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**Medical Policy Manual**

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

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

## DESCRIPTION[1]

### Hematopoietic Stem-Cell Transplantation

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

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

### Preparative Conditioning for Allogeneic Hematopoietic SCT

The conventional practice of allogeneic HSCT involves administration of myelotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow failure. Reduced-intensity conditioning (RIC) refers to chemotherapy regimens that seek to reduce adverse effects secondary to bone marrow toxicity. 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.[2] 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.[2] 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.[2]

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.[3] 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.[4] Early mortality is associated with bone marrow failure, infections, pulmonary complications, or malignancy.[4]

Mutations affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome, and Diamond-Blackfan anemia.[4] Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities and cytopenias, with some patients developing

aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially acute myelogenous leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow with 30% of patients also having a variety of physical anomalies.[4]

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.[5] The most severe defects (collectively known as severe combined immunodeficiency or SCID) cause an absence or dysfunction of T lymphocytes, and sometimes B lymphocytes and natural killer cells.[5] 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.[5] 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.[6]

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.[7] 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.[7] Hurler syndrome usually leads to premature death by 5 years of age.

Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs don't cross the blood-brain barrier, which results in ineffective treatment of the central nervous system. Stem-cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier.[7] 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.[7]

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.[7] 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.[7]

**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<br>MPS VI<br>MPS VII | Morquio A-B<br>Maroteaux-Lamy<br>Sly |
| **Sphingolipidosis** | Fabry's<br>Farber's<br>Gaucher's I-III<br>GM1 gangliosidosis<br>Niemann-Pick disease A and B<br>Tay-Sachs disease<br>Sandhoff's disease<br>Globoid leukodystrophy<br>Metachromatic leukodystrophy | <br>Lipogranulomatosis<br><br><br><br><br><br>Krabbe disease<br>MLD |
| **Glycoproteinosis** | Aspartylglucosaminuria<br>Fucosidosis<br>alpha-Mannosidosis<br>beta-Mannosidosis<br>Mucolipidosis III and IV | <br><br><br><br>Sialidosis |
| **Other lipidoses** | Niemann-Pick disease C<br>Wolman disease<br>Ceroid lipofuscinosis | <br><br>Type III-Batten disease |
| **Glycogen storage** | GSD type II | Pompe |
| **Multiple enzyme deficiency** | Galactosialidosis<br>Mucolipidosis type II | <br>I-cell disease |
| **Lysosomal transport defects** | Cystinosis<br>Sialic acid storage disease<br>Salla disease | |
| **Peroxisomal storage disorders** | Adrenoleukodystrophy<br>Adrenomyeloneuropathy | ALD<br>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.[8] Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis.

Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately 6 months of age, and severe hematologic malfunction with bone marrow failure.[8] Seventy percent of these patients die before the age of 6, often of recurrent infections.[8] HSCT is the only curative therapy for this fatal disease.

**MEDICAL POLICY CRITERIA**

Allogeneic hematopoietic stem cell transplantation, using myeloablative or reduced-intensity conditioning, may be considered **medically necessary** for selected patients with the following disorders:

I. Hemoglobinopathies

A. 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.

Factors associated with a high risk of stroke or end-organ damage include: recurrent chest syndrome, recurrent vaso-occlusive crises, red blood cell alloimmunization on chronic transfusion therapy.

B. Homozygous beta-thalassemia (i.e., thalassemia major)

II. Bone marrow failure syndromes

A. Hereditary

1. Inherited aplastic anemia

2. Fanconi anemia

3. Dyskeratosis congenita

4. Shwachman-Diamond

5. Diamond-Blackfan

B. Acquired

1. Bone marrow failure syndromes secondary to drug or toxin exposure

2. Acquired aplastic anemia (i.e., pancytopenia with hypocellular bone marrow)

III. Primary immunodeficiencies (See Policy Guideline #1.)

A. Absent or defective T-cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)

B. Absent or defective natural killer function (e.g. Chediak-Higashi syndrome)

C. Absent or defective neutrophil function (e.g. Kostmann syndrome, chronic granulomatous

disease, leukocyte adhesion defect)

