MEDICAL POLICY

POLICY TITLE	ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR GENETIC DISEASES AND ACQUIRED ANEMIAS
POLICY NUMBER	MP 9.055

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**11/1/2024**

I. POLICY

Allogeneic hematopoietic cell transplantation is considered **medically necessary** for select patients with the following disorders:

Hemoglobinopathies

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

Bone marrow failure syndromes

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

Primary immunodeficiencies

- Absent or defective T cell function (e.g., severe combined immunodeficiency, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome)
- Absent or defective natural killer function (e.g., Chediak-Higashi syndrome)
- Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect)
  (See Policy Guideline # 1.)

Inherited metabolic disease

- Lysosomal and peroxisomal storage disorders except Hunter, Sanfilippo, and Morquio syndromes
  (See Policy Guideline # 2)

Genetic disorders affecting skeletal tissue

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

POLICY GUIDELINES

Guideline 1

The following lists the immunodeficiencies that have been successfully treated by allogeneic hematopoietic cell transplantation (allo-HCT) (Gennery & Cant et al, 2008).

Lymphocyte Immunodeficiencies

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

Phagocytic Deficiencies

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

Other Immunodeficiencies

- Autoimmune lymphoproliferative syndrome
- Cartilage hair hypoplasia
- CD25 deficiency
- Hyper IgD and IgE syndromes
- Immunodeficiency, centromeric instability, and facial dysmorphism syndrome
- Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome
- Nuclear factor-κ B (NF-κB) essential modulator deficiency
- NF-κB inhibitor, alpha (IκB-alpha) deficiency
- Nijmegen breakage syndrome

Guideline 2

For inherited metabolic disorders, allo-HCT has been proven effective in some cases of Hurler, Maroteaux-Lamy, and Sly syndromes, childhood onset cerebral X-linked adrenoleukodystrophy, globoid cell leukodystrophy, metachromatic leukodystrophy, alpha-mannosidosis, and aspartylglucosaminuria. Allogeneic HCT is possibly effective for fucosidosis, Gaucher types 1 and 3, Farber lipogranulomatosis, galactosialidosis, GM_1 gangliosidosis, mucolipidosis II (I-cell disease), multiple sulfatase deficiency, Niemann-Pick disease, neuronal ceroid lipofuscinosis, sialidosis, and Wolman disease. Allogeneic HCT has not been effective in Hunter, Sanfilippo, or Morquio syndromes (Mehta, 2004).

The experience with reduced-intensity conditioning and allo-HCT for the diseases listed in this evidence review has been limited to small numbers of patients and has yielded mixed results, depending on the disease category. In general, the results have been most promising in the bone marrow failure syndromes and primary immunodeficiencies. In the hemoglobinopathies, success has been hampered by difficulties with high rates of graft rejection, and in adults, severe graft-versus-host-disease. Phase 2/3 trials are ongoing or completed examining the role of this type of transplant for these diseases, as outlined in the Ongoing and Unpublished Clinical Trials.

Cross references:

MP 9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.
MP 9.053 Hematopoietic Cell Transplantation for Autoimmune Diseases

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

FEP PPO:

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

TOP

Genetic Diseases and Acquired Anemias

Hemoglobinopathies

Thalassemias result from variants in the globin genes, resulting in reduced or absent hemoglobin production, thereby reducing oxygen delivery. The supportive treatment of β-thalassemia major requires life-long red blood cell transfusions that lead to progressive iron overload and the potential for organ damage and impaired cardiac, hepatic, and endocrine function. Sickle cell disease is caused by a single amino acid substitution in the beta chain of hemoglobin and, unlike thalassemia major, has a variable course of clinical severity. Sickle cell disease typically manifests clinically with anemia, severe painful crises, acute chest syndrome, stroke, chronic pulmonary and renal dysfunction, growth retardation, neurologic deficits, and premature death. The mean age of death for patients with sickle cell disease has been demonstrated as 42 years for men and 48 for women.

Treatment

The only definitive cure for thalassemia is to correct the genetic defect with allogeneic hematopoietic cell transplantation (allo-HCT).

