic deficiencies</u>
    - Chediak-Higashi syndrome
    - Chronic granulomatous disease
    - Hemophagocytic lymphohistiocytosis
    - Griscelli syndrome, type 2
    - Interferon-gamma receptor deficiencies
    - Leukocyte adhesion deficiency
    - Severe congenital neutropenias
    - Shwachman-Diamond syndrome
  - <u>Other immunodeficiencies</u>
    - 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

<u>Inherited metabolic disease</u>

- Alpha-mannosidosis
- Aspartylglycosaminuria
- Childhood onset cerebral X-linked adrenoleukodystrophy
- Farber lipogranulomatosis
- Fucosidosis
- Galactosialidosis
- Gangliosidosis
- Gaucher types 1 and 3
- Globoid-cell leukodystrophy
- GM1
- Hurler syndrome

- Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes
- Maroteaux-Lamy syndrome
- Metachromatic leukodystrophy
- Mucolipidosis II (I-cell disease)
- Multiple sulfatase deficiency
- Neuronal ceroid lipofuscinosis
- Niemann-Pick
- Sialidosis
- Sly syndromes
- Wolman disease.

Exclusions:
Allogeneic HSCT has not been effective in:
- Hunter syndrome
- Sanfilippo syndrome
- Morquio syndrome

Genetic disorders affecting skeletal tissue
- Infantile malignant osteopetrosis (Albers-Schönberg disease or marble bone disease)

CPT / HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

38204	38205	38207	38208	38209	38210
38211	38212	38213	38214	38215	38220
38221	38230	38240	38242	38243	81267
81270	81271	81272	81273	81274	81275
81268	81370	81371	81372	81373	81374
81375	81376	81377	81378	81379	81380
81382	81383	86816	86817	85821	86822
S2140	S2142	S2150			

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

Hemoglobinopathies
Two 2010 review articles summarize the experience to date with HSCT and the hemoglobinopathies. (9,10)

As of 2008, more than 1,600 patients worldwide have been treated for beta-thalassemia with allogeneic hematopoietic stem-cell transplant (HSCT). (1) Overall survival rates have ranged from 65–100% and thalassemia-free survival up to 73%. (1) The Pesaro risk stratification system classifies patients with thalassemia who are to undergo allogeneic HSCT into risk groups I through III on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with 2 risk factors, and III with all 3). (11) The outcome of allogeneic HSCT in more than 800 patients with thalassemia according to risk stratification has shown overall and event-free survival of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III. (11)

Most of the experience with allogeneic HSCT and sickle cell disease comes from three major clinical series. (1) The largest series to date consisted of 87 symptomatic patients, the majority of whom received donor allografts from siblings who are human leukocyte antigen (HLA) identical. The results from this series (12) and the other two (13,14) were similar, with overall survival rates ranging from 92–94% and event-free survival from 82–86%, with a median follow-up ranging from 0.9–17.9 years. (1)

Experience with reduced-intensity preparative regimens and allogeneic HSCT for the hemoglobinopathies is limited to a small number of patients. Challenges have been with high rates of graft rejection (10–30%) (9), and, in adult patients, severe GVHD has been observed with the use of RIC regimens. (10)

Bernardo and colleagues reported the results of 60 thalassemia patients (median age, 7 years; range, 1-37) who underwent allogeneic HSCT after a RIC regimen based on the treosulfan. (15) Before transplant, 27 children were assigned to risk class 1 of the Pesaro classification, 17 to class 2, and 4 to class 3; 12 patients were adults. Twenty patients were transplanted from an HLA-identical sibling and 40 from an unrelated donor. The cumulative incidence of graft failure and transplantation-related mortality was 9% and 7%, respectively. Eight patients experienced grade II-IV acute GVHD, the cumulative incidence being 14%. Among 56 patients at risk, 1 developed limited chronic GVHD. With a median follow-up of 36 months (range, 4-72), the 5-year probability of survival and thalassemia-free survival were 93% and 84%, respectively. Neither the class of risk nor the donor used influenced outcome.

