Molina Clinical Policy
Hematopoietic Stem Cell Transplantation for Non – Cancer Diseases
Policy No. 454

Last Approval: 06/11/2025
Next Review Due By: June 2026

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy covers hematopoietic stem cell transplantation for the following diseases:

Inborn Errors of Immunity	Inborn Errors of Metabolism: Mucopolysaccharidoses Lysosomal Disorders

Hematopoietic Stem Cell Transplantation (HSCT) refers to the infusion of multipotent hematopoietic stem cells into a recipient, using cells from either a donor or the patient's own body, to restore hematopoietic function. Hematopoietic stem cells are immature cells that can differentiate into erythrocytes, leukocytes, or platelets, and are typically harvested from bone barrow, peripheral blood, or umbilical cord blood. HSCT can be autologous (using the patient's own stem cells) or allogeneic (using donor-derived stem cells). In allogeneic HSCT, optimal outcomes are achieved when the donor is human leukocyte antigen (HLA)-identical, usually a sibling. HLA mismatched or haploidentical transplants increase the risk of graft rejection and non-malignant hematological conditions. HSCT can be utilized in the treatment of a variety of diseases from blood cancers to solid tumors (Negrin 2025; Chao 2024; Khaddour et al. 2023; Negrin 2022).

Haploidentical Allogeneic HSCT is becoming a viable alternative for patients in need of a bone marrow transplant but lack a fully matched donor of stem cells. In general, allogeneic hematopoietic cell transplantation may cure a broad variety of malignant and non-malignant disorders. The hematopoietic stem cells required are obtained from a related or unrelated donor's bone marrow or peripheral blood. For best outcomes, the stem cell donor is a human leukocyte antigen (HLA)-matched sibling; however, there is only a 25% chance a sibling will be a full match for a patient in need of a stem cell transplant. When there is not an HLA-matched sibling, alternative sources of donor grafts may be used, including suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical donors are options. Haploidentical related donors have a 50% match for important HLA markers. There are advantages and disadvantages of HLA-haploidentical HSCT. Advantages include the rapid availability of donor stem cell sources from family and graft versus leukemic effect which may improve overall survival. Haploidentical family members are available much faster than the many months it takes to conduct a nationwide search for unrelated donors, which means this alternative donor source may be especially relevant for minority ethnic groups for which well-matched unrelated donors are less common. The disadvantage of haploidentical allogeneic HSCT is alloreactivity, which can lead to graft rejection and graft versus host disease (Fuchs & Luznik 2024; NCCN 2025).

Inborn Errors of Immunity (IEIs), historically called primary immunodeficiency disorders, are inherited defects of the immune system that result in the impaired ability to fight pathogens and manifest in patients as failure to thrive, autoimmune disease, and recurrent or chronic infections. IEIs are a vast and growing cohort of hundreds of genetic mutations that can produce disease states that range from severe and life-threatening beginning in the neonatal period to mild disorders diagnosed in adulthood. IEIs may be the primary diagnosis, i.e., Severe Combined Immunodeficiency Disorder (SCID), or a part of an overarching genetic syndrome, and are treated based on the specific phenotype and severity of disease (Keller 2023). Treatment can include immunoglobulin therapy, antimicrobial therapies, enzyme

replacement therapy, gene therapy, HSCT, and more. HSCT is a critical therapy in the treatment of SCID, as allogeneic HSCT allows immune reconstitution. While HSCT is the primary curative treatment of choice for SCID, it may also be a treatment option for many other types of IEIs. However, as there are many life-threatening complications of allogeneic HSCT, risks and benefits must be weighed, especially for indications that are less clear (Dvorak 2024; Puck 2022).

Mucopolysaccharidoses (MPS) are a type of inborn errors of metabolism (IEM) caused by enzyme deficiencies required for the breakdown of glycosaminoglycans (GAGs), also known as mucopolysaccharides. Ineffective degradation of GAGs results in their accumulation in lysosomes causing cellular dysfunction. Hunter syndrome is an example of an MPS disorder (MPS type II) and is inherited in an X-linked pattern, however, most MPS disorders are autosomal recessive. MPS disorders are classified into as types (MPS I, MPS II, MPS III, MPS IV, MPS VI, MPS VII, and MPS IX) depending on the age of presentation, clinical presentation, and biochemical profile. The dominant clinical features can range from mild to severe and tend to be grouped as soft tissue storage and skeletal disease with or without brain disease, primarily skeletal disease without brain disease, and primarily central nervous system disorders. Age of clinical presentation can range from infancy to adulthood, with the more severe forms presenting earlier in life. The severity of the disease guides treatment, which may include a combination of enzyme replacement therapy, gene therapy, or HSCT, which is a standard of care for MPS IH (Hurler Syndrome) in children under approximately two years of age ([1-2]Hahn 2024).