Three major therapeutic options are available for sickle cell disease: chronic blood transfusions, hydroxyurea, and allo-HCT, the latter being the only possibility for cure.

Bone Marrow Failure Syndromes

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

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

Variants affecting ribosome assembly and function are associated with Shwachman-Diamond syndrome and Diamond-Blackfan syndrome. Shwachman-Diamond has clinical features that include pancreatic exocrine insufficiency, skeletal abnormalities, and cytopenias, with some patients developing aplastic anemia. As with other bone marrow failure syndromes, patients are at increased risk of myelodysplastic syndrome and malignant transformation, especially acute myeloid leukemia. Diamond-Blackfan anemia is characterized by absent or decreased erythroid precursors in the bone marrow, with 30% of patients also having a variety of physical anomalies.

Treatment
In Fanconi anemia, HCT is currently the only treatment that definitively restores normal hematopoiesis. Excellent results have been observed with the use of human leukocyte antigen (HLA)–matched sibling allo-HCT, with cure of the marrow failure and amelioration of the risk of leukemia.

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 severe combined immunodeficiency) cause an absence or dysfunction of T lymphocytes and sometimes B lymphocytes and natural killer cells.

Treatment
Without treatment, patients with severe combined immunodeficiency usually die by 12 to 18 months of age. With supportive care, including prophylactic medication, the lifespan of these patients can be prolonged, but long-term outlook is still poor, with many dying from infectious or inflammatory complications or malignancy by early adulthood. Bone marrow transplantation is the only definitive cure, and the treatment of choice for severe combined immunodeficiency and other primary immunodeficiencies, including Wiskott-Aldrich syndrome and congenital defects of neutrophil function.

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

Treatment
Exogenous enzyme replacement therapy is available for a limited number of the inherited metabolic diseases; however, these drugs do not cross the blood-brain barrier, which results in the ineffective treatment of the central nervous system. Stem cell transplantation provides a constant source of enzyme replacement from the engrafted donor cells, which are not impeded by the blood-brain barrier. The donor-derived cells can migrate and engraft in many organ systems, giving rise to different types of cells (eg, microglial cells in the brain and Kupffer cells in the liver).

Allogeneic HCT has been primarily used to treat the inherited metabolic diseases that belong to the lysosomal and peroxisomal storage disorders, as listed in Table 1. The first stem cell

transplant for an inherited metabolic disease was performed in 1980 in a patient with Hurler syndrome. Since that time, more than 1000 transplants have been performed worldwide.

Table PG1. Lysosomal and Peroxisomal Storage Disorders

Category	Diagnosis	Other Names
Mucopolysaccharidosis (MPS	MPS I MPS II MPS III A-D MPS IV A-B MPS VI MPS VII	Hurler syndrome or Hunter-Scheie syndrome Hunter syndrome Sanfilippo syndrome A-D Morquio syndrome A-B Maroteaux-Lamy syndrome Sly syndrome
Sphingolipidosis	Fabry disease Farber disease Gaucher disease types 1 and 3 GM gangliosidosis Niemann-Pick Diseases A and B Tay-Sach's Disease Sandhoff Disease Globoid cell leukodystrophy Metachromatic leukodystrophy	Lipogranulomatosis Krabbe Disease MLD
Glycoproteinosis	Aspartylglucosaminuria Fucosidosis Alpha-Mannosidosis Beta-Mannosidosis Mucolopidosis III and IV	Sialidosis
Other lipidoses	Niemann-Pick Disease C Wolman Disease Ceroid lipofuscinosis	Batten disease
Glycogen Storage	Glycogen Storage disease type II	Pompe disease
Multiple enzyme deficiency	Galactosialidosis Mucolipidosis type II	I-cell disease

Lysosomal transport defects	Cystinosis Sialic acid storage disease Salla disease	
Peroxisomal storage disorders	Adrenoleukodystrophy Adrenomyeloneuropathy	ALD AMN

