# Molina Clinical Policy
# Hematopoietic Stem Cell Transplantation for Hematologic Disorders
# Policy No. 456

**Initial 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:**

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|---|---|---|
| Aplastic Anemia | Beta Thalassemia Major | Congenital Amegakaryocytic Thrombocytopenia |
| Diamond-Blackfan Anemia | Dyskeratosis Congenital | Fanconi's Anemia |
| Myelodysplastic Syndromes | Paroxysmal Nocturnal Hemoglobinuria | Pure Red Cell Aplasia |
| Schwachman-Diamond Syndrome | Sickle Cell Disease | |

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**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 marrow, 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; Deeg & Sandmaier 2025; Negrin 2022).

**Haploidentical allogeneic HSCT** is an increasingly viable alternative for patients lacking a fully HLA-matched donor. The hematopoietic stem cells required are obtained from a related or unrelated donor's bone marrow or peripheral blood. For optimal outcomes, the preferred donor is a human leukocyte antigen (HLA)-matched sibling, though there is only a 25% chance a sibling will be a full match. 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 both benefits and challenges associated with HLA-haploidentical HSCT. Advantages include the greater and faster donor availability, particularly within families, and the potential for graft-versus-leukemic effect, which may improve long-term survival. Haploidentical donors are often accessible more quickly than the several months required to located a matched unrelated donors, a factor that is critical for patients of ethnic minor groups, for whom matched unrelated donors are less common. However, disadvantages include increased risk of graft rejection and graft-versus-host disease (GVHD) (Fuchs & Luznik 2024; NCCN 2025).

**Aplastic anemia**, also called hypoplastic anemia, is a potentially fatal bone marrow failure disorder marked by pancytopenia and hypocellular bone marrow. It can be acquired or congenital. The most common causes of acquired aplastic anemia include idiopathic etiology, hepatitis, certain medications, chemical exposures, autoimmune conditions, pregnancy, pure red cell anemia, paroxysmal nocturnal hemoglobinuria, and parvovirus B19 infection.

Congenital aplastic anemia is linked to genetic mutations in the hTR gene or to Fanconi anemia, a rare autosomal recessive inherited disorder. Affected individuals present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and fatigue from anemia. Diagnosis is confirmed through bone marrow aspiration and biopsy. Aplastic anemia is classified into non-severe, severe, and very severe categories, based on the degree of the cytopenia. Allogeneic HSCT from an HLA-matched sibling donor (MSD) offers a curative option for individuals with severe aplastic anemia. This approach is considered standard of care for individuals younger than 50 years of age, despite potential treatment-related morbidity and mortality. Older individuals or those without HLA-matched donors typically receive first-line therapy with immunosuppressive therapy. For individuals without a matched sibling, alternative donor transplantation – including HLA-matched unrelated donors or haploidentical related donors – may be a viable option (Khan & Myers 2024; Negrin 2024; Olson 2025; Olson & Dunbar 2023; Rogers & Myers 2025; Fuchs & Luznik 2024).

**Sickle cell disease (SCD)** is an inherited hemoglobinopathy characterized by chronic hemolytic anemia and intermittent vaso-occlusive episodes. The hallmark of SCD is the presence of sickle-shaped red blood cells on peripheral blood smear. While the disease can occur in individuals of all ethnicities, it is most prevalent in populations of African, Caribbean, Mediterranean, Middle Eastern, and Indian ancestry. In the U.S., approximately 1 in 500 African American infants are born with SCD, prompting the implementation of newborn screening programs. Approximately 60-70% of SCD cases in the United States are caused by a homozygous inheritance of the hemoglobin S (HbS) gene. Other forms of SCD have the variant known as hemoglobin C (HbC). **Thalassemias** are also inherited hemoglobin disorders characterized by defective hemoglobin synthesis and chronic anemia. These disorders are most common in individuals of Italian, Greek, Middle Eastern, South Asian, and African backgrounds. It is estimated that fewer than 1000 individuals in the U.S. have **beta thalassemia major**, the most severe form and the only form for which HSCT is considered a curative treatment (Krishnamurti & Nur 2025; Field & Vichinsky 2025; Vichinsky 2025; NHLBI 2022; [1-2]DynaMed 2025; SCDAA 2021).

