Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

Policy # 00055
Original Effective Date: 01/28/2002
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Autoimmune Diseases is addressed separately in medical policy 00050.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT) to be **eligible for coverage** for selected patients with the following disorders:

Hemoglobinopathies

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

Bone marrow failure syndromes

- Aplastic anemia including hereditary (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 [SCID], 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 (CGD), leukocyte adhesion defect)

(See Guideline 1.)

Inherited metabolic disease

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

(See Guideline 2.)

Genetic disorders affecting skeletal tissue

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

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) for any other condition not listed above to be **investigational.***

Policy Guidelines

GUIDELINE 1
The following guideline lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic cell transplantation (allo-HCT) (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
- Deoxyribionucleic acid (DNA) ligase IV deficiency syndrome
- Interleukin-7 receptor alpha deficiency
- Janus-associated kinase 3 deficiency
- Major histocompatibility class II deficiency
- Omenn syndrome
- Purine nucleoside phosphorylase deficiency
- Recombinase-activating gene 1/2 deficiency
- Reticular dysgenesis
- Winged helix deficiency
- Wiskott-Aldrich syndrome
- X-linked lymphoproliferative disease
- Zeta-chain-associated protein-70 deficiency

Phagocytic Deficiencies

- Chédiak-Higashi syndrome

- Chronic granulomatous disease (CGD)
- 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 immunoglobulin D (IgD) and immunoglobulin E (IgE) syndromes
- Immunodeficiency, centromeric instability, and facial dysmorphism syndrome
- Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
- Nuclear factor-κ B (NF-κB) essential modulator deficiency
- NF-κB inhibitor, NF-κB-α deficiency
- Nijmegen breakage syndrome

GUIDELINE 2

In the inherited metabolic disorders, allogeneic HCT (allo-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, and aspartylglucosaminuria. Allo-HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM_1 gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick disease, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allo-HCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes (Mehta, 2004).

The experience with reduced-intensity conditioning (RIC) and allo-HCT for the diseases listed in this evidence review has been limited to small numbers of patients and has yielded mixed results, depending on the disease category. In general, the results have been most promising in the bone marrow failure syndromes and primary immunodeficiencies. In the hemoglobinopathies, success has been hampered by difficulties with high rates of graft rejection, and in adults, severe graft-versus-host-disease (GVHD). 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.

Background/Overview

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. 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 discussed in greater detail in archived medical policy 00021.

Immunologic compatibility between infused hematopoietic cells and the recipient is a critical factor for achieving a good outcome with allo-HCT. 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 (except umbilical cord blood).

Preparative Conditioning for Allo-HCT
The conventional practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. 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 allogeneic 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.

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 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. The only definitive cure for thalassemia is to correct the genetic defect with allo-HCT.

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-HCT, 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. 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, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of HLA-matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

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

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 myeloid leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow, with 30% of patients also having a variety of physical anomalies.

Primary Immunodeficiencies
The primary immunodeficiencies are a genetically heterogeneous group of diseases that affect distinct components of the immune system. More than 120 gene defects have been described, causing more than 150 disease phenotypes. The most severe defects (collectively known as SCID) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells. Without treatment, patients with SCID usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the 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. 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.

Inherited Metabolic Diseases
Lysosomal storage disorders consist of many different rare diseases caused by a single gene defect, and most are inherited as an autosomal recessive trait. Lysosomal storage disorders are caused by specific enzyme deficiencies that result in defective lysosomal acid hydrolysis of endogenous macromolecules that subsequently accumulate as a toxic substance. Peroxisomal storage disorders arise due to a defect in a membrane transporter protein that leads to defects in the metabolism of long-chain fatty acids. Lysosomal storage disorders and peroxisomal storage disorders affect multiple organ systems, including the central and peripheral nervous systems. These disorders are progressive and often fatal in childhood due to both the accumulation of toxic substrate and a deficiency of the product of the enzyme reaction. Hurler syndrome usually leads to premature death by 5 years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in the 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 (e.g., microglial cells in the brain and Kupffer cells in the liver).

Allo-HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in 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 1000 transplants have been performed worldwide.