Genetic Disorders Affecting Skeletal Tissue
Osteopetrosis is a condition caused by defects in osteoclast development and/or function. The osteoclast (the cell that functions in the breakdown and resorption of bone tissue) is known to be part of the hematopoietic family and shares a common progenitor with the macrophage in the bone marrow. Osteopetrosis is a heterogeneous group of heritable disorders, resulting in several different types of variable severity. The most severely affected patients are those with infantile malignant osteopetrosis (Albers-Schonberg disease or marble bone disease). Patients with infantile malignant osteopetrosis suffer from dense bone, including a heavy head with frontal bossing, exophthalmos, blindness by approximately 6 months of age, and severe hematologic malfunction with bone marrow failure. Seventy percent of these patients die before the age of 6 years, often of recurrent infections.

Treatment
HCT is the only curative therapy for this fatal disease.

Hematopoietic Cell Transplantation
HCT refers to a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in evidence review 9.001.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of HLA using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning
The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate

substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVH disease.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

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

IV. RATIONALE

TOP

Summary of Evidence
For individuals who have a hemoglobinopathy, bone marrow failure syndrome, primary immunodeficiency, inherited metabolic syndrome disease (specifically those other than Hunter, Sanfilippo, or Morquio syndromes), or a genetic disorder affecting skeletal tissue who receive allo-HCT, the evidence includes mostly case series, case reports, and registry data. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. The evidence has shown that, for most of these disorders, there is a demonstrable improvement in overall survival and other disease-specific outcomes. Allo-HCT is likely to improve health outcomes in select patients with certain inherited and acquired

diseases. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have an inherited metabolic syndrome disease (specifically those including Hunter, Sanfilippo, and Morquio syndromes) who receive allo-HCT, the evidence includes case reports. Relevant outcomes are overall survival, disease-specific survival, symptoms, quality of life, and treatment-related morbidity. Use of allo-HCT to treat patients with Hunter, Sanfilippo, or Morquio syndromes does not result in improvements in neurologic, neuropsychologic, and neurophysiologic function. The evidence is insufficient to determine the effects of the technology on health outcomes.

V. DEFINITIONS TOP

NA

VI. BENEFIT VARIATIONS TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER TOP

Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

POLICY TITLE	ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR GENETIC DISEASES AND ACQUIRED ANEMIAS
POLICY NUMBER	MP 9.055

Procedure Codes								
S2150	38204	38205	38208	38209	38210	38212	38213	38214
38215	38230	38240	38242					

ICD-10-CM Diagnosis Code	Description
D56.1	Beta thalassemia
D57.01	Hb-SS disease with acute chest syndrome
D57.02	Hb-SS disease with splenic sequestration
D57.03	Hb-SS disease with cerebral vascular involvement
D57.04	Hb-SS disease with dactylitis
D57.09	Hb-SS disease with other specified complication
D57.1	Sickle-cell disease without crisis
D57.20	Sickle-cell/Hb-C disease without crisis
D57.211	Sickle-cell/Hb-C disease with acute chest syndrome
D57.212	Sickle-cell/Hb-C disease with splenic sequestration
D57.213	Sickle-cell/Hb-C disease with cerebral vascular involvement
D57.214	Sickle-cell/Hb-C disease with dactylitis
D57.218	Sickle-cell/Hb-C disease with crisis with other specified complication
D57.40	Sickle-cell thalassemia without crisis
D57.411	Sickle-cell thalassemia unspecified with acute chest syndrome
D57.412	Sickle-cell thalassemia unspecified with splenic sequestration
D57.413	Sickle-cell thalassemia, unspecified, with cerebral vascular involvement
D57.414	Sickle-cell thalassemia, unspecified, with dactylitis
D57.418	Sickle-cell thalassemia, unspecified, with crisis with other specified complication
D57.42	Sickle-cell thalassemia beta zero without crisis
D57.43	Sickle-cell thalassemia beta zero with crisis
D57.431	Sickle-cell thalassemia beta zero with acute chest syndrome
D57.432	Sickle-cell thalassemia beta zero with splenic sequestration
D57.433	Sickle-cell thalassemia beta zero with cerebral vascular involvement
D57.434	Sickle-cell thalassemia beta zero with dactylitis
D57.438	Sickle-cell thalassemia beta zero with crisis with other specified complication
D57.439	Sickle-cell thalassemia beta zero with crisis, unspecified
D57.44	Sickle-cell thalassemia beta plus without crisis
D57.45	Sickle-cell thalassemia beta plus with crisis
D57.451	Sickle-cell thalassemia beta plus with acute chest syndrome