## 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).**

### Aplastic Anemia

**Medically Necessary**

1. *Allogeneic HSCT* may be **considered medically necessary** in adults and children who have a **fully matched human leukocyte antigen (HLA) sibling donor** for the treatment of bone marrow failure syndrome when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
    a. Member is < 60 years of age
    b. Member has ANY of the following rare bone marrow failure disorders:
        i. Diamond-Blackfan anemia
        ii. Fanconi's anemia
        iii. Schwachman-Diamond syndrome

iv. Pure red cell aplasia
v. Paroxysmal nocturnal hemoglobinuria
vi. Congenital amegakaryocytic thrombocytopenia
vii. Dyskeratosis congenital

c. For Members with a diagnosis of aplastic anemia not caused by any of the bone marrow failures listed in criteria 1c AND > 50 years of age: Member must have failed at least one course of immunosuppressive therapy with antithymocyte globulin and cyclosporin
d. Member has a diagnosis of aplastic anemia (includes congenital and acquired) defined as ONE of the following:
   i. Severe aplastic anemia with ONE of the following:
      1. A marrow biopsy showing < 25% of normal cellularity
      2. A marrow biopsy showing < 50% normal cellularity in which fewer than 30% of the cells are hematopoietic and at least TWO of the following are present:
         a. Absolute reticulocyte count < 40,000/microL
         b. Absolute neutrophil count (ANC) < 500/microL
         c. Platelet count < 20,000/microL
   ii. Very severe aplastic anemia defined as an ANC of < 200/microL
e. Stem cells are obtained from bone marrow

2. *Haploidentical Allogeneic HSCT* may be **considered medically necessary** when there are no HLA matched sibling or well-matched donors, and ALL allogenic transplant criteria above are met in addition to ALL the following:
   a. Donor is medically, socially, and psychologically fit to donate
   b. Donor age <40 years preferred over donor age ≥40 years
   c. Absence of 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
   d. Matched cytomegalovirus (CMV) IgG serologic status between the donor and the recipient includes ONE of the following:
      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
   e. Use an ABO compatible donor over a minor ABO incompatible donor (ABO compatible transplants are O→O, A→A, B→B, or AB→AB).

3. *Allogeneic HSCT* may be **considered medically necessary** in adults and children who have an appropriate HLA well-matched donor for the treatment of bone marrow failure syndrome when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
   a. Member is < 60 years of age
   b. Member has ANY of the following rare bone marrow failure disorders:
      i. Diamond-Blackfan anemia
      ii. Fanconi's anemia
      iii. Schwachman-Diamond syndrome
      iv. Pure red cell aplasia
      v. Paroxysmal nocturnal hemoglobinuria
      vi. Congenital amegakaryocytic thrombocytopenia
      vii. Dyskeratosis congenital
   c. For Members with a diagnosis of aplastic anemia not caused by any of the bone marrow failure disorders listed in criteria 3c: Member has failed at least one course of immunosuppressive therapy with antithymocyte globulin and cyclosporin

d. Member has a diagnosis of aplastic anemia (includes congenital and acquired) defined as ONE of the following:
    i. Severe aplastic anemia including ONE of the following:
        1. A marrow biopsy showing < 25% percent of normal cellularity
        2. A marrow biopsy showing < 50% percent normal cellularity in which < 30% of the cells are hematopoietic and at least TWO of the following are present:
            a. Absolute reticulocyte count < 40,000/microL
            b. ANC < 500/microL
            c. Platelet count < 20,000/microL
    ii. Very severe aplastic anemia defined as an ANC of < 200/microL
e. Stem cells are obtained from bone marrow

**Investigational, Unproven, and/or Not Medically Necessary**

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

2. Autologous HSCT

3. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant

4. 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.*

## Sickle Cell Disease / Thalassemia Major

**Medically Necessary**

1. *Allogeneic HSCT* (ablative or non-myeloablative) from an appropriate HLA well-matched donor for the treatment of a child or adolescent at increased risk of complications of sickle cell disease or thalassemia major may be approved when ALL Transplant Evaluation criteria are met *and* ANY of the following criteria are met:
    a. Members with **sickle cell disease** who have at least ONE of the following:
        i. Stroke or central nervous system event lasting longer than 24 hours
        ii. Progressive neurologic deterioration (e.g., abnormal cerebral MRI and arteriogram) and impaired neuropsychiatric testing
        iii. Recurrent acute chest syndrome or Stage I or II sickle lung disease
        iv. Recurrent vaso-occlusive painful episodes
        v. Sickle nephropathy glomerular filtration rate 30-50% of predicted normal
        vi. Osteonecrosis of multiple joints
    b. Members with **thalassemia major** who have deterioration with conventional treatments including transfusions, splenectomy, and deferoxamine