COVERAGE POLICY

All transplants require prior authorization from the Corporate Transplant Department. Solid organ transplant requests will be reviewed by the Corporate Senior Medical Director or qualified clinical designee. All other transplants will be reviewed by the Corporate Senior Medical Director or covering Medical Director. If the criteria are met using appropriate NCD and/or LCD guidelines, State regulations, and/or MCP policies the Corporate Senior Medical Director's designee can approve the requested transplant.

Office visits with participating Providers do NOT require prior authorization. Providers should see the Member in office visits as soon as possible and without delay. Failure to see the Member in office visits may be considered a serious quality of care concern.

Please see *MCP-459 Pre-Transplant and Transplant Evaluation* for pre-transplant criteria and transplant evaluation criteria that must be met prior to hematopoietic stem cell transplantation (HSCT).

Inborn Errors of Immunity/ Immunodeficiency Disorders

Medically Necessary

1. *Allogenic HSCT (*ablative or non-myeloablative) may be **considered medically necessary** from an appropriate HLA matched sibling or well-matched donor when ALL MCP 459 Transplant Evaluation criteria are met, AND treatment is intended for ONE of the following:
    a. Absent, severely diminished, or dysregulated T-cell function, as seen in disorders such as SCID, non-SCID combined immunodeficiencies, hemophagocytic lymphohistiocytosis, Wiskott-Aldrich Syndrome, IPEX, and X-linked lymphoproliferative disease
    b. Absent, severely diminished, or dysregulated natural killer cell function, as seen in disorders such as Chediak-Higashi syndrome
    c. Absent, severely diminished, or dysregulated neutrophil function, as seen in disorders such as primary granulocyte dysfunction, chronic granulomatous disease, Omenn Syndrome, leukocyte adhesion deficiency, and Kostmann Syndrome

2. *Repeat Allogenic HSCT* may be **considered medically necessary** only once in the case of primary graft failure OR failure to engraft*

*NOTE: Engraftment is defined as an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L (or ≥ 500/mm^3) for three consecutive days or three consecutive laboratory values obtained on different days (CIBMTR 2024; NMDP 2022)

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive, or relapsed disease

2. Autologous HSCT

3. A planned tandem allogeneic HSCT

4. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant, including in utero collection

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation

Inborn Errors of Metabolism: Mucopolysaccharidoses (MPS) Lysosomal Storage Disorders

Medically Necessary

1. *Allogenic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** for the treatment of MPS Lysosomal Disorders from an appropriate HLA matched sibling or well-matched donor when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
    a. Diagnosis of an MPS Lysosomal Disorder
        i. MPS I (Hurler, Hurler – Scheie, or Scheie Syndrome)
        ii. MPS II (Hunter Syndrome)
        iii. MPS III (SanFilippo Syndrome)
        iv. MPS VI (Maroteaux – Lamy Syndrome)
        v. MPS VII (Sly Syndrome)
    b. Age < 2 years
    c. Neurologically intact or with mild developmental delay, as evidence by a Developmental Quotient > 70
    d. Failed conventional therapy (e.g., diet modification and/or enzyme replacement therapy), if applicable, for Hurler-Scheie, Scheie, Hunter, SanFilippo, Maroteaux-Lamy, and Sly Syndrome

2. *Repeat Allogenic HSCT* may be **considered medically necessary** only once in the case of primary graft failure OR failure to engraft*

*NOTE: Engraftment is defined as an absolute neutrophil count (ANC) ≥ 0.5 x 10^9/L (or ≥ 500/mm^3) for three consecutive days or three consecutive laboratory values obtained on different days (CIBMTR 2024; NMDP 2022)

Investigational, Unproven, and/or Not Medically Necessary

1. A second or repeat allogeneic (ablative or non-myeloablative) transplant due to persistent, progressive, or relapsed disease

2. Autologous HSCT

3. A planned tandem allogeneic HSCT

4. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant, including in utero collection