ICD-10-CM Diagnosis Code	Description
D57.452	Sickle-cell thalassemia beta plus with splenic sequestration
D57.453	Sickle-cell thalassemia beta plus with cerebral vascular involvement
D57.454	Sickle-cell thalassemia beta plus with dactylitis
D57.458	Sickle-cell thalassemia beta plus with crisis with other specified complication
D57.459	Sickle-cell thalassemia beta plus with crisis, unspecified
D57.80	Other sickle-cell disorders without crisis
D57.811	Other sickle-cell disorders with acute chest syndrome
D57.812	Other sickle-cell disorders with splenic sequestration
D57.813	Other sickle-cell disorders with cerebral vascular involvement
D57.814	Other sickle-cell disorders with dactylitis
D57.818	Other sickle-cell disorders with crisis with other specified complication
D61.01	Constitutional (pure) red blood cell aplasia
D61.02	Shwachman-Diamond syndrome
D61.09	Other constitutional aplastic anemia
D61.2	Aplastic anemia due to other external agents
D61.3	Idiopathic aplastic anemia
D61.89	Other specified aplastic anemias and other bone marrow failure syndromes
D70.0	Congenital agranulocytosis
D71	Functional disorders of polymorphonuclear neutrophils
D76.1	Hemophagocytic lymphohistiocytosis
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.5	Immunodeficiency with increased immunoglobulin M [IgM]
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.5	Purine nucleoside phosphorylase [PNP] deficiency
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.30	Adenosine deaminase deficiency, unspecified
D81.31	Severe combined immunodeficiency due to adenosine deaminase deficiency
D81.32	Adenosine deaminase 2 deficiency
D81.39	Other adenosine deaminase deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified

POLICY TITLE	ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR GENETIC DISEASES AND ACQUIRED ANEMIAS
POLICY NUMBER	MP 9.055

ICD-10-CM Diagnosis Code	Description
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D82.3	Immunodeficiency following hereditary defective response to Epstein-Barr virus
D82.4	Hyperimmunoglobulin E [IgE] syndrome
D82.8	Immunodeficiency associated with other specified major defects
D83.1	Common variable immunodeficiency with predominant immunoregulatory T-cell disorders
D84.8	Other specified immunodeficiencies
D84.89	Other immunodeficiencies
D89.82	Autoimmune lymphoproliferative syndrome [ALPS]
D89.84	IgG4-related disease
D89.9	Disorder involving the immune mechanism, unspecified
E70.330	Chediak-Higashi syndrome
E70.338	Other albinism with hematologic abnormality
E71.520	Childhood cerebral X-linked adrenoleukodystrophy
E75.19	Other gangliosidosis
E75.22	Gaucher disease
E75.23	Krabbe disease
E75.240	Niemann-Pick disease type A
E75.241	Niemann-Pick disease type B
E75.242	Niemann-Pick disease type C
E75.243	Niemann-Pick disease type D
E75.244	Niemann-Pick disease type A/B
E75.248	Other Niemann-Pick disease
E75.249	Niemann-Pick disease, unspecified
E75.25	Metachromatic leukodystrophy
E75.27	Pelizaeus-Merzbacher Disease
E75.29	Other sphingolipidosis
E75.3	Sphingolipidosis, unspecified
E75.4	Neuronal ceroid lipofuscinosis
E75.5	Other lipid storage disorders
E76.01	Hurler's syndrome
E76.02	Hurler-Scheie syndrome
E76.29	Other mucopolysaccharidoses
E76.03	Scheie's syndrome