2. *Repeat Allogeneic 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 autologous or allogeneic (ablative or non-myeloablative) HSCT due to persistent, progressive, or early relapsed disease

2. Autologous HSCT

3. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant

*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

### Aplastic Anemia

***Systematic Reviews and Meta-Analyses***

ElGohary et al. (2020) completed a meta-analysis and systematic review with the goal of assessing to evaluate the feasibility and safety of haploidentical HSCT in patients with severe and very severe aplastic anemia. The meta-analysis included 15 studies with a total of 577 patients. The primary outcomes measured included the incidence of grades II-IV acute graft-versus-host disease (GVHD), chronic GVHD, transplant-related mortality, and the engraftment success rate. Secondary outcomes measured included regimen-related toxicity, post-transplant lymphoproliferative disorder, hemorrhagic cystitis, and the occurrence of cytomegalovirus (CMV) and Epstein-Barr virus viremia within 100 days post-transplant. The pooled engraftment rate was 97.3%, with reduced intensity conditioning (RIC) regimens demonstrating superior outcomes compared to non-myeloablative conditioning (NMAC) regimens (97.7% vs 91.7%, p = 0.03). Engraftment success was not significantly affected by the choice of GVHD prophylaxis. The overall incidence of acute GVHD was 26.6%, with lower rates noted in NMAC regimens (18.7% vs 29.5%, p = 0.008). The use of post-transplant cyclophosphamide for GVHD prophylaxis were associated with a lower rate of acute GVHD compared to methotrexate and other prophylactic regimens (18.7% vs 28.6% vs 27.8% respectively; p = 0.02). Chronic GVHD occurred in 25% of patients, with no significant differences among conditioning regimens. The pooled transplant-related mortality rate was 6.7%, with no significant differences between RIC and NMAC regimens (5.3% vs 11.8%, p = 0.15). Post-transplant cyclophosphamide for GVHD prophylaxis was associated with a higher, though not statistically significant, annual mortality rate (27.9%) compared to methotrexate (6.5%) and other regimens (5.6%, p = 0.06). The pooled rate of regimen-related toxicity was 6.2% and the pooled rate of hemorrhagic cystitis was 21.6%, with no significant differences noted based on conditioning regimen or GVHD prophylaxis. The rate of CMV infection was 44.3% with significantly lower rates in the NMAC group compared to RIC (21.61% vs 53.3%, p = 0.04). Post-transplant cyclophosphamide was associated with significantly lower CMV infection rates compared to methotrexate and other regimens (10.4% vs 55.7% and 38.6%, p < 0.001). The study found that both post-transplant cyclophosphamide and methotrexate regimens had significantly reduced CMV infection rates in high-risk patients compared to other prophylactic strategies (0% and 2.1% vs 33.0%, p < 0.001). Epstein-Barr viral infections occurred in 23.8% of patients, while post-transplant lymphoproliferative disease was observed in 1.5%, with no notable differences across conditioning or prophylactic strategies. Overall, the study concluded that haploidentical HSCT is a promising option when matched sibling or unrelated donor are unavailable. However, further research is needed to determine the optimal conditioning regimen, GVHD prophylaxis, and graft source to improve transplant outcomes.