Table 1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis	Mucopolysaccharidosis I H or H/S	Hurler syndrome or Hurler-Scheie syndrome
	Mucopolysaccharidosis II	Hunter syndrome
	Mucopolysaccharidosis III A-D	Sanfilippo syndrome A-D
	Mucopolysaccharidosis IV A-B	Morquio syndrome A-B
	Mucopolysaccharidosis VI	Maroteaux-Lamy syndrome
	Mucopolysaccharidosis VII	Sly syndrome
Sphingolipidosis	Fabry disease	
	Farber disease	Lipogranulomatosis
	Gaucher disease types 1 and 3	
	GM_1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff disease	
	Globoid cell leukodystrophy	Krabbe disease
	Metachromatic leukodystrophy	MLD
Glycoproteinosis	Aspartylglucosaminuria	
	Fucosidosis	
	Alpha-mannosidosis	
	Beta-mannosidosis	
	Mucolipidosis III and IV	Sialidosis
Other lipidoses	Niemann-Pick disease C	
	Wolman disease	
	Ceroid lipofuscinosis type III	Batten disease
Glycogen storage	Glycogen storage disease type II	Pompe disease
Multiple enzyme deficiency	Galactosialidosis	
	Mucolipidosis type II	I-cell disease
Lysosomal transport defects	Cystinosis	
	Sialic acid storage disease	
	Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy	ALD
	Adrenomyeloneuropathy	AMN

Genetic Disorders Affecting Skeletal Tissue
Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow. 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. HCT is the only curative therapy for this fatal disease.

HCT for autoimmune disease, such as rheumatoid arthritis or multiple sclerosis, is considered separately in medical policy 00050.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
The U.S. FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

HEMOGLOBINOPATHIES
Review articles summarize the experience to date with HCT and the hemoglobinopathies.

β-Thalassemia
More than 3000 patients worldwide have been treated for β-thalassemia with allo-HCT. Overall survival (OS) rates have ranged from 65% to 98% at 5 years, up to 87% at 15 years, up to 89% at 20 years, and thalassemia-free survival has been reported to be as high as 86% at 6 years. The Pesaro risk stratification system classifies patients with thalassemia who plan to undergo allo-HCT into risk groups I through III based 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 risk factors). The outcome of allo-HCT in more than 800 patients with thalassemia according to risk stratification has shown overall and event-free survival (EFS) of 95% and 90% for Pesaro class I, 87% and 84% for class II, and 79% and 58% for class III.

A 2015 study of 489 patients with nonmalignant hematologic disorders who underwent allo-HCT between 1997 and 2012 included 152 patients with β-thalassemia. Mean age at transplantation was 5.7 years

(range, 1.1-23 years). At the time of transplantation, 26 (17%) patients had Pesaro class I, 103 (68%) had class II, and 23 (15%) had class III; 132 patients received peripheral blood stem cells and 20 received bone marrow grafts. Mean times to neutrophil and platelet engraftment were 21.4 days (range, 8-69 days) and 32.8 days (range, 7-134 days), respectively. The incidence of graft rejection was significantly lower in patients who received peripheral blood stem cells than in those who received bone marrow grafts (9% vs 25%; p=0.036). Acute GVHD grade II, III, and IV occurred in 15% of β-thalassemia patients, and chronic GVHD occurred in 12%. The incidence of transplant-related mortality for this group was 18%. After a median follow-up period of 12 years, the OS rate for these patients was 82.4%. The disease-free survival (DFS) rate of the whole group of β-thalassemia patients was 72.4% (74% in the peripheral blood cell transplantation group vs 64% in the bone marrow cell transplantation group; p=0.381), which may be attributed to the higher incidence of graft rejection in bone marrow groups.

Bernardo et al (2012) reported on the results of 60 thalassemia patients (median age, 7 years; range, 1-37 years) who underwent allo-HCT after an RIC regimen based on treosulfan. Before transplant, 27 children were assigned to class 1 of the Pesaro risk stratification system, 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, III, or IV acute GVHD, the cumulative incidence being 14%. Among 56 patients at risk, one developed limited chronic GVHD. With a median follow-up of 36 months (range, 4-72 months), 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 the outcome.