ClinicalTrials.gov
A nonrandomized Phase II/III trial is recruiting patients with a high-risk hemoglobinopathy to undergo an allogeneic HSCT using a preparative regimen to achieve stable mixed chimerism. Patients will either receive a myeloablative preparative regimen or a nonmyeloablative one if they do not have an HLA-identical sibling donor or are otherwise ineligible for a myeloablative regimen. Primary outcome measure is regimen-related toxicity, and secondary outcome measures include incidence of chimerism and GVHD, quality of life, and overall and disease-free survival. Estimated enrollment is 30 with a study completion date of June 2014. (NCT00176852)

Bone marrow failure syndromes
Two 2010 review articles summarize the experience to date with HSCT and the bone marrow failure syndromes. (9,16)

Fanconi anemia

In a summary of allogeneic HSCT from matched related donors over the past 6 years in Fanconi anemia, totaling 103 patients, overall survival ranged from 83–88%, with transplant-related mortality ranging from 8%–18.5% and average chronic GVHD of 12%. (17)

The outcomes in patients with Fanconi anemia and an unrelated donor allogeneic HSCT have not been as promising. The European Group for Blood and Marrow Transplantation (EBMT) working party has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median 2-year survival was 28 +/- 8%. (3) Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. (3) The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year overall survival rates were 13% and 52% in patients who received non-fludarabine- versus fludarabine-based regimens. (3)

Zanis-Neto and colleagues reported the results of 30 patients with Fanconi anemia treated with reduced-intensity conditioning (RIC) regimens, consisting of low-dose cyclophosphamide. (18) Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade 2-3 acute GVHD rates were 57% and 14% for patients who received the higher and lower doses, respectively (p=0.001). Four of the 7 patients who received the higher dose were alive at a median of 47 months (range: 44-58), and 22 of 23 given the lower dose were alive at a median of 16 months (range: 3-52). The authors concluded that a lower dose of cyclophosphamide conditioning had lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the CIBMTR, Wagner and colleagues reported that fludarabine-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year overall survival (OS) (52% vs. 13%, respectively; p less than 0.001) compared with non-fludarabine regimens. (19)

<u>Other</u>
Results with allogeneic HSCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis. (3) Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results are available at this time. (3)

Experience with allogeneic HSCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease. (3) Cesaro and colleagues reported 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Bone Marrow Transplantation registry given HSCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myelogenous leukemia (MDS-AML) (n=9); or another diagnosis (n=1). (19) Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n= 6), mismatched related (n= 1), or unrelated graft (n=19). Graft failure occurred in 5 (19%) patients, and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, OS was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

In Diamond-Blackfan anemia, allogeneic HSCT is an option in corticosteroid-resistant disease. (3) In a report from the Diamond-Blackfan anemia registry, 20 of 354 registered patients underwent allogeneic HSCT, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts but were poor in recipients of alternative donors. (3) The CIBMTR reported the results in 61 patients who underwent HSCT between 1984 and 2000. (20) Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of OS after transplantation for patients transplanted from an HLA-identical sibling donor (versus an alternative donor) was 78% versus 45% (p=0.01) at 1 year and 76% versus 39% (p=0.01) at 3 years, respectively.
ClinicalTrials.gov

A Phase III randomized study is recruiting patients to compare the regimen related toxicities and transplantation related mortality after allogeneic HSCT for bone marrow failure syndrome using cyclophosphamide and anti-thymocyte globulin (ATG) versus fludarabine and ATG. Estimated enrollment is 98 and estimated study completion date is February 2016 (NCT01145976).

An open label Phase II/III trial is recruiting participants to determine toxicity, risk of disease progression, immune reconstitution and GVHD using a RIC regimen in select patients with nonmalignant diseases (including those with bone marrow failure, osteopetrosis and severe combined immunodeficiency [SCID]). Estimated enrollment is 50, with an estimated study completion date of May 2013 (NCT01019876).