***Non-Randomized Studies, Retrospective Reviews, and Other Evidence***

Zhang et al. (2019) conducted a single-center, retrospective study to evaluate the feasibility of upfront unrelated donor HSCT as a first-line treatment for adult patients with aplastic anemia. Inclusion criteria were a diagnosis of aplastic anemia based on the International AA Study Group criteria, receipt of allogeneic HSCT as initial therapy, and no prior

treatment with horse antithymocyte globulin (ATG) or cyclosporine A within the past 6 months. The study included 81 patients, with 23 receiving transplants from unrelated donors and 58 from matched sibling donors (MSD). Among those with unrelated donors, seven underwent mismatched HSCT, with single HLA mismatches at HLA-A (n=2), HLA-C (n=2), and HLA-DQB1 (n=3). Conditioning regimens were tailored based on donor type. Engraftment was defined as achieving an absolute neutrophil count ≥ $0.5x10^9$/L for three consecutive days and a platelet count ≥ $20x10^9$/L for seven consecutive days without platelet transfusion. The primary outcome was failure-free survival (FFS), with death, graft failure (primary or secondary), or relapse considered treatment failure. The secondary outcome was overall survival (OS). The study also reported on engraftment rates, GVHD incidence, and complications. Results showed no significant differences in neutrophil or platelet engraftment rates between groups, although the time to engraftment was significantly longer in the unrelated donor group (median 101 days vs 50.5 days; $p < 0.001$). The 5-year FFS was 82.0% ± 10.2% in the unrelated donor group and 89.3% ± 4.6% in the MSD group ($p = 0.404$), while the 5-year OS was 87.0% ± 9.1% versus 94.2% ± 3.3%, respectively ($p = 0.501$). The incidence of grade II acute GVHD was higher in the unrelated donor group (21.7% vs 3.4%, $p = 0.007$), though there were no cases of grades III-IV acute GVHD in either group. Chronic GVHD and extensive chronic GVHD were more frequent in the unrelated donor group but did not reach statistical significance (18.2% vs 8.8%, $p = 0.285$). CMV infection rates were comparable between groups (82.6% vs 70.7%, $p = 0.270$), and no significant differences were observed in the incidence of Epstein-Barr viral infection or post-transplantation lymphoproliferative disorder. Researchers that unrelated donor HSCT is a viable alternative when a matched sibling donor is not available for patients aged 14-55 years. They highlighted the need for additional comparative studies evaluating upfront mismatched related donor HSCT versus first-line MSD HSCT or immunosuppressive therapy.

## Sickle Cell Disease/Thalassemia Major

The published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of SCD and thalassemia major in selected individuals and consists of systematic reviews, retrospective and prospective multi-center clinical studies and case series. Several studies evaluated up to 485 SCD and thalassemia major symptomatic patients, the majority of whom received donor allografts from siblings who were HLA identical. The results from these series 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 (Arnold et al. 2017; Dedeken et al. 2014; Locatelli et al. 2013; Oringanje et al. 2013; Kavanagh et al. 2011).

Improved outcomes have not been demonstrated for autologous HSCT compared with allogeneic HSCT and conventional chemotherapy in individuals with sickle cell disease and thalassemia major therefore the role of autologous HSCT for this indication has not been established. Clinical trials are evaluating the role of unrelated donor HSCT in treating severe SCD and thalassemia major and enrolling children with a history of severe symptoms manifesting as strokes, frequent pain crises, or acute chest syndrome. Experience with myeloablative HSCT in older teenagers and adults with SCD and thalassemia major is insufficient and the role for this age group has not been established. A summary of the most relevant medical evidence is outlined below.

### *Non-Randomized Studies, Retrospective Reviews, and Other Evidence*

Arnold et al. (2017) performed a retrospective study of children transplanted for SCD in the USA during 2000-2013 using two large databases. Univariate and Cox models were used to estimate associations of demographics, SCD severity, and transplant-related variables with mortality and chronic graft-versus-host disease. Among 161 patients with a 2-year overall survival rate of 90% (95% confidence interval [CI] 85-95%) mortality was significantly higher in those who underwent late transplantation versus early (hazard ratio (HR) 21, 95% CI 2.8-160.8, P=0.003) and unrelated compared to MSD transplantation (HR 5.9, 95% CI 1.7-20.2, $p = 0.005$). Chronic GVHD was significantly more frequent among those transplanted late (HR 1.9, 95% CI 1.0-3.5, $p = 0.034$) and those who received an unrelated graft (HR 2.5, 95% CI 1.2-5.4; $p = 0.017$).