In a 2014 report on RIC HCT, 98 patients with class 3 thalassemia were transplanted with related or unrelated donor stem cells. Seventy-six of patients less than 10 years of age received a conventional myeloablative conditioning regimen (cyclophosphamide, busulfan, with or without fludarabine). The remaining 22 patients were 10 years of age or older with hepatomegaly and in several instances, additional comorbidity problems, who underwent HCT with a novel RIC regimen (fludarabine and busulfan). Rates of EFS (86% vs 90%, respectively), and OS (95% vs 90%, respectively) did not differ significantly between groups. However, a higher incidence of serious treatment-related complications was observed in the group that received myeloablative conditioning. Furthermore, graft failures occurred in 6 patients in the myeloablated group (8%), although none occurred in the RIC group.

Sickle Cell Disease
Approximately 500 to 600 patients with sickle cell disease have undergone allo-HCT, and most of the experience with allo-HCT and sickle cell disease comes from 3 major clinical series. The largest series to date consists of 87 symptomatic patients, most of whom received donor allografts from siblings who are HLA identical. The results from this series and the 2 others were similar, with rates of OS ranging from 92% to 94% and EFS from 82% to 86%, with a median follow-up ranging from 0.9 to 17.9 years.

A Cochrane systematic review published in 2013 and updated in 2016, identified no randomized controlled trials (RCTs) that assessed a risk or benefit of any method of HCT in patients with sickle cell disease.

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

A 2014 article reported on results from 30 patients aged 16 to 65 years with severe sickle cell phenotype who were enrolled in an RIC allo-HCT study, consisting of alemtuzumab (1 mg/kg in divided doses), total body irradiation (300 centigray), sirolimus, and infusion of unmanipulated filgrastim mobilized peripheral blood stem cells from HLA-matched siblings. The primary end point was treatment success at 1 year after the transplant, defined as a full-donor-type hemoglobin for patients with sickle cell disease and transfusion independence for patients with thalassemia. Secondary end points included the level of donor leukocyte chimerism; incidence of acute and chronic GVHD; and sickle cell–thalassemia DFS, immunologic recovery, and changes in organ function. Twenty-nine patients survived a median 3.4 years (range, 1-8.6 years), with no nonrelapse mortality. One patient died from intracranial bleeding after relapse. The normalized hemoglobin and resolution of hemolysis among engrafted patients were accompanied by stabilization in brain imaging, a reduction of echocardiographic estimates of pulmonary pressure, and allowed for phlebotomy to reduce hepatic iron. A total of 38 serious adverse events were reported: pain and related management, infections, abdominal events, and sirolimus-related toxic effects.

BONE MARROW FAILURE SYNDROMES
Review articles summarize the experience to date with HCT and bone marrow failure syndromes.

Fanconi Anemia
In a 2008 summary of patients with Fanconi anemia who received allo-HCT from matched related donors over the 6 years before publication (total N=103 patients), OS rates ranged from 83% to 88%, with transplant-related mortality ranging from 8% to 18.5% and average chronic GVHD of 12%.

The outcomes in patients with Fanconi anemia and an unrelated donor allo-HCT have not been as promising. The European Group for Blood and Marrow Transplantation has analyzed the outcomes using alternative donors in 67 patients with Fanconi anemia. Median 2-year survival was 28%. Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplant Research analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year OS rates were 13% and 52%, respectively, in patients who received non-fludarabine- or fludarabine-based regimens.

Zanis-Neto et al (2005) reported on the results of 30 patients with Fanconi anemia treated with RIC regimens, consisting of low-dose cyclophosphamide. Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade II or III 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 months), and 22 of 23 given the lower dose were alive at a median of 16 months (range, 3-52 months). 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 Center for International Blood and Marrow Transplant Research, Wagner et al (2007) reported that fludarabine-based (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year OS rates (52% vs 13%, respectively; p<0.001) compared with non-fludarabine-based regimens.

Dyskeratosis Congenita
Results with allo-HCT in dyskeratosis congenita have been disappointing because of severe late effects, including diffuse vasculitis and lung fibrosis. Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results have been published.