Haploidentical Allogenic HSCT

Medically Necessary

1. *Haploidentical Allogenic HSCT* may be **considered medically necessary** when there are no HLA matched sibling or well-matched donors, and ALL the following criteria are met:
    a. Member receiving transplant has met all disease specific criteria for HSCT transplantation
    b. Donor must be medically, socially, and psychologically fit to donate
    c. Donor age <40 years preferred over donor age ≥40 years
    d. No major ABO incompatibility between donor and recipient; major ABO incompatibilities include:
        i. Recipient blood type O: Donor type A, B, or AB
        ii. Recipient blood type A: Donor blood type B or AB
        iii. Recipient blood type B: Donor blood type A or AB
        iv. Recipient blood type AB: No major ABO incompatibilities
    e. Matched CMV IgG serologic status between donor and recipient include:
        i. For a recipient who is CMV IgG negative, use a CMV IgG negative donor
        ii. For a recipient who is CMV IgG positive, use a CMV IgG positive donor
    f. Use an ABO compatible donor over a minor ABO incompatible donor (ABO compatible transplants are O→O, A→A, B→B, or AB→AB)

Investigational, Unproven, and/or Not Medically Necessary

1. Haploidentical HSCT is considered **investigational** when the following contraindications are present:
    a. Donor is medically or psychologically unfit
    b. Recipient has anti-donor HLA antibodies of sufficient strength to result in a positive crossmatch result by flow cytometry or by complement-dependent cytotoxicity assay

Continuation of Therapy criteria may be found in MCP 459 Pre-Transplant and Transplant Evaluation

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Inborn Errors of Immunity (IEIs)

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Cheminant et al. (2023) conducted a retrospective analysis of outcomes in adults with IEIs who received allogeneic HSCT versus those who were not transplanted and received conservative management. A total of 281 patients were included (79 transplanted, 202 non-transplanted) with a median age of 21 years at the time of transplantation and median follow up of 4.8 years (interquartile range, 2.5-7.2). The 79 transplanted patients underwent allogeneic HSCT between 2008 and 2018 for IEIs such as chronic granulomatous disease (n = 20) and various combined immune deficiencies (n = 59). To control for variables as much as possible the non-transplanted patients were selected from the French Centre de Référence Déficits Immunitaires Héréditaires registry and matched for birth decade, age at last review greater than index patient age at allogeneic HSCT, chronic granulomatous disease or combined immune deficiencies, and autoimmune/lymphoproliferative complications. One-year transplant-related mortality rate was 13%, and the estimated 5 – year disease free survival rate of 58% and 33% in transplanted vs non-transplanted patients, respectively. Non-transplanted patients had increased recurrent events compared to transplanted patients, leading the authors to conclude that allogeneic HSCT prevents progressive morbidity associated with IEIs in adults, which may outweigh the negative impact of transplant-related mortality.

Miyamoto et al. (2022) conducted a retrospective analysis on HSCT for non-SCID inborn errors of immunity between the years 1985 – 2016 utilizing data from the Japanese national database, Transplant Registry Unified Management Program. A total of 566 underwent allogeneic HSCT during the 31-year analysis period. The 10-year OS and event-free survival (EFS) were 74% and 64%, respectively. Donor source of all HSCTs were 39% unrelated bone marrow donor, 33% sibling matched bone marrow donor, and 28% unrelated cord blood donor, with 10-year OS rates being 79%, 81%, and 69% respectively. The analysis revealed that the intensity of conditioning was not associated with OS or neutrophil recovery; however, myeloablative conditioning was more frequently associated with infection-related death. The authors did note that OS has increased in the most recent decade.

Marsh et al. (2018) conducted an analysis of the indications, practice changes, and survival of patients with inborn errors of immunity treated with allogeneic HSCT between 1974–2016 using data from the Center for International Blood and Marrow Transplant Research (CIBMTR). Due to the passage of the Stem Cell Therapeutic and Research Act of 2005 all allogeneic transplants in the United States are reported to the CIBMTR, thus the authors categorized transplantations by broad disease category (SCID vs non-SCID) and transplant periods: 1974–1989, 1990–1999, 2000–2009, and 2010–2016. A total of 981 SCID and 1902 non-SCID patients underwent allogeneic HCT between 1974–2016. The number of transplantations increased over time, culminating in 352 SCID and 816 non-SCID transplants performed between 2010-2016. The median age for transplantation was 0.5 years for SCID and 2 years for non-SCID patients, with both indications and pre-transplant regimens evolving over the decades. Overall survival rates increased across all diagnoses and ages resulting with 3 – year overall survival (OS) rates prior to 2000 being 64% for SCID (95% confidence interval [CI] 58–69%) and 62% for non-SCID (CI 57–67%), versus from 2000–2009 being 73% for SCID (CI 68–78%) and 70% for non-SCID , and from being 2010–2016 80% for SCID (CI 76–85%) and 75% for non-SCID (CI 72–79%) (p<0.001). SCID was added to newborn screening in 2010, and likely accounts for the superior increase in SCID survival after 2010, as those diagnosed by newborn screening experienced a 94% 3-year survival probability (CI 89–98%).