Dedeken et al. (2014) reported on the outcomes of 50 consecutive children with severe SCD that received HSCT between November 1988 and April 2013 were reported. The stem cell source was bone marrow (n = 39), cord blood (n = 3), bone marrow and cord blood (n = 7) and peripheral blood stem cells (n = 1). All patients had > 1 severe manifestation: 37 presented with recurrent vaso-occlusive crises/acute chest syndrome, 27 cerebral vasculopathy and 1 nephropathy. The conditioning regimen consisted of busulfan +cyclophosphamide (BuCy) before November 1991 and BuCy + rabbit antithymocyte globulin after that date. Since 1995, all patients have been treated with hydroxycarbamide prior to transplantation for a median duration of 27 years. The median age at transplantation and

median follow-up was 8.3 and 7.7 years, respectively. Acute GVHD and chronic GVHD were observed in 11 and 10 patients, respectively. An excellent outcome was achieved, with 8-year overall survival and event-free survival rates of 94.1% and 85.6%, respectively. Since hydroxycarbamide introduction, no graft failure occurred, and event-free survival reached 97.4%. Prior treatment with hydroxycarbamide may have contributed to successful engraftment.

Locatelli et al. (2013) reported on the largest case series analyzed the outcomes of 485 patients with thalassemia major or SCD receiving HLA-identical sibling cord blood transplantation (CBT, n = 96) or bone marrow transplantation (BMT, n = 389). Compared with patients given BMT, CBT recipients were significantly younger (median age 6 vs 8 years, p = 0.02), and were treated more recently (median year 2001 vs 1999, p < 0.01). A higher proportion of patients with thalassemia major belonging to classes II-III of the Pesaro classification received BMT (44%) compared with CBT (39%, p < 0.01). In comparison with patients receiving BMT (n = 259, TM; n = 130, SCD), those given CBT (n = 66, TM; n = 30, SCD) had slower neutrophil recovery, less acute GVHD and none had extensive chronic GVHD. With a median follow-up of 70 months, the 6- year overall survival was 95% and 97% after BMT and CBT, respectively (p = 0.92). The 6-year disease-free survival was 86% and 80% in TM patients after BMT and CBT, respectively, whereas disease-free survival in SCD patients was 92% and 90%, respectively. The cell dose infused did not influence the outcome of patients given CBT. In multivariate analysis, Disease-free survival did not differ between CBT and BMT recipients. Patients with thalassemia major or SCD have excellent outcomes after both HLA identical sibling CBT and BMT.

## Haploidentical Transplantation for Sickle Cell Disease

***Randomized Controlled Trials***

Kassim et al. (2024) reported phase 2 results of a prospective, multicenter international trial of 70 individuals with sickle cell anemia treated with nonmyeloablative haploidentical bone marrow transplant (NCT01850108). Participants were aged 1-70 years and had an ECOG performance score of 0 or 1 or a Karnofsky score > 70. No adults were excluded because of stroke or severe pre-existing heart, lung, or kidney disease. Participants lacked an HLA matched sibling donor but had a haploidentical donor available. Thiotepa was added to the conditioning regimen to improve engraftment and post-transplant cyclophosphamide was added to reduce GVHD.

Overall survival at one year was 96% and 94% at 2 years. This transplant protocol is a marked improvement over historical haploidentical transplants that had a 40% graft failure rate. The overall survival in this study approaches those seen in HLA matched allogeneic stem cell transplants. Graft failure occurred in 11.4% of participants, all of which were less than 18 years old. All participants with failed grafts received autologous reconstitution and were alive at follow-up. There were five deaths from infectious complications. Additional evaluations will be needed to understand why graft failure occurred more often in adolescents.

Leonard et al. (2023) reported data from another prospective, phase 2 trial (NCT03263559) of haploidentical HSCT in individuals with severe sickle cell anemia. This trial was a multi-center, single arm trial that also used reduced intensity myeloablative conditioning with thiotepa and post-transplant cyclophosphamide. The trial differed from the Kassim et al. (2024) haploidentical HSCT trial in that it included hydroxyurea and red blood cell transfusion preconditioning. There were 42 participants that proceeded to HSCT. The main indications for transplant were recurrent vaso-occlusive pain episodes, acute chest syndrome, or overt stroke. The primary outcome, event free survival at 2 years, was 88%, and the 2-year overall survival was 95%. There were 2 deaths related to organ failure and acute respiratory distress syndrome.