ICD-10-CM Diagnosis Code	Description
E76.8	Other disorders of glucosaminoglycan metabolism
E76.9	Glucosaminoglycan metabolism disorder, unspecified
E77.0	Defects in post-translational modification of lysosomal enzymes
E77.1	Defects in glycoprotein degradation
E77.8	Other disorders of glycoprotein metabolism
E77.9	Disorder of glycoprotein metabolism, unspecified
E83.59	Other disorders of calcium metabolism
Q78.2	Osteopetrosis
Q78.8	Other specified osteochondrodysplasias
Q82.8	Other specified congenital malformations of skin
Q87.89	Other specified congenital malformation syndromes, not elsewhere classified

IX. REFERENCES

TOP

1. Bhatia M, Walters MC. Hematopoietic cell transplantation for thalassemia and sickle cell disease: past, present and future. Bone Marrow Transplant. Jan 2008;41(2):109-117. PMID 18059330

2. 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; 2004:281-316

3. Gluckman E, Wagner JE. Hematopoietic stem cell transplantation in childhood inherited bone marrow failure syndrome. Bone Marrow Transplant. Jan 2008;41(2):127-132. PMID 18084332

4. Gennery AR, Cant AJ. Advances in hematopoietic stem cell transplantation for primary immunodeficiency. Immunol Allergy Clin North Am. May 2008;28(2):439-456, x-xi. PMID 18424341

5. Porta F, Forino C, De Martiis D, et al. Stem cell transplantation for primary immunodeficiencies. Bone Marrow Transplant. Jun 2008;41(Suppl 2):S83-86. PMID 18545252

6. Prasad VK, Kurtzberg J. Emerging trends in transplantation of inherited metabolic diseases. Bone Marrow Transplant. Jan 2008;41(2):99-108. PMID 18176609

7. Askmyr MK, Fasth A, Richter J. Towards a better understanding and new therapeutics of osteopetrosis. Br J Haematol. Mar 2008;140(6):597-609. PMID 18241253

8. MacMillan ML, Walters MC, Gluckman E. Transplant outcomes in bone marrow failure syndromes and hemoglobinopathies. Semin Hematol. Jan 2010;47(1):37-45. PMID 20109610

9. *Smiers FJ, Krishnamurti L, Lucarelli G. Hematopoietic stem cell transplantation for hemoglobinopathies: current practice and emerging trends. Pediatr Clin North Am. Feb 2010;57(1):181-205. PMID 20307718*
10. *Angelucci E, Matthes-Martin S, Baronciani D, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease: indications and management recommendations from an international expert panel. Haematologica. May 2014;99(5):811-820. PMID 24790059*
11. *Mathews V, Srivastava A, Chandy M. Allogeneic stem cell transplantation for thalassemia major. Hematol Oncol Clin North Am. Dec 2014;28(6):1187-1200. PMID 25459187*
12. *Locatelli F, Kabbara N, Ruggeri A, et al. Outcome of patients with hemoglobinopathies given either cord blood or bone marrow transplantation from an HLA-identical sibling. Blood. Aug 08 2013;122(6):1072-1078. PMID 23692854*
13. *Mehta P. Hematopoietic stem cell transplantation for hemoglobinopathies. In: Mehta P, ed. Pediatric Stem Cell Transplantation. Sudbury, MA: Jones and Bartlett; 2004:259-279*
14. *Mahmoud HK, Elhaddad AM, Fahmy OA, et al. Allogeneic hematopoietic stem cell transplantation for non-malignant hematological disorders. J Adv Res. May 2015;6(3):449-458. PMID 26257943*
15. *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. Jul 12 2012;120(2):473-476. PMID 22645178*
16. *Anurathapan U, Pakakasama S, Mekjaruskul P, et al. Outcomes of thalassemia patients undergoing hematopoietic stem cell transplantation by using a standard myeloablative versus a novel reduced-toxicity conditioning regimen according to a new risk stratification. Biol Blood Marrow Transplant. Dec 2014;20(12):2066-2071. PMID 25064743*
17. *Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev. May 31 2013(5):CD007001. PMID 23728664*
18. *Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev. May 19 2016(5):CD007001. PMID 27194464*
19. *Bernaudin F, Socie G, Kuentz M, et al. Long-term results of related myeloablative stem-cell transplantation to cure sickle cell disease. Blood. Oct 1 2007;110(7):2749-2756. PMID 17606762*
20. *Walters MC, Patience M, Leisenring W, et al. Bone marrow transplantation for sickle cell disease. N Engl J Med. Aug 8 1996;335(6):369-376. PMID 8663884*
21. *Walters MC, Storb R, Patience M, et al. Impact of bone marrow transplantation for symptomatic sickle cell disease: an interim report. Multicenter investigation of bone marrow transplantation for sickle cell disease. Blood. Mar 15 2000;95(6):1918-1924. PMID 10706855*
22. *Hsieh MM, Fitzhugh CD, Weitzel RP, et al. Nonmyeloablative HLA-matched sibling allogeneic hematopoietic stem cell transplantation for severe sickle cell phenotype. JAMA. Jul 02 2014;312(1):48-56. PMID 25058217*

