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Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias

Policy # 00055
Original Effective Date: 01/28/2002
Current Effective Date: 04/23/2014

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.

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 stem-cell transplantation (HSCT) 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, leukocyte adhesion defect)

Inherited metabolic disease

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

Genetic disorders affecting skeletal tissue

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

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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 stem-cell transplantation (HSCT) for any other condition not listed above to be **investigational.***

Background/Overview

Hematopoietic Stem-Cell Transplantation
Hematopoietic stem-cell transplantation 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. Human leukocyte antigen 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 Hematopoietic Stem-Cell Transplantation
The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide [Cy], 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. 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 nearly 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. 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. 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.

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. 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.

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.

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia. Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities and pancytopenia. 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 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. 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.

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 five 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. 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.

Allogeneic HSCT has been used primarily 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 in 1980 in a patient with Hurler syndrome. Since that time, more than 1,000 transplants have been performed worldwide.

Table 1 Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other names
Mucopolysaccharidosis (MPS)	MPS I	Hurler, Scheie, H-S
	MPS II	Hunter
	MPS III A-D	Sanfilippo A-D
	MPS IV A-B	Morquio A-B
	MPS VI	Maroteaux-Lamy
	MPS VII	Sly
Sphingolipidosis	Fabry's	
	Farber's	Lipogranuomatosis
	Gaucher's I-III	
	GM_1 gangliosidosis	
	Niemann-Pick disease A and B	
	Tay-Sachs disease	
	Sandhoff's disease	
	Globoid 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	GSD type II	Pompe
Multiple enzyme deficiency	Galactosialidosis	

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	Mucolipidosis type II	I-cell Disease
Lysosomal transport defects	Cystinosis	
	Sialic acid storage disease	
	Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy	ALD
	Adrenomyeloneuropathy	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. 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 six months of age, and severe hematologic malfunction with bone marrow failure. Seventy percent of these patients die before the age of six, often of recurrent infections. Hematopoietic stem-cell transplantation is the only curative therapy for this fatal disease.

1. The following lists the immunodeficiencies that have been successfully treated by allogeneic 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
Interleuken-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

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Phagocytic deficiencies
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

Other immunodeficiencies
Autoimmune lymphoproliferative syndrome
Cartilage hair hypoplasia
CD25 deficiency
Hyper IgD and IgE syndromes
CF syndrome
IPEX syndrome
NEMO deficiency
NF-KB inhibitor, alpha (IKB-alpha) deficiency
Nijmegen breakage syndrome

2. In the inherited metabolic disorders, allogeneic HSCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid-cell leukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis and aspartylglucosaminuria. Allogeneic HSCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM_1, gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HSCT has not been effective in Hunter, Sanfilippo or Morquio syndromes.

The experience with RIC and allogeneic HSCT for the diseases listed in this policy has been limited to small numbers of patients, and have yielded mixed results, depending upon 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 adult patients, severe graft versus host disease (GVHD). Several Phase II/III trials are ongoing examining the role of this type of transplant for these diseases, as outlined in the clinical trial section under each disease type.

Rationale/Source

Hemoglobinopathies

Two 2010 review articles summarize the experience to date with HSCT and the hemoglobinopathies.

As of 2008, more than 1,600 patients worldwide have been treated for beta-thalassemia with allogeneic HSCT. Overall survival rates have ranged from 65–100% and thalassemia-free survival up to 73%. The

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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). 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.

Most of the experience with allogeneic HSCT and sickle cell disease comes from three major clinical series. The largest series to date consisted of 87 symptomatic patients, the majority of whom received donor allografts from siblings who are HLA identical. The results from this series and the other 2 were similar, with overall survival (OS) rates ranging from 92–94% and event-free survival from 82–86%, with a median follow-up ranging from 0.9–17.9 years.

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%), and, in adult patients, severe GVHD has been observed with the use of RIC regimens.

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. 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.

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

Online site 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)

Several Phase II trials are also recruiting patients with a hemoglobinopathy for allogeneic HSCT, including with RIC.

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Bone marrow failure syndromes
Two 2010 review articles summarize the experience to date with HSCT and the bone marrow failure syndromes.

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

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%. Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease. The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year OS rates were 13% and 52% in patients who received nonfludarabine (non-Flu) versus fludarabine (Flu)-based regimens.