Outcomes after allo-HCT were reported in 2013 for 34 patients with dyskeratosis congenita who underwent transplantation between 1981 and 2009. Median age at transplantation was 13 years (range, 2-35 years). Approximately 50% of transplantations were from related donors. The day-28 probability of neutrophil recovery was 73%, and the day-100 platelet recovery was 72%. The day-100 probability of grade II, III, or IV acute GVHD and the 3-year probability of chronic GVHD were 24% and 37%, respectively. The 10-year probability of survival was 30%, and at the time of publication, 14 patients were still alive at last follow-up. Ten deaths occurred within 4 months from transplantation because of graft failure (n=6) or other transplantation-related complications; 9 of these patients had undergone transplantation from mismatched related or unrelated donors. Another 10 deaths occurred after 4 months; six of them occurred more than 5 years after transplantation, and four of these were attributed to pulmonary failure. Transplantation regimen intensity and transplantations from mismatched related or unrelated donors were associated with early mortality. Transplantation of grafts from HLA-matched siblings with cyclophosphamide-containing nonradiation regimens was associated with early low toxicity. Late mortality was attributed mainly to pulmonary complications and likely related to the underlying disease.

Shwachman-Diamond Syndrome
Experience with allo-HCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease. Cesaro et al (2005) reported on 26 patients with Shwachman-Diamond syndrome from the European Group for Blood and Marrow Transplantation registry, who received HCT for treatment of severe aplastic anemia (n=16); myelodysplastic syndrome-acute myeloid leukemia (n=9); or another diagnosis (n=1). 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 myelodysplastic syndrome-acute myeloid leukemia or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

Diamond-Blackfan Syndrome
In Diamond-Blackfan syndrome, allo-HCT is an option in corticosteroid-resistant disease. In a report from the Diamond-Blackfan syndrome registry (2008), 20 of 354 registered patients underwent allo-HCT, and the 5-year survival rates were 87.5% when recipients received HLA-identical sibling grafts but were poor in recipients of alternative donors. Another team of investigators (2005) examined outcomes reported to the International Bone Marrow Transplant Registry between 1984 and 2000 for 61 patients with Diamond-Blackfan syndrome who underwent HCT. 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 (vs an alternative donor) was 78% vs 45% (p=0.01) at 1 year and 76% vs 39% (p=0.01) at 3 years, respectively.

Aplastic Anemia
A randomized phase 3 trial (2012) compared 2 conditioning regimens in patients (n=79) with high-risk aplastic anemia who underwent allo-HCT. Patients in the cyclophosphamide plus antithymocyte globulin (ATG) arm (n=39) received cyclophosphamide at 200 mg/kg; those in the cyclophosphamide-fludarabine-ATG arm (n=40) received cyclophosphamide at 100 mg/kg and fludarabine at 150 mg/m^2. No difference in engraftment rates was reported between arms. Infection with an identified causative organism and sinusoidal obstruction syndrome, hematuria, febrile episodes, and death from any cause tended to be more frequent among those receiving cyclophosphamide-ATG but did not differ significantly between treatment arms. At 4 years, OS rates did not differ significantly between the cyclophosphamide-ATG and cyclophosphamide-fludarabine-ATG arms (78% vs 86%, respectively, p=0.41). Although this study was underpowered to detect real differences between the conditioning regimens, the results suggested that an RIC regimen with cyclophosphamide-fludarabine-ATG appears to be as safe as a more conventional myeloablative regimen comprising cyclophosphamide-ATG in allo-HCT.

A 2015 study analyzed outcomes reported to the European Group for Blood and Marrow Transplantation of children with idiopathic aplastic anemia, according to treatment received. Front-line immunosuppressive therapy (IST) was compared with front-line HCT from an HLA-matched family donor, to evaluate the outcomes of patients who, after having failed IST, underwent rescue HCT, and to compare their outcomes with front-line HCT and those who did not fail IST (IST with no subsequent transplant). Additional outcomes that were evaluated were the cumulative incidence of posttherapy tumors and prognostic factors that may affect the outcome of the disease. Included in the analysis were records from 563 consecutive children (313 boys, 250 girls [age range, 0-12 years]) diagnosed between 2000 and 2009. Geographical origin, if known, was distributed as follows: 383 patients from Europe, 51 from Africa, 51 from the Middle East, 2 from Australia, and 1 from Brazil. The median age at diagnosis was 7.8 years (range, 0.01-11.9 years). A total of 167 children received front-line IST (consisting of ATG plus cyclosporine); of these, 91 (55%) failed IST as front-line treatment and underwent subsequent rescue HCT (HCT post-IST failure) whereas IST was the only treatment received (IST alone) for 76 patients. The 3-year probability of OS and EFS rates for the whole population was 90% and 86%, respectively. The 3-year OS rate was 91% after matched family donor front-line HCT and 87% after first-line IST (p=0.18). The 3-year probability of OS after HCT post-IST failure was 83%, after matched family donor front-line HCT 91% and after IST alone 97% (p=0.017). A subgroup analysis showed no significant difference between IST alone and matched family donor front-line HCT