Primary immunodeficiencies
Two 2010 review articles summarize the experience to date with HSCT and the primary immunodeficiencies. (22,23)

HSCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies, such as SCID, Wiskott-Aldrich syndrome and other prematurely lethal X-linked immunodeficiencies, in approximately 90% of cases. (23) According to a European series of 475 patients collected between 1968 and 1999, survival rates for SCID were approximately 80% with a matched sibling donor, 50% with a haploidentical donor and 70% with a transplant from an unrelated donor. (24) Since 2000, OS for patients with SCID who have undergone HSCT is 71%. (4)

Hassan and colleagues reported a multicenter retrospective study, which analyzed the outcome of HSCT in 106 patients with adenosine deaminase deficient-SCID who received a total of 119 transplants. (25) HSCT from matched sibling and family donors had significantly better OS (86% and 81%) in comparison to HSCT from matched unrelated (66%; $p<0.05$) and haploidentical donors (43%; $p<0.0001$). Superior OS was also seen in patients who received unconditioned transplants in comparison to myeloablative procedures (81% vs. 54%; $p<0.003$) although in unconditioned haploidentical donor HSCT, non-engraftment was a major problem. Long-term immune recovery showed that regardless of transplant type, overall T cell numbers were similar, although a faster rate of T cell recovery was observed following matched sibling and family donor HSCT. Humoral immunity and donor B-cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HSCT.

For Wiskott-Aldrich syndrome, an analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes. (24) Fifty-five transplants were from HLA-

identical sibling donors, with a 5-year probability of survival of 87% (95% confidence interval [CI]: 74–93%); 48 were from other relatives, with a 5-year probability of survival of 52% (37–65%); and 67 were from unrelated donors with a 5-year probability of survival of 71% (58–80%; p=0.0006).

Moratto and colleagues retrospectively reported the long-term outcome and donor-cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HSCT in the period 1980-2009. (27) Overall survival was 84.0% and was even higher (89.1% 5-year survival) for those who received HSCT since the year 2000, reflecting recent improvement of outcome after transplantation from mismatched family donors and for patients who received HSCT from an unrelated donor at older than 5 years. Patients who went to transplantation in better clinical condition had a lower rate of post-HSCT complications. Retrospective analysis of lineage-specific donor-cell engraftment showed that stable full donor chimerism was attained by 72.3% of the patients who survived for at least 1 year after HSCT. Mixed chimerism was associated with an increased risk of incomplete reconstitution of lymphocyte counts and post-HSCT autoimmunity, and myeloid donor cell chimerism <50% was associated with persistent thrombocytopenia.

For patients with genetic immune/inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the current results with allogeneic HSCT are 60–70% 5-year disease-free survival.

For patients with other immunodeficiencies, OS rates are 74%, with even better results (90%) with well-matched donors for defined conditions, such as chronic granulomatous disease. (4)

Studies so far indicate that RIC regimens may have an important role in treating patents with primary immunodeficiency. (23) In the absence of prospective or larger registry studies, it is not possible to prove superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae, e.g., infertility and growth retardation, may be avoided or reduced. Currently, RIC HSCT using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (older than 5 years of age), and chronic granulomatous disease with ongoing inflammatory or infective complications. Minimal intensity conditioning HSCT may be particularly suited to unrelated donor HSCT in young SCID patients with significant comorbidities.

ClinicalTrials.gov
A nonrandomized Phase II/III trial is recruiting participants to determine the efficacy of a preparative regimen of busulfan, cyclophosphamide and antithymocyte globulin (ATG) plus allogeneic HSCT in the treatment of immune deficiencies and histiocytic disorders. Outcome measures include time to transplant engraftment, severe toxicities, disease-free survival, GVHD and graft failure. Estimated enrollment is 40, with estimated study completion date of September 2011 (NCT00176826).

A Phase III trial has been completed comparing the health and well-being of children treated with a reduced-intensity allogeneic HSCT for chronic granulomatous disease with that of children receiving standard of care treatment. Patients underwent reduced-intensity allogeneic HSCT with peripheral blood stem cells from an HLA identical family member and were compared to patients who were considered transplant-eligible but lacked an HLA identical family member. The latter group of patients was treated using the current standard of care. Estimated enrollment was 60, with a completion date of June 2004 (NCT00023192).