Mucopolysaccharidoses Lysosomal Storage Disorders

Systematic Reviews and Meta-Analyses

Abbasi et al. (2025) conducted a systematic review to evaluate the impact of HSCT, and especially bone marrow transplantation (BMT), on growth outcomes in pediatric patients with mucopolysaccharidosis (MPS). Outcomes included height, weight, body mass index (BMI), head circumference, and pubertal development following HSCT. The review excluded single patient case reports. Quality assessment was performed using the Newcastle-Ottawa Scale for cohort studies and the Joanna Briggs Institute for case series. The review included patients across various MPS subtypes, but most notably MPS I, II, and VI, with sample sizes ranging from small case series to a multicenter cohort of 217 patients. Overall findings indicate that HSCT generally leads to improvements in height, weight, and BMI, particularly when performed at a younger age (ideally before 2 years of age). However, despite improvements, many patients continued to experience declining height z-scores over time and did not achieve normal adult stature. A decrease in height z-scores was typically more pronounced in patients treated at an older age, and some studies found associations between short stature and conditioning regimens such as total body irradiation. Sitting heigh was often disproportionately affected, contributing to short stature due to poor spinal growth. While growth hormone (rhGH) therapy in HSCT patients sometimes led to temporary improvements, it generally did not result in significant long-term gains in height z-scores or normalization of adult height. For BMI, HSCT was associated with initial improvement, and children with MPS I showed normalization of weight and BMI after HSCT particularly when treated early. However, some patients, especially those entering adolescence, developed elevated BMI levels. Macrocephaly was common prior to HSCT, particularly in MPS IH patients. HSCT helped to normalize head growth over time, and while some patients retained disproportionately large head circumferences, the degree of macrocephaly was generally reduced post-transplant. Most patients proceeded through puberty at normal ages, with bone age generally consistent with chronological age. Overall, the authors concluded that HSCT shows promise for improving growth outcomes, including height, weight, and BMI for patients with MPS; however, long-term growth challenges such as short stature, disproportionate weight gain, and incomplete resolution of macrocephaly persist. Long-term post-HSCT monitoring of growth and pubertal progression in patients with MPS is critical.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Qu et al. (2022) completed a single-center study of 42 children with MPS who received HSCT and a follow-up of ≥ 1 year following transplant. Children included in the study had MPS type I (n=9), type II (n=14), type IV (n=15), or type VI (n=4) and received either peripheral blood stem cells (n=24) or umbilical cord stem cells (n=18). Those that received

umbilical cord stem cells received the blood from a matched family fresh cord blood donor (n=1), a mismatched unrelated cord blood donor (7/10 to 9/10 HLA-matched [n=15]), or from a double-mismatched unrelated cord blood donor (1 from a 6/10 to 8/10 HLA-matched donor and 1 from a 6/10 to 7/10 HLA-matched donor). Those that received peripheral blood stem cells received the blood from a matched family donor (n=4), a matched unrelated donor (n=10), a mismatched unrelated donor (7/10 to 9/10 HLA-matched [n=4]), or from a haploid donor (n=6). Children receiving peripheral blood stem cell transplants were condition with intravenous busulfan every 6 hours for 16 doses, intravenous cyclophosphamide, and antihuman thymocyte globulin. Specific lysosomal enzyme levels returned to normal in all recipients and 95.2% achieved full chimerism. The estimated OS at 1-year was 92.9% with no significant difference between peripheral or umbilical cord blood transplants. There was also no significant difference in acute or chronic GVHD between either group. High rates of pneumonia were noted in both groups (45.8% for peripheral blood and 33.3% for umbilical blood). A total of 3 deaths were reported following peripheral blood HSCT, 1 each due to grade III and IV GVHD, thrombotic microangiopathy, and combined grade III and IV GVHD and thrombotic microangiopathy. No patients with MPS type IV or VI died following transplantation. Researchers noted improvement in respiratory and CNS functions following HSCT. Valvular heart disease improved in some patients but progressed in others.