IV. Inherited metabolic disorders (See Policy Guideline # 2.)

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

V. Genetic disorders affecting skeletal tissue

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

**Policy Guidelines**

1. Immunodeficiencies

The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem-cell transplantation (HSCT)[5]

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

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
ICF syndrome
IPEX syndrome
NEMO deficiency
NF-KB inhibitor, alpha (IKB-alpha) deficiency
Nijmegen breakage syndrome

2. Inherited metabolic disorders

Allogeneic HSCT has been proven effective in some cases of:

Alpha-mannosidosis
Aspartylglucosaminuria
Childhood onset cerebral X-linked adrenoleukodystrophy
Globoid-cell leukodystrophy
Hurler Syndrome
Maroteaux-Lamy Syndrome
Metachromatic leukodystrophy
Sly Syndromes,

Allogeneic HSCT is possibly effective for:

Farber lipogranulomatosis
Fucosidosis
Galactosialidosis
Gangliosidosis
Gaucher types 1 and 3
$GM_1$
Mucolipidosis II (I-cell disease)
Multiple sulfatase deficiency
Niemann-Pick disease
Neuronal ceroid lipofuscinosis
Sialidosis
Wolman disease.

Allogeneic HSCT has not been effective in:

Hunter syndrome
Morquio syndrome
Sanfilippo syndrome[9]

## SCIENTIFIC EVIDENCE[1]

The experience with reduced-intensity conditioning (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).

### Hemoglobinopathies

In a 2013 Cochrane review, authors determined whether stem cell transplantation improves survival and prevent symptoms and complications associated with sickle cell disease.[10] In addition, authors examined the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease. Selection criteria was limited to randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, gender and setting. Though 10 trials were identified, no trials met the inclusion criteria for the review. Authors conclude that studies on the use of hematopoietic stem cell for treatment of sickle cell disease are limited to observational and other less robust studies. Authors did not identify any randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations. This systematic review identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.

Most of the experience with allogeneic HSCT and sickle cell disease comes from three major clinical series[2] and were included in the review process of the Cochrane review described above. The largest series to date consisted of 87 symptomatic patients, the majority of whom received donor allografts from siblings who are human leukocyte antigen (HLA) identical. The results from this series[11] and the other two[12,13] were similar, with overall survival rates ranging from 92%–94% and event-free survival from 82%–86% with a median follow-up ranging from 0.9–17.9 years.[2] However, these described studies did not meet criteria to be included in the 2013 Cochrane review.

More than 1,600 patients worldwide have been treated for beta-thalassemia with allogeneic hematopoietic stem-cell transplant (HSCT).[2] Overall survival rates have ranged from 65%–100% and thalassemia-free survival up to 73%.[2] The Pesaro risk stratification system classifies patients with thalassemia who are to undergo allogeneic HSCT into risk groups I through III on the presence of hepatomegaly, portal fibrosis, or adequacy of chelation (class I having no risk factors, II with 2 risk factors, and III with all 3).[14] The outcome of allogeneic HSCT in over 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.[14]

Experience with reduced-intensity preparative regimens and allogeneic HSCT for the hemoglobinopathies is limited to a small number of patients. In adult patients, severe GVHD has been observed with the use of RIC regimens.[15] Challenges with high rates of graft rejection (10%–30%) may be due to hemoglobinopathy patients possibly being allosensitized due to repeated blood transfusions and, as opposed to cancer patients who may undergo RIC allogeneic transplants, patients with hemoglobinopathies have received no prior immunosuppressive therapies and may even have significant bone marrow hyperplasia.[14]

Bernardo and colleagues reported the results of 60 thalassemia patients (median age, 7 years; range, 1-37) who underwent allogeneic HSCT after a reduced-intensity conditioning regimen based on the treosulfan.[16] 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.