An open label Phase II/III trial is recruiting participants to determine the toxicity, risk of disease progression, immune reconstitution and GVHD using a RIC regimen in select patients with non-malignant diseases (including those with bone marrow failure, osteopetrosis and SCID). Estimated enrollment is 50 with an estimated study completion date of May 2013. (NCT01019876).

Inherited metabolic diseases

Two 2010 review articles summarize the experience to date with HSCT and the inherited metabolic diseases. (28,29)

In the past 25 years, HSCT has been performed in approximately 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders. (6) The majority (more than 80%) have been in patients with mucopolysaccharidosis I (MPS I; Hurler syndrome), other MPS syndromes (MPS II, MPS III A and B, MPS VI), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid leukodystrophy. (6) With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up. (30) The benefit of allogeneic HSCT appears limited to select subsets of patients with few types of lysosomal storage diseases and is not effective in patients who have developed overt neurologic symptoms or in those with aggressive infantile forms. (30)

Impressive results have been observed with allogeneic HSCT in Hurler syndrome. The benefits that have been observed include improvement of neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others. (6) Survival of engrafted Hurler syndrome patients has been radically changed from that of untransplanted patients, with long-term survival data indicating that life span will be extended many decades. (8) An analysis of nearly 150 transplanted patients with Hurler syndrome showed an overall survival rate of more than 80%. (31)

Experience with allogeneic HSCT and a reduced-intensity preparative regimen has been reported in 7 patients with Hurler syndrome. (29) Six of the patients received transplants from unrelated donors and 1 received the transplant from a sibling. All patients had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the 7 children were alive at a median of 1,014 days (range: 726–2,222 days) post-transplant.

The few patients with Maroteaux-Lamy and Sly syndrome that have received transplants have shown promising results, with clinical improvement post-transplant. (8)

Outcomes with the leukodystrophies and allogeneic HSCT have been variable but somewhat promising. In boys and men with X-linked adrenoleukodystrophy; outcomes have depended on disease status at transplant and transplant-related complications (8), but reports of preservation of neuropsychologic and neurologic function have been made.

Fewer than 40 patients with globoid-cell leukodystrophy have undergone allogeneic HSCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic and neurophysiologic function. (8)

Many patients with metachromatic leukodystrophy who have undergone allogeneic HSCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival. (8)

Mynarek and colleagues reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HSCT. (30) Patients were diagnosed with the disease at a median age of 2.5 years (range 1.1-23 years) and underwent HSCT at a median age of 3.6 years (1.3-23.1 years). After a median follow-up of 5.5 years (2.1-12.6 years), OS was 88%. One patient died 76 days after HSCT from sepsis, GVHD and pulmonary hemorrhage and another patient died on day 135 due to viral infections and multi-organ failure. Before HSCT, the extent of developmental delay in the 17 patients varied over a wide range. After HSCT, patients made developmental progress, however normal development was not achieved. Hearing ability improved in some but not all of the patients.

Hunter syndrome is composed of two distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged life span, minimal to no central nervous system involvement, and a slow progression. (8) Experience with allogeneic HSCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly. (8) Some authors suggest that HSCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits. (8)

Eight patients with Hunter syndrome received an allogeneic HSCT between the ages of 3 and 16 years. (34) In 6 cases, the donor was a sibling with identical HLA status, in 1 case, the donor was unrelated HLA-compatible, and in 1 case, the donor was a mismatched unrelated donor. The severity of disease prior to transplant was rated by assessing the age at diagnosis, behavior and intelligence quotient (IQ) at the time of graft and genotype. Five patients were considered to have severe CNS involvement (i.e., diagnosis before the age of 4 years and an IQ less than 80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years and normal IQ), and 1 as intermediate (i.e., diagnosis after the age of 4 and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive with the exception of 1 patient who died of unrelated causes. Successful engraftment was achieved in all patients and cardiovascular abnormalities stabilized in all patients, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. Neuropsychological outcome was variable: the 2 patients with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four patients with the severe form of the syndrome deteriorated after the graft, and their IQ/ developmental quotient had declined below 50 at the time of the last evaluation. Of the patients with the severe form, 3 lost the ability to walk in their early teens, 2 lost language at 9 and 11 years, and 2 developed epilepsy. The remaining 2 patients with the severe form required special schooling and had poor social and language skills.