(p=0.21), but significantly higher OS of both matched family donor front-line HCT (p=0.02) and IST alone (p=0.047) over HCT post-IST failure.

In the 2015 study (discussed earlier), which examined 489 patients with nonmalignant hematologic disorders who underwent allo-HCT, 273 patients with severe aplastic anemia were included. Of these subjects, 212 were men, and 61 were women, and the mean age at transplantation was 19.7 years (range, 1.5-51 years). Mean times to neutrophil and platelet engraftment were 13.9 days (range, 10-26 days) and 14.1 days (range, 8-83 days), respectively. Graft rejection occurred in1% of patients. Acute GVHD grade II-IV occurred in 15%, and chronic GVHD occurred in 28% of patients. The incidence of transplant-related mortality was 22%. At 8 years, OS and DFS rates were both 74%. Conditioning regimens differed among the patients, with 181 receiving fludarabine and cyclophosphamide and 92 receiving cyclophosphamide and ATG. No statistically significant differences between conditioning groups were observed regarding mean time to neutrophil engraftment and incidence of extensive chronic GVHD (p=0.136 and 0.651, respectively). Mean time to platelet engraftment was significantly longer in the cyclophosphamide plus ATG group (p=0.016). The incidence of transplant-related mortality in the fludarabine plus cyclophosphamide group was 17%, which was significantly lower than in the cyclophosphamide plus ATG group (33%; p=0.002). After a median follow-up of 8 years, the OS rate was statistically significantly better in the fludarabine plus cyclophosphamide group than in the cyclophosphamide plus ATG group of patients (80% vs 64%, respectively; p=0.021).

PRIMARY IMMUNODEFICIENCIES
Review articles summarize experience with HCT and the primary immunodeficiencies. Additional individual studies are reported next.

Chronic Granulomatous Disease
In patients with CGD, HCT outcomes were compared with those of conventional treatment in a study of 41 patients in Sweden who were diagnosed with CGD between 1990 and 2012. From 1997 to 2012, 14 patients (aged 1 to 35 years) underwent HCT and received grafts either from an HLA-matched sibling donor or a matched unrelated donor. Thirteen (93%) of the 14 transplanted patients were reported alive and well at publication in 2013. The mean age at transplantation was 10.4 years and the mean survival time was 7.7 years. In contrast, 7 of 13 men or boys with X-linked CGD who were treated conventionally died from complications of CGD at a mean age of 19 years, while the remainder suffered life-threatening infections.

A 2014 prospective study in 16 centers across 10 countries worldwide enrolled CGD patients aged 0 to 40 years to examine the effects of an RIC regimen before HCT, consisting of high-dose fludarabine, serotherapy, or low-dose alemtuzumab, and low-dose (50% to 72% of myeloablative dose) or targeted busulfan administration. Unmanipulated bone marrow or peripheral blood stem cells from HLA-matched related donors or HLA-9/10 or HLA-10/10 matched unrelated donors were infused. The primary end points were OS and EFS, probabilities of OS and EFS at 2 years, the incidence of acute and chronic GVHD, achievement of at least 90% myeloid donor chimerism, and incidence of graft failure after at least 6 months of follow-up. A total of 56 patients (median age 12.7 years) were included; 42 (75%) patients had high-risk features (i.e., intractable infections and autoinflammation) and 25 (45%) were adolescents and young adults

(age range, 14-39 years). Median time to engraftment was 19 days for neutrophils and 21 days for platelets. At a median follow-up of 21 months, OS was 93%, and EFS was 89%. The 2-year probability of OS was 96% (95% confidence interval [CI], 86.46% to 99.09%) and of EFS was 91% (95% CI, 79.78% to 96.17%). Graft failure occurred in 5% of patients. The cumulative incidence of acute GVHD grade III or IV was 4% and of chronic GVHD was 7%. Stable (≥90%) myeloid donor chimerism was documented in 52 (93%) surviving patients.