Gentner et al. (2021) reported interim results on an ongoing phase 1-2, non-randomized, single-center study involving 8 children diagnosed with MPS type I who lacked a suitable allogeneic donor for HSCT. The participants received autologous HSCT, and progenitor cells transduced ex vivo with an alpha-L-iduronidase (IDUA) encoding lentiviral vector after myeloablative conditioning. Median age at time of autologous HSCT was 1.9±0.5 years. Primary safety end points of the study include overall survival, hematologic engraftment by day 45, short- and long-term safety of drug-product infusion, and adverse event monitoring. The primary efficacy end point is blood IDUA activity at 1-year post-treatment. Secondary efficacy end points include anti-IDUA antibody immune response and engraftment of transduced cells at levels of 30% or more, normalization of GAGs, and growth velocity at 1- and 3-years post-treatment. The study has an expected 5-year duration and is currently at a median follow-up period of 2.1 years. Patients will continue to be followed for at least 15 years. Interim results reported showed hematologic engraftment that was rapid and consistent in all patients. Neutrophil recovery occurred at a median of 20 days and early spontaneous platelet recovery occurred at a median of 14 days. There were no reports of graft-versus-host disease due to the autologous nature of transplantation. A total of 19 serious adverse events were reported with only 1 of those (an acute allergic reaction) potentially related to the treatment. Previously undetectable levels of IDUA in the cerebrospinal fluid at baseline were detectable starting at 3-months post-treatment and persisting through each subsequent follow-up. GAG levels in the cerebrospinal fluid were also noted to decline. The IDUA and GAG results suggest a rapid and profound metabolic correction of the central nervous system. All patients also progressively acquired motor skills with 6 patients having a total motor performance within normal range or in the low average of normal. Other typical clinical manifestations, such as coarse facial features, upper airway obstruction, hearing loss, and corneal opacity, which were evident at the time of treatment showed improvement or stabilization at 1- and 2-year follow-ups.

Aldenhoven et al. (2015) evaluated the survival and graft outcomes of MPS patients receiving HSCT. Two consecutive conditioning regimens were used, busulfan/cyclophosphamide or fludarabine/busulfan-based, both with exposure-targeted intravenous busulfan. A noncarrier matched sibling donor (MSD), matched unrelated cord blood (UCB), or matched unrelated donor (MUD) were preferred donors; however, if none were available, a mismatched UCB donor was used. A total of 62 MPS patients (56 MPS type I-Hurler, 2 MPS type II, 2 MPS type III, and 2 MPS type VI) received HSCT (41 UCB, 17 MSD, 4 MUD) at median age of 13.5 months. High overall survival (95.2%) and event-free survival (90.3%) were achieved with only low toxicity: 13.3% acute graft-versus-host disease aGVHD) grades II to IV and 14.8% chronic GVHD (1.9% extensive). A mismatched donor predicted a lower event-free survival (P = .04). A higher age at HSCT was a predictor for both aGVHD (P = .001) and chronic GVHD (P = .01). The use of a mismatched donor was a predictor for aGVHD (P = .01). Higher rates of full donor chimerism were achieved in successfully transplanted UCB recipients compared with MSD/MUD (P = .002). HSCT in MPS patients results in high safety and efficacy when international HSCT guidelines are followed, which allows extension of HSCT to more attenuated MPS types. Due to a reduction in HSCT related toxicity being associated with younger age at transplantation, newborn screening may further increase safety.

Two case reports support an increased quality of life following HSCT in patients with MPS VII Sly Syndrome. Yamada (1998) reported on a 12-year-old female who underwent successful HSCT and had almost normal levels of beta-glucuronidase activity in her lymphocytes and excretion of glycosaminoglycans in the urine was greatly diminished in the 31 months post HSCT. In addition to ultrastructural findings demonstrating no abnormal vacuoles and inclusion

bodies in the cytoplasm of her rectal mucosal cells, the patient was able to walk alone for a long time without aid, ride a bicycle, and take a bath independently. The patient's recurrent upper respiratory and middle ear infections decreased in frequency and severity, as well as a decrease in the patient's dyspnea on exertion, severe snoring, and vertigo. Orii (2020) reported the 22 year follow up of the patient and revealed that her β-glucuronidase activity in leukocytes remained at normal levels, and urinary glycosaminoglycan excretion was reduced and kept within normal levels. Presently the patient remains able to walk independently and climb stairs, as well as sustain simple conversation. Due to the long-term stabilization of this patient's clinical picture, HSCT for MPS VII is a viable therapeutic option.