Experience with allogeneic HSCT in patients with MPS III (Sanfilippo syndrome) has also been disappointing, with no alteration in the course of neuropsychologic deterioration seen in these patients. (8) The literature addressing the use of HSCT in Sanfilippo disease consists of 2 case reports. (35,36) Vellodi and colleagues reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HSCT and were followed up for 9 years. (35) At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next 8 years, both girls had a steady decline in cognitive development, and both functioned in

the area of significant developmental delay. The authors postulated that a possible reason for continued deterioration in the twins, despite the demonstration of full chimerism, was a very low level of enzyme throughout the years after transplant. One other patient with MPS III who had received a transplant was 5.3 years old at the time of the transplant and continued to regress post-transplant. (36)

ClinicalTrials.gov
A nonrandomized, open label, uncontrolled, Phase II/III study is completed, which used HSCT for Hurler syndrome, Maroteaux-Lamy syndrome, mannosidosis, or I-cell disease, to determine the safety and engraftment of donor hematopoietic cells using a certain conditioning regimen. Secondary outcome measures include survival. The estimated enrollment was 41, with an estimated study completion date of May 2010 (NCT00176917).

An open-label Phase II/III trial is recruiting participants to determine the toxicity, risk of disease progression, immune reconstitution and GVHD using an RIC regimen in select patients with nonmalignant diseases (including those with bone marrow failure, osteopetrosis and SCID). Estimated enrollment is 50, with an estimated study completion date of May 2013. (NCT01019876).

Infantile Malignant Osteopetrosis
A 2010 review article summarizes the experience to date with HSCT and osteopetrosis. (37)
The success of allogeneic HSCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a 5-year disease-free survival of 73–79% versus transplantation with an unrelated or mismatched donor of 13–45%. (7)

A retrospective analysis of 122 children who received an allogeneic HSCT for autosomal recessive osteopetrosis between 1980 and 2001 reported 5-year disease-free survival of 73% for recipients of a genotype HLA-identical HSCT (n=40), 43% for those of a phenotype HLA-identical or 1 HLA-antigen mismatch graft from a related donor (n=21), 40% for recipients of a graft from a matched unrelated donor (n=20), and 24% for patients who received an HLA-haplotype-mismatch graft from a related donor (n=41). (38)

ClinicalTrials.gov
Two open-label nonrandomized Phase II/III trials are recruiting participants, one assessing survival and GVHD after allogeneic HSCT for osteopetrosis, with an estimated enrollment of 10 and estimated study completion date of July 2011 (NCT01087398) and the other assessing engraftment, mortality, toxicity, and GVHD with a RIC regimen, with an estimated enrollment of 23 and estimated study completion date of October 2015 (NCT00775931)

An open-label Phase II/III trial is recruiting participants to determine the toxicity, risk of disease progression, immune reconstitution and GVHD using a RIC regimen in select patients with nonmalignant diseases (including those with bone marrow failure, osteopetrosis and SCID). Estimated enrollment is 50, with an estimated study completion date of May 2013. (NCT01019876).

Physician Specialty Society and Academic Medical Center Input

In response to requests, BCBSA received input from 1 physician specialty society and 3 academic medical centers while this policy was under review for September 2009. There was general agreement with the policy statements. In particular, the reviewers were specifically asked to address the issue of the use of HSCT 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.

Summary
In summary, as of August 2012, no trials have been published that would alter the current policy statement; this is considered medically necessary for all the listed indications, with the exception of the inherited metabolic diseases Hunter, Sanfilippo and Morquio syndromes.