23. *Mehta P, Locatelli F, Stary J, et al. Bone marrow transplantation for inherited bone marrow failure syndromes. Pediatr Clin North Am. Feb 2010;57(1):147-170. PMID 20307716*
24. *Miano M, Dufour C. The diagnosis and treatment of aplastic anemia: a review. Int J Hematol. Jun 2015;101(6):527-535. PMID 25837779*
25. *Bacigalupo A. Bone marrow transplantation for acquired severe aplastic anemia. Hematol Oncol Clin North Am. Dec 2014;28(6):1145-1155. PMID 25459184*
26. *Dufour C, Svahn J. Fanconi anaemia: new strategies. Bone Marrow Transplant. Jun 2008;41 (Suppl 2):S90-95. PMID 18545254*
27. *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. Jul 2005;130(1):99-106. PMID 15982351*
28. *Wagner JE, Eapen M, MacMillan ML, et al. Unrelated donor bone marrow transplantation for the treatment of Fanconi anemia. Blood. Mar 1 2007;109(5):2256-2262. PMID 17038525*
29. *Gadalla SM, Sales-Bonfim C, Carreras J, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with dyskeratosis congenita. Biol Blood Marrow Transplant. Aug 2013;19(8):1238-1243. PMID 23751955*
30. *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. Oct 2005;131(2):231-236. PMID 16197455*
31. *Roy V, Perez WS, Eapen M, et al. Bone marrow transplantation for Diamond-Blackfan anemia. Biol Blood Marrow Transplant. Aug 2005;11(8):600-608. PMID 16041310*
32. *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. Sep 2012;91(9):1459-1469. PMID 22526363*
33. *Dufour C, Pillon M, Socie G, et al. Outcome of aplastic anaemia in children. A study by the severe aplastic anaemia and paediatric disease working parties of the European group blood and bone marrow transplant. Br J Haematol. May 2015;169(4):565-573. PMID 25683884*
34. *Smith AR, Gross TG, Baker KS. Transplant outcomes for primary immunodeficiency disease. Semin Hematol. Jan 2010;47(1):79-85. PMID 20109615*
35. *Szabolcs P, Cavazzana-Calvo M, Fischer A, et al. Bone marrow transplantation for primary immunodeficiency diseases. Pediatr Clin North Am. Feb 2010;57(1):207-237. PMID 20307719*
36. *Ahlin A, Fugelang J, de Boer M, et al. Chronic granulomatous disease-haematopoietic stem cell transplantation versus conventional treatment. Acta Paediatr. Nov 2013;102(11):1087-1094. PMID 23937637*
37. *Gungor T, Teira P, Slatter M, et al. Reduced-intensity conditioning and HLA-matched haemopoietic stem-cell transplantation in patients with chronic granulomatous disease: a prospective multicentre study. Lancet. Feb 01 2014;383(9915):436-448. PMID 24161820*
38. *Filipovich A. Hematopoietic cell transplantation for correction of primary immunodeficiencies. Bone Marrow Transplant. Aug 2008;42(Suppl 1):S49-S52. PMID 18724301*