Severe Combined Immunodeficiency
HCT using HLA-identical sibling donors can correct underlying primary immunodeficiencies, such as SCID, Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies, in approximately 90% of cases. According to a 2008 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. Another 2008 report found an OS rate for patients with SCID who have undergone HCT to be 71%.

Hassan et al (2012) reported on a multicenter retrospective study, which analyzed HCT outcomes in 106 patients with adenosine deaminase deficient–SCID who received a total of 119 transplants. HCT from matched sibling and family donors had significantly better OS (86% and 81%, respectively) compared with HCT from matched unrelated (66%; $p<0.05$) and haploidentical donors (43%; $p<0.001$). Superior OS was also seen in patients who received unconditioned transplants in comparison with myeloablative procedures (81% vs 54%; $p<0.003$), although in unconditioned haploidentical donor HCT, nonengraftment 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 HCT. Humoral immunity and donor B-cell engraftment was achieved in nearly all evaluable surviving patients and was seen even after unconditioned HCT.

Wiskott-Aldrich Syndrome
For Wiskott-Aldrich syndrome, a 2001 analysis of 170 patients transplanted between 1968 and 1996 demonstrated the impact of donor type on outcomes. Fifty-five transplants were from HLA-identical sibling donors, with a 5-year probability of survival of 87% (95% CI, 74% to 93%); 48 were from other relatives, with a 5-year probability of survival of 52% (95% CI, 37% to 65%); and 67 were from unrelated donors with a 5-year probability of survival of 71% (95% CI, 58% to 80%; $p<0.001$).

Moratto et al (2011) retrospectively reported on the long-term outcome and donor cell engraftment in 194 patients with Wiskott-Aldrich syndrome treated by HCT from 1980 to 2009. The OS rate was 84.0% and was even higher (89.1% 5-year survival) for those who received HCT since the year 2000, reflecting the recent improvement in outcome after transplantation from mismatched family donors and for patients who received HCT from an unrelated donor older than 5 years of age. Also, patients who proceeded to transplantation in better clinical condition had a lower rate of post-HCT 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 HCT. Mixed chimerism was associated with an

increased risk of incomplete reconstitution of lymphocyte counts and post-HCT autoimmunity, and myeloid donor cell chimerism less than 50% was associated with persistent thrombocytopenia.

X-Linked Lymphoproliferative Disease
X-linked lymphoproliferative disease type 1 (XLP1) is a rare, deadly immune deficiency caused by variants in *SH2D1A*. Allo-HCT is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using RIC regimens for these patients. One study (2014) reported on an 8-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allo-HCT between 2006 and 2013 after an RIC regimen consisting of alemtuzumab, fludarabine, and melphalan. Fourteen of 16 patients received fully HLA-matched (8/8) unrelated or related bone marrow grafts, whereas 2 patients received mismatched unrelated grafts. All patients had hematopoietic recovery. No cases of hepatic veno-occlusive disease or pulmonary hemorrhage were reported. One (6%) patient developed acute GVHD and later also developed chronic GVHD. Five (31%) patients developed mixed chimerism. One-year survival estimated by Kaplan-Meier analysis was 80%, with long-term survival estimated at 71%. There were no occurrences of lymphoma after HCT.

Other Immunodeficiencies
For patients with genetic immune/inflammatory disorders, such as hemophagocytic lymphohistiocytosis, the 5-year DFS rates with allo-HCT ranged from 60% to 70%.

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

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

INHERITED METABOLIC DISEASES INCLUDING HUNTER, SANFILIPPO, OR MORQUIO SYNDROMES

Hunter Syndrome
Hunter syndrome is composed of 2 distinct clinical entities, a severe and an attenuated form. The attenuated form is characterized by a prolonged lifespan, minimal to no central nervous system involvement, and a slow progression. Experience with allo-HCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly. Some authors have suggested that HCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits.