Related Policies

- BMT – Autologous, for Malignant Astrocytomas and Gliomas
- BMT – Hematopoietic Stem Cell Transplantation for Breast Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Treatment of Multiple Myeloma
- BMT – Hematopoietic Stem Cell Transplantation for Acute Lymphoblastic Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma - Autologous or Allogeneic
- BMT – Hematopoietic Stem Cell Transplantation for Chronic Myelogenous Leukemia
- BMT – Hematopoietic Stem Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Stem Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Stem Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Stem Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Stem Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Stem Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Hematopoietic Stem Cell Transplantation in the Treatment of Germ-Cell Tumors
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Stem-Cell Transplant

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Government Regulations

National:
National Coverage Determinations Manual, Pub. 100-03, section 110.8.1: Stem Cell Transplantation (Rev. 127, Issued: 10-08-10, Effective: 08-04-10, Implementation: 11-10-10)

A. General
The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high dose

chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, no steps are covered.

The following uses of allogeneic HSCT are covered under Medicare:
i. Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
ii. Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
iii. Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.

The MDS refers to a group of diverse blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. These disorders are varied with regard to clinical characteristics, cytologic and pathologic features and cytogenetics. The abnormal production of blood cells in the bone marrow leads to low blood cell counts, referred to as cytopenias, which are a hallmark feature of MDS along with a dysplastic and hypercellular-appearing bone marrow.

Medicare payment for these beneficiaries will be restricted to patients enrolled in an approved clinical study. In accordance with the Stem Cell Therapeutic and Research Act of 2005 (US Public Law 109-129) a standard dataset is collected for all allogeneic transplant patients in the United States by the Center for International Blood and Marrow Transplant Research. (See NCD for specific details regarding clinical study requirements.)

Effective for services performed on or after May 24, 1996, allogeneic HSCT is not covered as treatment for multiple myeloma.

Local:
Refer to NCD.

Michigan Department of Community Health:
All bone marrow transplant charges are reimbursed at the hospital’s cost to charge ratio.
For other organ transplant services not described by a specific DRG, the hospital must provide a note/remark on the claim of the type of transplant (i.e., small bowel transplant) performed. All organ transplant claims suspend for manual review of documentation. A copy of the PA letter must be submitted with the claims. Providers must note "PA Letter submitted" in the Remarks section of the claim.

For those transplants requiring PA, MDCH requires a beneficiary to be evaluated at an accepted transplant center approved by the OMA to determine if he is a good transplant candidate. If the transplant is to take place at a Medicaid-enrolled, in-state hospital, then only the transplant needs PA. If the transplant is to be performed at an out-of-state hospital, then both the evaluation and the transplant must be separately prior authorized. Results from the evaluation must be submitted to the OMA when requesting PA for the transplant.

If the beneficiary is Medicaid-eligible and the donor is not Medicaid-eligible, providers must bill all services under the beneficiary's ID Number and provide complete documentation. If the donor and beneficiary are both Medicaid-enrolled, providers must bill the services under their respective Medicaid ID numbers.

When the donor search does not result in an organ acquisition and transplant, MDCH reimburses for a donor search and related charges. These services must be billed as outpatient services, and providers are required to submit a copy of the PA letter for transplant with the claim. Providers must make a reference or remark on the claim format that the donor search failed at the time of claim submission.

There is a $1 million lifetime limit in coverage for BMTs.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/7/12, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/12	12/14/11	1/31/12	Joint policy established. **Note: This policy was generated from former combined policies on established allogeneic bone marrow transplants*
3/1/13	12/11/12	12/31/12	Policy updated with literature search; references 15, 25 and 27 added; no change in policy statements. Added CPT code 38243 effective 1/1/13. Updated CPT verbiage as needed. Added definition of progenitor cell infusions. Added relative contraindications to policy.

Next Review Date: 4th Qtr, 2013

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BONE MARROW TRANSPLANT, ALLOGENIC HEMATOPOIETIC STEM CELL, FOR GENETIC DISEASES AND ACQUIRED ANEMIAS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply.
BCNA (Medicare Advantage)	Covered; criteria apply.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.
BlueCaid	Covered; criteria apply.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.