39. *Hassan A, Booth C, Brightwell A, et al. Outcome of hematopoietic stem cell transplantation for adenosine deaminase-deficient severe combined immunodeficiency. Blood. Oct 25 2012;120(17):3615-3624; quiz 3626. PMID 22791287*
40. *Filipovich AH, Stone JV, 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. Mar 15 2001;97(6):1598-1603. PMID 11238097*
41. *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. Aug 11 2011;118(6):1675-1684. PMID 21659547*
42. *Marsh RA, Bleesing JJ, Chandrakasan S, et al. Reduced-intensity conditioning hematopoietic cell transplantation is an effective treatment for patients with SLAM-associated protein deficiency/X-linked lymphoproliferative disease type 1. Biol Blood Marrow Transplant. Oct 2014;20(10):1641-1645. PMID 24923536*
43. *Mehta P. Metabolic diseases. In: Mehta P, ed. Pediatric Stem Cell Transplantation. Sudbury, MA: Jones and Bartlett; 2004:233-258*
44. *Guffon N, Bertrand Y, Forest I, et al. Bone marrow transplantation in children with Hunter syndrome: outcome after 7 to 17 years. J Pediatr. May 2009;154(5):733-737. PMID 19167723*
45. *Vellodi A, Young E, New M, et al. Bone marrow transplantation for Sanfilippo disease type B. J Inherit Metab Dis. 1992;15(6):911-918. PMID 1293388*
46. *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; 1989:114-119.*
47. *Boelens JJ, Prasad VK, Tolar J, et al. Current international perspectives on hematopoietic stem cell transplantation for inherited metabolic disorders. Pediatr Clin North Am. Feb 2010;57(1):123-145. PMID 20307715*
48. *Prasad VK, Kurtzberg J. Transplant outcomes in mucopolysaccharidoses. Semin Hematol. Jan 2010;47(1):59-69. PMID 20109613*
49. *Rovelli AM. The controversial and changing role of haematopoietic cell transplantation for lysosomal storage disorders: an update. Bone Marrow Transplant. Jun 2008;41(Suppl 2):S87-89. PMID 18545253*
50. *Aldenhoven M, Wynn RF, Orchard PJ, et al. Long-term outcome of Hurler syndrome patients after hematopoietic cell transplantation: an international multicenter study. Blood. Mar 26 2015;125(13):2164-2172. PMID 25624320*
51. *Boelens JJ, Wynn RF, O'Meara A, et al. Outcomes of hematopoietic stem cell transplantation for Hurler's syndrome in Europe: a risk factor analysis for graft failure. Bone Marrow Transplant. Aug 2007;40(3):225-233. PMID 17529997*
52. *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. Feb 2008;41(4):349-353. PMID 18026148*
53. *Mynarek M, Tolar J, Albert MH, et al. Allogeneic hematopoietic SCT for alpha-mannosidosis: an analysis of 17 patients. Bone Marrow Transplant. Mar 2012;47(3):352-359. PMID 21552297*