Eight patients with Hunter syndrome received an allo-HCT between the ages of 3 and 16 years. In 6 cases, the donor was an HLA-identical sibling; in 1 case, an HLA-compatible unrelated donor was used, and in another, a mismatched unrelated donor was used. The severity of disease before the transplant was rated by assessing the age at diagnosis, behavior, and IQ at the time of graft and genotype. Five patients were considered to have severe central nervous system involvement (i.e., diagnosis before the age of 4 years and an IQ <80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years of age and normal IQ), and 1 as intermediate (i.e., diagnosis after the age of 4 years and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive except 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. The 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 intelligence quotient (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 of age, respectively, and 2 developed epilepsy. The remaining 2 patients with the severe form required special schooling and had poor social and language skills.

Sanfilippo Syndrome
Experience with allo-HCT in patients with Sanfilippo syndrome (MPS III) has shown no alteration in the course of neuropsychologic deterioration seen in these patients. The literature addressing the use of HCT in Sanfilippo syndrome consists of 2 case reports. Vellodi et al (1992) reported on the outcomes of twin girls diagnosed with Sanfilippo syndrome who underwent allo-HCT and were followed for 9 years. 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 the 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 Sanfilippo syndrome who had received allo-HCT was 5.3 years old at the time of the transplant and continued to regress posttransplant.

Morquio Syndrome
Allo-HCT has not been effective in Morquio syndromes (Mehta, 2004).

INHERITED METABOLIC DISEASES EXCLUDING HUNTER, SANFILIPPO, OR MORQUIO SYNDROMES
Review articles summarize the experience with HCT and the inherited metabolic diseases.

Lysosomal Storage Disorders
In the past 25 years, HCT has been performed in approximately 20 of the estimated 40 known lysosomal storage disorders and peroxisomal storage disorders. Most instances (>80%) have been in patients with Hurler syndrome (mucopolysaccharidosis I [MPS I]) or other MPS syndromes (Hunter syndrome [MPS II], Sanfilippo syndrome types A [MPS IIIA] and B [MPS IIIB], Maroteaux-Lamy syndrome [MPS VI]), adrenoleukodystrophy, metachromatic leukodystrophy, and globoid cell leukodystrophy. Except Hurler and

globoid cell leukodystrophy, most published data are from single-case reports or small series with short follow-up. The benefit of allo-HCT appears to be 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.

Hurler syndrome is a lysosomal storage disease that if left untreated, results in progressive multisystem morbidity including neuro-developmental deterioration, severe orthopedic manifestations, and cardiopulmonary complications leading to death in early childhood. Although enzyme replacement therapy is available, HCT remains the only treatment that delivers the deficient enzyme to the central nervous system. Impressive results have been observed with allo-HCT in Hurler syndrome. The benefits that have been observed include improvements in neurocognitive functioning, joint integrity, motor development, linear growth, corneal clouding, cardiac function, and others. Survival of engrafted Hurler syndrome patients has been radically changed from that of untransplanted patients, with long-term survival data indicating that lifespan can be extended by many decades. An analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%.

In 2015, an international retrospective analysis reported on long-term results of 217 patients with Hurler syndrome who successfully underwent allo-HCT between 1985 and 2011. Median follow-up was 9.2 years (range, 3-23 years), median age at diagnosis was 9 months (range, 0-42 months), and median age at transplant was 16 months (range, 2-47 months). Primary study end points were neurodevelopmental outcomes and growth; secondary end points included outcomes involving several different organ systems. Pre-HCT, 56.9% of patients showed normal neurodevelopment, and 26.6% showed only mildly impaired neurodevelopment. At last follow-up post-HCT, normal or only mildly impaired neurodevelopment was observed in 26.9% and 28.3% of the patients, respectively, and 44.9% suffered from moderate to severely impaired neurodevelopment. Predictors of better outcomes posttransplant were higher baseline developmental and IQs pretransplant, younger age at transplant, and a normal α-L-iduronidase enzyme level posttransplant.

Experience with allo-HCT and an RIC regimen was reported in 2008 for 7 patients with Hurler syndrome. Six of the patients received transplants from unrelated donors, and one 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 1014 days (range, 726–2222 days) posttransplant.