National and Specialty Organizations

The **American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma & Immunology** published the *Practice Parameter on Diagnosis and Management of Primary Immunodeficiency* to provide consultant allergists/immunologists or other practitioners with a practical guide for the clinical recognition and diagnosis of immunodeficiency, along with the general principles that guide management of these disorders. In addition, the practice parameter organizes current knowledge and practice in the diagnosis and management of PID diseases. The guidelines also note that patients with SCID are fragile and extremely susceptible to infection. Definitive HSCT should be sought as quickly as possible, as early HSCT is associated with better outcomes, whereas complications before HSCT indicate a poorer prognosis. HSCT may be a therapeutic indication for combined immunodeficiencies (e.g., SCID [IL2RG, ADA, other forms], CD40L), immunodeficiency syndromes (e.g., Wiskott-Aldrich Syndrome), immune dysregulation disorders (e.g., familial hemophagocytic lymphohistiocytosis, autoimmune lymphoproliferative syndrome, IPEX syndrome), phagocytic cell defects (e.g., neutropenia, chronic granulomatous disease, leukocyte adhesion deficiency), innate immune defects, (e.g., NEMO deficiency and other NF-kB defects). HSCT is not indicated for autoinflammatory disorders, complement deficiencies, antibody deficiencies, or cytokine autoantibody-mediated disorders (Bonilla et al. 2015).

The **American Society for Transplantation and Cellular Therapy (ASTCT**) published *Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy* which stipulates the various indications and uses for autologous and allogenic HSCT for malignant and non-malignant diseases (Kanate et al. 2020).

For pediatric patients, allogeneic HSCT is classified as standard of care for severe aplastic anemia, thalassemia, and hemophagocytic disorders, supported by high-quality evidence. Additionally, allogeneic HSCT is considered standard of care for Fanconi anemia, congenital amegakaryocytic thrombocytopenia, SCID and SCID, variants, Wiskott-Aldrich syndrome, IPEX syndrome, severe congenital neutropenia, chronic granulomatous disease, other phagocytic cell disorders, and other autoimmune and immune dysregulation disorders (e.g., mucopolysaccharidosis I, severe recessive osteopetrosis, globoid cell leukodystrophy, metachromatic leukodystrophy, and cerebral X-linked adrenoleukodystrophy); however, as these disease are rare, supporting high-quality evidence is not feasible and therefore treatment must be evaluated on a case-by-case basis with careful evaluation of risks and benefits. Other mucopolysaccharidoses (II, IV, VI) are considered developmental indications where preclinical and/or early-phase clinical studies show HSCT to be a promising treatment option and may be reclassified as standard of care as more evidence comes available (Kanate et al. 2020).

For adults, allogeneic HSCT is classified as standard of care for severe aplastic anemia (both newly diagnosed and refractory), sickle cell disease, and refractory hemophagocytic syndromes, supported by high-quality evidence. For Wiskott-Aldrich syndrome, HSCT is classified as standard of care with sufficient clinical evidence available to support its use after careful evaluation of risks and benefits. Additionally, allogeneic HSCT is considered standard of care for Fanconi anemia, dyskeratosis congenita, common variable immunodeficiency, chronic granulomatous disease, cerebral X-linked adrenoleukodystrophy, and other inherited marrow failure syndromes; however, supporting high-quality evidence is not feasible and therefore treatment must be evaluated on a case-by-case basis with careful evaluation of risks and benefits. Several autoimmune and metabolic disorders, such as multiple sclerosis, systemic sclerosis, rheumatoid arthritis, lupus, Crohn's disease, and osteopetrosis are classified as developmental indications (Kanate et al. 2020).

The ASTCT guidelines also emphasize that for many rare, nonmalignant diseases, the appropriateness of allogeneic HSCT depends on disease severity, progression, and patient-specific factors. Since prospective trials are lacking in

such cases, recommendations are based on expert opinion and small studies. Individualized risk-benefit discussions, referral to experienced centers, and consideration for clinical trial enrollment are encouraged. Donor and graft source selection is also critical. Although HLA-matched sibling donors are preferred, excellent outcomes have been achieved with matched unrelated donors, umbilical cord blood, and haploidentical donors (Kanate et al. 2020).

The **Center for International Blood and Marrow Transplant Research (CIBMTR)** (2024), in the *Forms Instruction Manual*, states the following:

- *Comprehensive Baseline & Follow-up Manuals: 2100: Post-Infusion Follow-Up (Q10-16):*
  - Absolute neutrophil recovery (ANC) recovery is defined as an ANC of ≥ 500/mm^3 (or ≥ 0.5 × 109/L) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is ≥ 500/mm^3. At some institutions, the laboratory reports display the ANC value once there are sufficient white blood cells to perform a differential count. At other institutions, the laboratory reports do not display the ANC, and it must be calculated from the white blood cell count and the percent of segmented and band neutrophils. If the laboratory report displays an automated ANC value of exactly 500/mm^3, the actual ANC value should be calculated from the manual differential if available. The calculated value from the manual differential will determine ANC recovery.
  - Traditionally, the definition of ANC recovery required selecting the first date of three consecutive days in which the recipient's ANC was ≥ 0.5×10^9/L (500/mm^3). For various reasons it may not be possible to obtain daily laboratory values. Under those circumstances, report ANC recovery based upon three consecutive laboratory values (drawn more than a day apart) as long as the ANC remains ≥ 0.5×10^9/L (500/mm^3).