Zanis-Neto and colleagues reported the results of 30 patients with Fanconi anemia treated with RIC regimens, consisting of low-dose Cy. Seven patients were treated with Cy 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 Cy 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 Flu-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year OS (52% vs. 13%, respectively; p less than 0.001) compared with non-Flu regimens.

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

Experience with allogeneic HSCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease. 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). 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 five (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. 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. The CIBMTR reported the results in 61 patients who underwent HSCT between 1984 and 2000. 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.

A randomized Phase III trial compared 2 different conditioning regimens in high-risk aplastic anemia patients (n = 79) who underwent allogeneic HSCT. Patients in the Cy plus anti-thymocyte globulin (ATG) arm (n = 39) received Cy at 200 mg/kg; those in the Cy-Flu-ATG group (n = 40) received Cy at 100 mg/kg and Flu at 150 mg/m^2 (NCT01145976). 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 in the Cy-ATG arm but did not differ significantly between arms. Overall survival at 4 years did not differ between the Cy-ATG and Cy-Flu-ATG arms (78% vs. 86%, respectively, p = 0.41). Although this study was underpowered to detect real differences between the conditioning regimens, the results suggest an RIC regimen with Cy-Flu-ATG appears to be as safe as a more traditional myeloablative regimen comprising Cy-ATG in allogeneic HSCT.

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 Cy and ATG versus Flu 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 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.

Hematopoietic stem cell transplantation 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. 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. Since 2000, OS for patients with SCID who have undergone HSCT is 71%.

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. 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. Fifty-five transplants were from HLA-identical sibling donors, with a 5-year probability of survival of 87% (95% 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. 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.

Studies so far indicate 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 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 five 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 ongoing to determine the efficacy of a preparative regimen of busulfan, Cy, and 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 ongoing 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.

In the past 25 years, HSCT has been performed in approximately 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders. 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. With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up. 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.

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. 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. An analysis of nearly 150 transplanted patients with Hurler syndrome showed an OS rate of more than 80%.

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Experience with allogeneic HSCT and a reduced-intensity preparative regimen has been reported in seven 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 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.

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, but reports of preservation of neuropsychologic and neurologic function have been made.

Miller and colleagues reported the results of 60 boys who underwent allogeneic HSCT for cerebral adrenoleukodystrophy (cALD) between 2000 to 2009. The median age at HSCT was 8.7 years; conditioning regimens and allograft sources varied. At HSCT, 50% demonstrated a Loes radiographic severity score ≥ 10, and 62% showed clinical evidence of neurologic dysfunction. A total of 78% (n = 47) are alive at a median 3.7 years after HSCT. The estimate of 5-year survival for boys with Loes score < 10 at HSCT was 89%, whereas that for boys with Loes score ≥ 10 was 60% (p = 0.03). The 5-year survival estimate for boys absent of clinical cerebral disease at HSCT 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%. Post-transplantation progression of neurologic dysfunction depended significantly on the pre-HSCT Loes score and clinical neurologic status.

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.

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.

Mynarek and colleagues reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HSCT. 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. Experience with allogeneic HSCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly. Some authors suggest that HSCT would not be justifiable in the attenuated form because the risks outweigh the possible benefits.

Eight patients with Hunter syndrome received an allogeneic HSCT between the ages of 3 and 16 years. 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 two 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 two 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. The literature addressing the use of HSCT in Sanfilippo disease consists of two case reports. Vellodi and colleagues reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HSCT and were followed up for nine years. At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next eight 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.

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).

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An open–label, nonrandomized Phase II study for allogeneic HSCT for high-risk inherited inborn errors using a RIC regimen is currently recruiting patients. Outcome measures are to evaluate the ability to achieve donor cell engraftment and to determine the toxicity associated with this regimen. The estimated enrollment is 30, and the estimated study completion date is September 2011 (NCT00383448).

Infantile Malignant Osteopetrosis
A 2010 review article summarizes the experience to date with HSCT and osteopetrosis.

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%.

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 one 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).

ClinicalTrials.gov
Two open-label nonrandomized Phase II/III trials are ongoing, 1 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 ongoing 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, input was received from 3 reviewers from 1 physician specialty society and 3 academic medical centers while this policy was under review for September 2009. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. 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.