**Bone Marrow Failure Syndromes**

Two 2010 review articles summarize the experience to date with HSCT and the bone marrow failure syndromes.[17,18]

Fanconi anemia

In Fanconi anemia, bone marrow transplant 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.[3]

In a summary of allogeneic HSCT from matched related donors over the past 6 years in Fanconi anemia, totaling 103 patients, overall survival ranged from 83%–88% with transplant-related mortality ranging from 8%–18.5% and average chronic graft-versus-host disease (GVHD) of 12%.[19]

The outcomes in patients with Fanconi anemia and an unrelated donor allogeneic HSCT are not 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%.[4] Causes of death included infection, hemorrhage, acute and chronic GVHD, and liver veno-occlusive disease.[4] The Center for International Blood and Marrow Transplantation (CIBMTR) analyzed 98 patients transplanted with unrelated donor marrow between 1990 and 2003. Three-year overall survival rates were 13% and 52% in patients who received non-fludarabine versus fludarabine-based regimens.[4]

Zanis-Neto and colleagues reported the results of 30 patients with Fanconi anemia treated with reduced-intensity conditioning (RIC) regimens, consisting of low-dose cyclophosphamide.[20] Seven patients were treated with cyclophosphamide at 80 mg/kg and 23 with 60 mg/kg. Grade 2-3 acute GVHD rates were 57% and 14% for patients who received the higher and lower doses, respectively (p=0.001). Four of the 7 patients who received the higher dose were alive at a median of 47 months (range: 44-58), and 22 of 23 given the lower dose were alive at a median of 16 months (range: 3-52). The authors concluded

that a lower dose of cyclophosphamide conditioning had lower rates of GVHD and was acceptable for engraftment.

In a retrospective study of 98 unrelated donor transplantations for Fanconi anemia reported to the CIBMTR, Wagner and colleagues reported that fludarabine-containing (reduced-intensity) regimens were associated with improved engraftment, decreased treatment-related mortality, and improved 3-year overall survival (OS) (52% vs. 13%, respectively; p less than 0.001) compared with nonfludarabine regimens.[21]

Other

Results with allogeneic HSCT in dyskeratosis congenita have been disappointing due to severe late effects, including diffuse vasculitis and lung fibrosis.[4] Currently, nonmyeloablative conditioning regimens with fludarabine are being explored; however, very few results are available at this time.[4]

Experience with allogeneic HSCT in Shwachman-Diamond syndrome is limited, as very few patients have undergone allogeneic transplants for this disease.[4] 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).[22] Various preparative regimens were used; most included either busulfan (54%) or total body irradiation (23%) followed by an HLA-matched sibling (n= 6), mismatched related (n= 1), or unrelated graft (n=19). Graft failure occurred in 5 (19%) patients, and the incidence of grade III to IV acute and chronic GVHD were 24% and 29%, respectively. With a median follow-up of 1.1 years, OS was 65%. Deaths were primarily caused by infections with or without GVHD (n=5) or major organ toxicities (n=3). The analysis suggested that presence of MDS-AML or use of total body irradiation–based conditioning regimens were factors associated with a poorer outcome.

In Diamond-Blackfan anemia, allogeneic HSCT is an option in corticosteroid-resistant disease.[4] 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% if recipients received HLA-identical sibling grafts, but poor in recipients of alternative donors.[4] The CIBMTR reported the results in 61 patients who underwent HSCT between 1984 and 2000.[23] Sixty-seven percent of patients were transplanted with an HLA-identical sibling donor. Probability of overall survival after transplantation for patients transplanted from an HLA-identical sibling donor (versus an alternative donor) was 78% versus 45% [p=.01] at 1 year and 76% versus 39% [p=.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.[24] Patients in the cyclophosphamide (Cy) plus anti-thymocyte globulin (ATG) arm (n=39) received Cy at 200 mg/kg; those in the Cy-fludarabine (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 reported to be underpowered by authors 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.