Mynarek et al (2012) reported on the results of a retrospective, multicenter analysis of 17 patients with α-mannosidosis who underwent allo-HCT. Patients were diagnosed with the disease at a median age of 2.5 years (range, 1.1-23 years) and underwent allo-HCT 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), the OS rate was 88%. One patient died 76 days after transplantation from sepsis, GVHD, and pulmonary hemorrhage, and another patient died on day 135 posttransplant due to viral infections and multi-organ failure. Before allo-HCT, the extent of developmental delay in the 17 patients varied over a wide range. After allo-HCT, patients made some developmental progress; however, normal development was not achieved. Hearing ability improved in some but not all patients.

Fewer than 40 patients with globoid cell leukodystrophy have undergone allo-HCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.

Many patients with metachromatic leukodystrophy who have undergone allo-HCT and had long-term engraftment have had amelioration of the disease signs and symptoms and prolonged survival.

The few patients with Maroteaux-Lamy syndrome (MPS VI) or Sly syndrome (MPS VII) who have received transplants have shown promising results, with clinical improvement posttransplant.

Peroxisomal Disorders
Outcomes with allo-HCT 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, but reports of preservation of neuropsychologic and neurologic function have been presented.

Miller et al (2011) reported on the results of 60 boys who underwent allo-HCT for cerebral adrenoleukodystrophy between 2000 and 2009. Median age at transplantation was 8.7 years; conditioning regimens and allograft sources varied. At HCT, 50% demonstrated a Loes radiographic severity score of 10 or more, and 62% showed clinical evidence of neurologic dysfunction. A total of 78% (n=47) were alive at a median 3.7 years after allo-HCT. The 5-year survival estimate for boys with a Loes score less than 10 at HCT was 89%, whereas that for boys with a Loes score of 10 or more was 60% (p=0.03). The 5-year survival estimate for boys absent of clinical cerebral disease at HCT was 91%, whereas that for boys with neurologic dysfunction was 66% (p=0.08). The cumulative incidence of transplantation-related mortality at day 100 was 8%. Posttransplantation progression of neurologic dysfunction depended significantly on the pre-HCT Loes score and clinical neurologic status.

GENETIC DISORDERS AFFECTING SKELETAL TISSUE
A review article summarizes the experience with HCT and osteopetrosis.

The success of allo-HCT in infantile malignant osteopetrosis has depended greatly on the type of donor, with patients receiving grafts from HLA-identical siblings having a 5-year DFS rates of 73% to 79% vs transplantation with an unrelated or mismatched donor of 13% to 45%.[7]

A 2003 retrospective analysis of 122 children who received an allo-HCT for autosomal recessive osteopetrosis between 1980 and 2001 reported 5-year DFS rates of 73% for recipients of a genotype HLA-identical HCT (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).

SUMMARY OF EVIDENCE
For individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome disease, 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 OS, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in OS and other disease-specific outcomes. The exception has been the use of allo-HCT in the inherited metabolic diseases like Hunter, Sanfilippo, and Morquio syndromes. 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.

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04/15/2009	Medical Policy Committee approval. Coverage eligibility unchanged
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Entire policy redone.
04/07/2011	Medical Policy Committee approval
04/13/2011	Medical Policy Implementation Committee approval. No change to coverage.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/04/2013	Coding updated
04/04/2013	Medical Policy Committee review
04/24/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/03/2014	Medical Policy Committee review
04/23/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
10/29/2015	Medical Policy Committee review
11/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. “Stem” removed from title and Policy. HSCT changed to HCT in Policy and Policy Guidelines and text. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2018

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2016 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. *Applicable FARS/DFARS apply.*

Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias

Policy # 00055
Original Effective Date: 01/28/2002
Current Effective Date: 12/20/2017

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	D56.0-D56.8, D57.00-D57.02, D57.1, D57.20-D57.219, D57.40-D57.419, D57.80, D57.811-D57.819, D60.0-D60.9, D61.01-D61.09, D61.1-D61.3, D61.810-D61.818, D61.82, D61.89, D61.9, D70.0, D82.0, E75.21-E75.22, E75.240-E75.249, E75.3, E76.01-E76.03, E76.1, E76.210-E76.219, E76.22, E76.29, E76.3, E76.8-E76.9, E77.0-E77.9, Q78.2

*****Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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