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

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Allogeneic Hematopoietic Stem-Cell Transplantation for Genetic Diseases and Acquired Anemias", 8.01.22, 9:2013.
2. Bhatia M, Walters MC. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. Bone Marrow Transplant 2008; 41(2):109-17.
3. Mehta P. Hematopoietic stem cell transplantation for inherited bone marrow failure syndromes. In: Mehta P, ed. *Pediatric Stem Cell Transplantation* . Sudbury, MA: Jones and Bartlett Publishers; 2004:281-316.
4. Gluckman E, Wagner JE. Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome. Bone Marrow Transplant 2008; 41(2):127-32.
5. Gennery AR, Cant AJ. Advances in hematopoietic stem cell transplantation for primary immunodeficiency. Immunol Allergy Clin North Am 2008; 28(2):439-56.
6. Porta F, Forino C, De Martiis D et al. Stem cell transplantation for primary immunodeficiencies. Bone Marrow Transplant 2008; 41(suppl 2):S83-6.
7. Prasad VK, Kurtzberg J. Emerging trends in transplantation of inherited metabolic diseases. Bone Marrow Transplant 2008; 41(2):99-108.
8. Askmyr MK, Fasth A, Richter J. Towards a better understanding and new therapeutics of osteopetrosis. Br J Haematol 2008; 140(6):597-609.
9. Mehta P. Metabolic diseases. In: Mehta P, ed. *Pediatric Stem Cell Transplantation* . Sudbury, MA: Jones and Bartlett Publishers; 2004:233-58.
10. MacMillan ML, Walters MC, Gluckman E. Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies. Semin Hematol 2010; 47(1):37-45.
11. Smiers F, Krishnamurti L, Lucarelli G. Hematopoietic stem cell transplantation for hemoglobinopathies: current practice and emerging trends. Pediatr Clin N Am 2010; 57(1):181-205.
12. Mehta P. Hematopoietic stem cell transplantation for hemoglobinopathies. In: Mehta P, ed. *Pediatric Stem Cell Transplantation* . Sudbury, MA: Jones and Bartlett Publishers; 2004:259-79.
13. Bernaudin F, Socie G, Kuentz M et al. Long-term results of related, myeloablative stem cell transplantation to cure sickle cell disease. Blood 2007; 110(7):2749-56.
14. Walters MC, Patience M, Leisenring W et al. Bone marrow transplantation for sickle cell disease. N Engl J Med 1996; 335(6):369-76.
15. Walters MC, Storb R, Patience M et al. Impact of bone marrow transplantation for symptomatic sickle cell disease an interim report: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. Blood 2000; 95(6):1918-24.
16. Bernardo ME, Piras E, Vacca A et al. Allogeneic hematopoietic stem cell transplantation in thalassemia major: results of a reduced-toxicity conditioning regimen based on the use of treosulfan. Blood 2012; 120(2):473-6.
17. Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev 2013; 5:CD007001.
18. Mehta P, Locatelli F, Stary J et al. Bone marrow transplantation for inherited bone marrow failure syndromes. Pediatr Clin N Am 2010; 57(1):147-70.
19. Dufour C, Svahn J. Fanconi anaemia: new strategies. Bone Marrow Transplant 2008; 41(suppl 2):S90-5.
20. Zanis-Neto J, Flowers ME, Medeiros CR et al. Low-dose cyclophosphamide conditioning for haematopoietic cell transplantation from HLA-matched related donors in patients with Fanconi anaemia. Br J Haematol 2005; 130(1):99-106.
21. Wagner JE, Eapen M, MacMillan ML et al. Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. Blood 2007; 109(5):2256–62.
22. Cesaro S, Oneto R, Messina C et al. Haematopoietic stem cell transplantation for Shwachman-Diamond disease: a study from the European Group for Blood and Marrow Transplantation. Br J Haematol 2005; 131(2):231-6.
23. Roy V, Perez WS, Eapen M et al. Bone marrow transplantation for Diamond-Blackfan anemia. Biol Blood Marrow Transplant 2005; 11(8):600-8.