**Primary Immunodeficiencies**

Two 2010 review articles summarize the experience to date with HSCT and the primary immunodeficiencies.[25,26]

Currently, HSCT using HLA-identical sibling donors can provide correction of underlying primary immunodeficiencies such as severe combined immunodeficiency (SCID), Wiskott-Aldrich syndrome, and other prematurely lethal X-linked immunodeficiencies in approximately 90% of cases.[27] 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.[27] Since 2000, overall survival for patients with SCID who have undergone HSCT is 71%.[5]

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.[28] 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.[29] Fifty-five transplants were from HLA-identical sibling donors, with a 5-year probability of survival of 87% (95% confidence interval [CI]: 74–93%); 48 were from other relatives, with a 5-year probability of survival of 52% (37–65%); and 67 were from unrelated donors with a 5-year probability of survival of 71% (58%–80%; p=.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.[30] 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 in outcomes 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, overall survival rates are 74%, with even better results (90%) with well-matched donors for defined conditions such as chronic granulomatous disease.[5]

Studies so far indicate that RIC regimens may have an important role in treating patients with primary immunodeficiency.[26] In the absence of prospective or larger registry studies, it is not possible to prove superiority of RIC in more stable patients with primary immunodeficiency; however, RIC does offer the advantage that long-term sequelae, e.g., infertility and growth retardation, may be avoided or reduced. Currently, RIC HSCT using unrelated donors may offer a survival advantage in patients with T-cell deficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich syndrome (older than 5 years of age), and chronic granulomatous disease with ongoing inflammatory or infective complications. Minimal intensity conditioning HSCT may be particularly suited to unrelated donor HSCT in young SCID patients with significant comorbidities.

**Inherited Metabolic Disorders**

Two 2010 review articles summarize the experience to date with HSCT and the inherited metabolic diseases.[31,32]

In the past 25 years, HSCT has been performed in about 20 of the approximately 40 known lysosomal storage disorders and peroxisomal storage disorders.[7] The majority (>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.[7] With the exception of Hurler and globoid cell leukodystrophy, most published data are single case reports or small series with short follow-up.[33] 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 neurological symptoms or in those with aggressive infantile forms.[33]

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.[7] 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.[9] An analysis of nearly 150 transplanted patients with Hurler syndrome showed an overall survival rate of more than 80%.[34]

Experience with allogeneic HSCT and a reduced-intensity preparative regimen has been reported in 7 patients with Hurler syndrome.[35] Six of the patients received transplants from unrelated donors and 1 received the transplant from a sibling. All patients had initial donor engraftment at 100 days, and there were no reports of severe acute GVHD. Six of the 7 children were alive at a median of 1,014 days (range: 726–2,222 days) post-transplant.

The few patients with Maroteaux-Lamy and Sly syndrome that have received transplants have shown promising results, with clinical improvement post-transplant.[9]

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

Fewer than 40 patients with globoid-cell leukodystrophy have undergone allogeneic HSCT; however, there have been reports of dramatic improvements in neurologic, neuropsychologic, and neurophysiologic function.[9]

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.[9]

Mynarek and colleagues reported the results of a retrospective, multicenter analysis of 17 patients with alpha-mannosidosis who underwent allogeneic HSCT.[36] 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.[9] Experience with allogeneic HSCT in patients with severe Hunter syndrome has shown that it has failed to alter the disease course favorably or significantly.[9] Some authors suggest that HSCT would not be justifiable in the attenuated form, because the risks outweigh the possible benefits.[9]