The CIBMTR is a research collaboration between the Medical College of Wisconsin and the National Marrow Donor Program (NMDP). In an NMDP *IND Annual Report (BB-IND #7555-0136)* for *A Centralized Cord Blood Registry to Facilitate Allogeneic, Unrelated Donor Umbilical Cord Blood Transplantation,* neutrophil engraftment is defined as achievement of an ANC of ≥ 500 neutrophils/mm^3 sustained for three consecutive laboratory measurements on different days (NMDP 2022).

The **National Marrow Donor Program (NMDP)** provides evidence-based pre- and post-HSCT guidelines to patients and providers, including: *Consultation Guidelines and Outcomes; Engraftment; Disease-Specific HCT Indications and Outcomes Data; HCT Guidelines for Consultation Timing; Patient Eligibility for HCT; Post-Transplant Care; and Treatment Before Transplant* (NMDP 2023; NMDP 2024; [1-5]NMDP date unknown).

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
	Collection Codes
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
	Cell Processing Services
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal

38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	Cell infusion codes
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions
38243	Hematopoietic progenitor cell (HPC); HPC boost
	Histocompatibility codes
86812	HLA typing; A, B, or C (e.g., A10, B7, B27), single antigen
86813	HLA typing; A, B, or C, multiple antigens
86816	HLA typing; DR/DQ, single antigen
86817	HLA typing; DR/DQ, multiple antigens

HCPCS (Healthcare Common Procedure Coding System)

Codes	Description
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood derived stem-cell transplantation, allogeneic
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including pheresis and cell preparation/storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre-and post-transplant care in the global definition

APPROVAL HISTORY

06/11/2025 Policy revised. Removed numerical HLA matching criteria. Changed definition of engraftment and ANC criteria in coverage policy to align with current guidelines.

06/12/2024 New policy comprised of retired MCPs 265 (Immunodeficiency) and 256 (MPSs) into condensed HSCT for Non-Cancerous Diseases. Haploidentical transplant added to coverage criteria. IRO Peer Reviewed on May 24, 2024, by a practicing physician board certified in Pediatrics and Pediatric Hematology/Oncology.

REFERENCES

1. Abbasi F, Khalili Dehkordi A, Mohsenipour R. Impact of hematopoietic stem cell transplantation on growth outcomes in mucopolysaccharidosis: a systematic review. Clin Exp Pediatr. 2025 Mar 11. doi: 10.3345/cep.2024.01725. Epub ahead of print. PMID: 40083105.
2. Aldenhoven M, Jones SA, Bonney D, et al. Hematopoietic cell transplantation for mucopolysaccharidosis patients is safe and effective: results after implementation of international guidelines. Biol Blood Marrow Transplant. 2015 Jun;21(6):1106-9. doi: 10.1016/j.bbmt.2015.02.011. PMID: 25708213.
3. Bonilla FA, Khan DA, Ballas ZK, et al. Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol. 2015 Nov;136(5):1186-205.e1-78. doi: 10.1016/j.jaci.2015.04.049. PMID: 26371839.
4. Center for International Blood and Marrow Transplant Research (CIBMTR). Forms instruction manual. Updated August 27, 2024. Accessed May 8, 2025. https://www.manula.com/manuals/cibmtr/fim/1/en/topic/f2100-q6-12
5. Chao NJ. Selection of an umbilical cord blood graft for hematopoietic cell transplantation. Updated March 20, 2024. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
6. Cheminant M, Fox TA, Alligon M, et al. Allogeneic stem cell transplantation compared to conservative management in adults with inborn errors of immunity. Blood. 2023 Jan 5;141(1):60-71. doi: 10.1182/blood.2022015482. PMID: 36167031.