54. *Miller WP, Rothman SM, Nascene D, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. Aug 18 2011;118(7):1971-1978. PMID 21586746*
55. *Steward CG. Hematopoietic stem cell transplantation for osteopetrosis. Pediatr Clin North Am. Feb 2010;57(1):171-180. PMID 20307717*
56. *Driessen GJ, Gerritsen EJ, Fischer A, et al. Long-term outcome of haematopoietic stem cell transplantation in autosomal recessive osteopetrosis: an EBMT report. Bone Marrow Transplant. Oct 2003;32(7):657-663. PMID 13130312*
57. *Majhail NS, Farnia SH, Carpenter PA, et al. Indications for autologous and allogeneic hematopoietic cell transplantation: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015;21(11):1863-1869. PMID 26256941*
58. *Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. Jan 2016;172(2):187-207. PMID 26568159*
59. *Barone A, Lucarelli A, Onofrillo D, et al. Diagnosis and management of acquired aplastic anemia in childhood. Guidelines from the Marrow Failure Study Group of the Pediatric Haemato-Oncology Italian Association (AIEOP). Blood Cells Mol Dis. Jun 2015;55(1):40-47. PMID 25976466*
60. *Oringanje C, Nemecek E, Oniyangi O. Hematopoietic stem cell transplantation for people with sickle cell disease. Cochrane Database Syst Rev. Jul 03 2020; 7: CD007001. PMID 32617981*
61. *Yabe M, Morio T, Tabuchi K, et al. Long-term outcome in patients with Fanconi anemia who received hematopoietic stem cell transplantation: a retrospective nationwide analysis. Int J Hematol. Jan 2021; 113(1): 134-144. PMID 32949371*
62. *Myers K, Hebert K, Antin J, et al. Hematopoietic Stem Cell Transplantation for Shwachman-Diamond Syndrome. Biol Blood Marrow Transplant. Aug 2020; 26(8): 1446-1451. PMID 32428734*
63. *Cesaro S, Pillon M, Sauer M, et al. Long-term outcome after allogeneic hematopoietic stem cell transplantation for Shwachman-Diamond syndrome: a retrospective analysis and a review of the literature by the Severe Aplastic Anemia Working Party of the European Society for Blood and Marrow Transplantation (SAAWP-EBMT). Bone Marrow Transplant. Sep 2020; 55(9): 1796-1809. PMID 32203264*
64. *ElGohary G, El Fakih R, de Latour R, et al. Haploidentical hematopoietic stem cell transplantation in aplastic anemia: a systematic review and meta-analysis of clinical outcome on behalf of the severe aplastic anemia working party of the European group for blood and marrow transplantation (SAAWP of EBMT). Bone Marrow Transplant. Oct 2020; 55(10): 1906-1917. PMID 32346079*
64. *Chiesa R, Wang J, Blok HJ, et al. Hematopoietic cell transplantation in chronic granulomatous disease: a study of 712 children and adults. Blood. Sep 03 2020; 136(10): 1201-1211. PMID 32614953*
65. *Burroughs LM, Petrovic A, Brazauskas R, et al. Excellent outcomes following hematopoietic cell transplantation for Wiskott-Aldrich syndrome: a PIDTC report. Blood. Jun 04 2020; 135(23): 2094-2105. PMID 32268350*

66. Blue Cross Blue Shield Association Medical Policy Reference Manual 8.01.22, Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias, March 2021

X. POLICY HISTORY

TOP

MP 9.055	**CAC 5/20/14 Minor review**. Information on HCT for Genetic Diseases and Acquired Anemias was extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. No change to policy statements. References updated. Policy guidelines and rationale section added. Policy coded.
	CAC 6/2/15 Consensus review. No changes to the policy statements. References and rationale updated. Codes reviewed.
	CAC 5/31/16 Consensus review. Policy statements unchanged. Description/Background, Rationale and References updated. Coding reviewed.
	1/1/17 Administrative update. Product variation section reformatted.
	CAC 5/23/17 Consensus review. Name changed to "Allogeneic HCT for Genetic Diseases and Acquired Anemias" No changes to the policy statements. References updated. Codes reviewed.
	1/1/18 Administrative update. Medicare variations removed from Commercial Policies.
	2/6/18 Consensus review. No change to the policy statements. Background, rationale, and references updated. Coding Reviewed.
	2/6/19 Consensus review. No change to the policy statements. Rationale condensed. References updated.
	10/1/19 Coding update. Diagnosis codes effective 10/1/19 updated.
	2/28/20 Consensus review. References and literature reviewed. No changes to policy statements.
	10/1/20 Administrative update. Added ICD10 new codes and revised definition of D57.411 and D57.412 (added "unspecified"); effective 10-1-20.
	2/24/2021 Consensus review. No change to policy statement. Background and References updated.
	9/8/2021 Administrative update. New code E75.244 added. Effective 10/1/2021
	8/5/2022 Consensus review. No change to policy statement. FEP and references updated. Coding reviewed, no changes.
	8/18/2023 Consensus review. No change to policy statement. References reviewed. Coding reviewed.
	8/29/2023 Administrative review. 9 ICD-10-CM new codes added. Effective date 10/1/2023.

Top