Eight patients with Hunter syndrome received an allogeneic HSCT between the ages of 3 and 16 years.[37] In 6 cases, the donor was a sibling with identical HLA status, in 1 case, the donor was unrelated HLA-compatible, and in 1 case, the donor was a mismatched unrelated donor. The severity of disease prior to transplant was rated by assessing the age at diagnosis, behavior, and intelligence quotient (IQ) at the time of graft and genotype. Five patients were considered to have severe CNS involvement (i.e., diagnosis before the age of 4 years and an IQ less than 80), 2 were considered to have the attenuated form (i.e., diagnosis at 5 years and normal IQ), and 1 as intermediate (i.e., diagnosis after the age of 4 and IQ between 80 and 90). After follow-up ranging from 7 to 17 years, all were still alive with the exception of 1 patient who died of unrelated causes. Successful engraftment was achieved in all patients and cardiovascular abnormalities stabilized in all patients, hepatosplenomegaly resolved, and joint stiffness improved. Perceptual hearing defects remained stable, and transmission hearing defects improved. Neuropsychological outcome was variable: the 2 patients with the attenuated phenotype reached adulthood with normal IQ, social and scholastic development, and no language impairment. Four patients with the severe form of the syndrome deteriorated after the graft, and their IQ/developmental quotient had declined below 50 at the time of the last evaluation. Of the patients with the severe form, 3 lost the ability to walk in their early teens, 2 lost language at 9 and 11 years, and 2 developed epilepsy. The remaining 2 patients with the severe form required special schooling and had poor social and language skills.

Experience with allogeneic HSCT in patients with MPS III (Sanfilippo syndrome) has also been disappointing, with no alteration in the course of neuropsychologic deterioration seen in these patients.[9] The literature addressing the use of HSCT in Sanfilippo disease consists of 2 case reports.[38,39] Vellodi and colleagues reported the outcomes of twin girls diagnosed with MPS III who underwent allogeneic HSCT and were followed up for 9 years.[38] At the time of transplant, both girls were functioning in the low average range of intellectual development. Over the next 8 years, both girls had a steady decline in cognitive development and both functioned in the area of significant developmental delay. The authors postulated that a possible reason for continued deterioration in the twins, despite the demonstration of full chimerism, was a very low level of enzyme throughout the years after transplant. One other patient with MPS III who had received a transplant was 5.3 years old at the time of the transplant, and continued to regress post-transplant.[39]

**Infantile Malignant Osteopetrosis**

A 2010 review article summarizes the experience to date with HSCT and osteopetrosis.[40]

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%.[8]

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).[41]

**Summary**

Overall, the evidence suggests that for certain genetic diseases and acquired anemias, allogeneic hematopoietic stem cell transplant may improve health outcomes; therefore, this procedure may be considered medically necessary for the conditions listed in the policy criteria.

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| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| CPT | 38204 | Management of recipient hematopoietic cell donor search and cell acquisition |
| | 38205 | Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic |

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| | 38206 | ;autologous |
| | 38207 | Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage |
| | 38208 | ;thawing of previously frozen harvest, without washing, per donor |
| | 38209 | ;thawing of previously frozen harvest with washing, per donor |
| | 38210 | ;specific cell depletion with harvest, T cell depletion |
| | 38211 | ;tumor cell depletion |
| | 38212 | ;red blood cell removal |
| | 38213 | ;platelet depletion |
| | 38214 | ;plasma (volume) depletion |
| | 38215 | ;cell concentration in plasma, mononuclear, or buffy coat layer |
| | 38220 | Bone marrow; aspiration only |
| | 38221 | Bone marrow; biopsy, needle or trocar |
| | 38230 | Bone marrow harvesting for transplantation; allogeneic |
| | 38232 | Bone marrow harvesting for transplantation; autologous |
| | 38240 | Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic |
| | 38241 | ;autologous |
| | 38242 | Allogeneic donor lymphocyte infusions |
| | 38243 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor, HPC boost |
| HCPCS | J9000–J9999 | Chemotherapy drugs code range |
| | Q0083–Q0085 | Chemotherapy administration code range |
| | S2140 | Cord blood harvesting for transplantation; allogeneic |
| | S2142 | Cord blood derived stem-cell transplantation, allogeneic |

| CODES | NUMBER | DESCRIPTION |
|---|---|---|
| | S2150 | Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services) |