7. Dvorak CC. Hematopoietic cell transplantation for severe combined immunodeficiencies. Updated November 8, 2024. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
8. Gentner B, Tucci F, Galimberti S, et al. MPSI Study Group. Hematopoietic Stem- and Progenitor-Cell Gene Therapy for Hurler Syndrome. N Engl J Med. 2021 Nov 18;385(21):1929-1940. doi: 10.1056/NEJMoa2106596. PMID: 34788506.
9. Fuchs EJ, Luznik L. HLA-haploidentical hematopoietic cell transplantation. Updated July 10, 2024. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com.
10. [1]Hahn S. Mucopolysaccharidoses: Clinical features and diagnosis. Updated September 4, 2024. Literature review current through March 2025. Accessed April 24, 20245. https://www.uptodate.com
11. [2]Hahn S. Mucopolysaccharidoses: Treatment. Updated May 06, 2024. Literature review current through March 2025. Accessed April 24, 2025. https://www.uptodate.com
12. Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020 Jul;26(7):1247-1256. doi: 10.1016/j.bbmt.2020.03.002. PMID: 32165328.
13. Keller M. Inborn errors of immunity (primary immunodeficiencies): Overview of management. Updated October 26, 2023. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
14. Khaddour K, Hana CK, Mewawalla P. Hematopoietic Stem Cell Transplantation. In: StatPearls [Internet]. Treasure Island, FL. Updated May 6, 2023. Accessed April 23, 2025. https://www.ncbi.nlm.nih.gov/books/NBK536951/
15. Marsh RA, Hebert KM, Keesler D, et al. Practice pattern changes and improvements in hematopoietic cell transplantation for primary immunodeficiencies. J Allergy Clin Immunol. 2018 Dec;142(6):2004-2007. doi: 10.1016/j.jaci.2018.08.010. PMID: 30170121; PMCID: PMC6289686.
16. Miyamoto S, Umeda K, Kurata M, et al. Hematopoietic Cell Transplantation for Inborn Errors of Immunity Other than Severe Combined Immunodeficiency in Japan: Retrospective Analysis for 1985-2016. J Clin Immunol. 2022 Apr;42(3):529-545. doi: 10.1007/s10875-021-01199-w. PMID: 34981329.
17. National Comprehensive Cancer Network (NCCN). Hematopoietic cell transplantation (ver. 1.2025). Updated February 28, 2025. Accessed April 23, 2025. https://www.nccn.org/guidelines/category_3
18. [1]National Marrow Donor Program (NMDP). Consultation guidelines & outcomes. [date unknown]. Accessed April 25, 2025. https://nmdp.org
19. National Marrow Donor Program (NMDP). Disease-specific HCT indications and outcomes data. Published 2023. Accessed May 8, 2025. https://nmdp.org
20. [2]National Marrow Donor Program (NMDP). Engraftment. [date unknown]. Accessed May 8, 2025. https://nmdp.org
21. National Marrow Donor Program (NMDP). HCT guidelines for consultation timing. Published 2024. Accessed May 8, 2025. https://nmdp.org
22. National Marrow Donor Program (NMDP). IND annual report BB-IND #7555-0136. Published May 2022. Accessed May 8, 2025. https://nmdp.org
23. [3]National Marrow Donor Program (NMDP). Patient eligibility for HCT. [date unknown]. Accessed May 8, 2025. https://nmdp.org
24. [4]National Marrow Donor Program (NMDP). Post-transplant care. [date unknown]. Accessed April 25, 2025. https://nmdp.org
25. [5]National Marrow Donor Program (NMDP). Treatment before transplant. [date unknown]. Accessed May 8, 2025. https://nmdp.org
26. Negrin RS. Donor selection for hematopoietic cell transplantation. Updated November 21, 2022. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
27. Negrin RS. Immunotherapy for the prevention and treatment of relapse following allogeneic hematopoietic cell transplantation. Updated March 17, 2025. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
28. Orii K, Suzuki Y, Tomatsu S, Orii T, Fukao T. Long-Term Follow-up Posthematopoietic Stem Cell Transplantation in a Japanese Patient with Type-VII Mucopolysaccharidosis. Diagnostics (Basel). 2020 Feb 16;10(2):105. doi: 10.3390/diagnostics10020105. PMID: 32079065; PMCID: PMC7168249.
29. Puck JM. Hematopoietic cell transplantation for non-SCID inborn errors of immunity. Updated July 06, 2022. Literature review current through March 2025. Accessed April 23, 2025. https://www.uptodate.com
30. Qu Y, Liu H, Wei L, Nie S, Ding W, Liu S, Liu H, Jiang H. The Outcome of Allogeneic Hematopoietic Stem Cell Transplantation from Different Donors in Recipients with Mucopolysaccharidosis. Front Pediatr. 2022 Jun 30; 10:877735. doi: 10.3389/fped.2022.877735. PMID: 35844734.
31. Yamada Y, Kato K, Sukegawa K, et al. Treatment of MPS VII (Sly disease) by allogeneic BMT in a female with homozygous A619V mutation. Bone Marrow Transplant. 1998 Mar;21(6):629-34. doi: 10.1038/sj.bmt.1701141. PMID: 9543069.