24. Kim H, Lee JH, Joo YD et al. A randomized comparison of cyclophosphamide vs. reduced dose cyclophosphamide plus fludarabine for allogeneic hematopoietic cell transplantation in patients with aplastic anemia and hypoplastic myelodysplastic syndrome. Ann Hematol 2012; 91(9):1459-69.
25. Smith AR, Gross TG, Baker KS. Transplant outcomes for primary immunodeficiency disease. Semin Hematol 2010; 47(1):79-85.
26. Szabolcs P, Cavazzana-Calvo M, Fischer A et al. Bone marrow transplantation for primary immunodeficiency diseases. Pediatr Clin N Am 2010; 57(1):207-37.
27. Filipovich AH. Hematopoietic cell transplantation for correction of primary immunodeficiencies. Bone Marrow Transplant 2008; 42(suppl 1):S49-52.
28. Hassan A, Booth C, Brightwell A et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase deficient severe combined immunodeficiency. Blood 2012 [Epub ahead of print].
29. Filipovich AH, Stone J, Tomany SC et al. Impact of donor type on outcome of bone marrow transplantation for Wiskott-Aldrich syndrome: collaborative study of the International Bone Marrow Transplant Registry and the National Marrow Donor Program. Blood 2001; 97(6):1598-603.
30. Moratto D, Giliani S, Bonfim C et al. Long-term outcome and lineage-specific chimerism in 194 patients with Wiskott-Aldrich syndrome treated by hematopoietic cell transplantation in the period 1980-2009: an international collaborative study. Blood 2011; 118(6):1675-84.
31. Boelens JJ, Prasad VK, Tolar J et al. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. Pediatr Clin North Am 2010; 57(1):123-45.
32. Prasad VK, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. Semin Hematol 2010; 47(1):59-69.
33. Rovelli AM. The controversial and changing role of haematopoietic cell transplantation for lysosomal storage disorders: an update. Bone Marrow Transplant 2008; 41(suppl 2):S87-9.
34. Boelens JJ, Wynn RF, O'Meara A et al. Outcomes of haematopoietic cell transplantation for MPS-1 in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant 2007; 40(3):225-33.
35. Hansen MD, Filipovich AH, Davies SM et al. Allogeneic hematopoietic cell transplantation (HCT) in Hurler's syndrome using a reduced intensity preparative regimen. Bone Marrow Transplant 2008; 41(4):349-53.
36. Mynarek M, Tolar J, Albert MH et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant 2012; 47(3):352-9.
37. Guffon N, Bertrand Y, Forest I et al. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. J Pediatr 2009; 154(5):733-7.
38. Vellodi A, Young E, New M et al. Bone marrow transplantation for Sanfilippo disease type B. J Inherit Metab Dis 1992; 15(6):911-8.
39. Bordigoni P, Vidailbet M, Lena M et al. Bone marrow transplantation for Sanfilippo syndrome. In: Hobbs JR, ed. *Correction of Certain Genetic Diseases by Transplantation* . London: Cogent; 1989:114-9.
40. Steward CG. Hematopoietic stem cell transplantation for osteopetrosis. Pediatr Clin N Am 2010; 57(1):171-80.
41. Driessen GJ, Gerritsen EJ, Fischer A et al. Long-term outcome of hematopoietic stem cell transplantation in autosomal recessive osteopetrosis: an EBMT report. Bone Marrow Transplant 2003; 32(7):657-63.

Coding

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Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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
HCPCS	S2140, S2142, S2150
ICD-9 Diagnosis	272.7, 277.5, 279.12, 282.41 thru 282.49, 282.60 thru 282.69, 284.01 thru 284.9, 288.01, 756.52
ICD-9 Procedure	41.00, 41.02, 41.03, 41.05, 41.06, 41.08, 41.91, 99.79

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12/06/2000	Medical Policy Committee review
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04/20/2004	Medical Policy Committee review. Format revision. No substance change to policy.
04/26/2004	Managed Care Advisory Council approval
04/05/2005	Medical Director review
04/27/2005	Medical Policy Committee review. Format revisions. Policy unchanged.
05/23/2005	Managed Care Advisory Council approval
05/03/2006	Medical Director review
05/17/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. Coverage eligibility unchanged.
04/02/2009	Medical Director review
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.
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*****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:
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    3. reference to federal regulations.

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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.

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