While there is an unmet need for disease modifying treatments in individuals with advanced sickle cell disease and end organ damage, a phase three trial has not yet been conducted. Until then, patients with advanced sickle cell disease with end organ damage are best treated and monitored within a clinical trial.

## Haploidentical Transplantation

***Randomized Controlled Trials***

DeZern et al. (2023) reported results from a phase 2 trial (NCT02833805). The trial design was a single arm, single center, prospective, bone marrow transplantation for patients with severe aplastic anemia who do not have a fully matched HLA donor. This phase 2 trial used non-myeloablative conditioning and transplantation of partially HLA-Mismatched/Haploidentical related or matched unrelated donor bone marrow. The median patient age was 25 years and median follow-up time was 40.9 months. The protocol for the HLA-haploidentical HSCT included post

transplantation cyclophosphamide based GVHD prophylaxis and reduced intensity conditioning. The haploidentical HSCT group that received 400cGy of total body irradiation had 100% overall survival with minimal GVHD in 20 consecutive patients.

***Systematic Reviews and Meta-Analyses***
Yang et al. (2019) published a systematic review and meta-analysis of haploidentical versus matched donor stem cell transplantation for patients with hematologic malignancies. Twenty-five studies enrolling 11,359 patients were included (haploidentical HSCT n = 2677; Matched HSCT n = 8682). Matched HSCT and haploidentical HSCT had similar risks for all primary endpoints including acute and chronic GVHD, nonrelapse mortality, and 1-year cumulative incidence of relapse. The authors concluded that haploidentical HSCT is a safe and effective transplant option for those that lack a matched donor, however a caveat was noted with regard to its suitability for patients who receive reduced intensity chemotherapy.

**National and Specialty Organizations**

The **American Society for Transplantation and Cellular Therapy (ASTCT)** published guidelines for indications for HSCT and immune effector cell therapy (Kanate et al. 2020). The guidelines make recommendations for allogeneic and autologous HSCT based on the strength and availability of published evidence for each disease process. Recommendations are also made based on patient age (< 18 years and ≥ 18 years).

The **American Society of Hematology (ASH)** published *2021 Guidelines for Sickle Cell Disease: Stem Cell Transplantation* (Kanter et al. 2021). The guidelines make the following recommendations regarding HSCT for SCD:

- "The ASH guideline panel suggests HLA-matched related HSCT rather than standard of care (hydroxyurea/transfusion) in patients with SCD who have experienced an overt stroke or have an abnormal transcranial Doppler ultrasound (conditional recommendation, very low certainty in the evidence).
    - Consideration for transplantation should occur in all patients with neurologic injury who have a matched related sibling donor.
    - When considering transplantation for neurologic injury, children younger than age 16 years who receive MSD HSCT have better outcomes than those older than age 16 years.
- For patients with frequent pain, the ASH guideline panel *suggests* using related matched allogeneic transplantation…[for] patients who do not respond or have an inadequate response to standard of care, such as hydroxyurea, new targeted therapies, or chronic transfusion therapies (conditional recommendation, very low certainty in the evidence about effects).
- For patients with recurrent episodes of [acute coronary syndrome]…[despite optimal standard of care], the ASH guideline panel *suggests* using matched related allogeneic transplantation over standard of care (e.g., hydroxyurea, L-glutamine, crizanlizumab, and chronic transfusion therapy) (conditional recommendation, very low certainty in the evidence about effects).
- For patients with SCD with an indication for HSCT who lack a MSD, the ASH guideline panel *suggests* using transplants from alternative donors in the context of a clinical trial (conditional recommendation, very low certainty in the evidence about effects).
- For allogeneic HSCT, the ASH guideline panel *suggests* using either total-body irradiation ≤ 400 cGy or chemotherapy-based conditioning regimens (conditional recommendation, very low certainty in the evidence about effects).
- For children with SCD who have an indication for allogeneic HSCT and a MSD, the ASH guideline panel *suggests* using myeloablative conditioning over reduced intensity conditioning that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects).
- For adults with SCD who have an indication for allogeneic HSCT and an MSD, the ASH guideline panel *suggests* nonmyeloablative conditioning over reduced intensity conditioning that contains melphalan/fludarabine regimens (conditional recommendation, very low certainty in the evidence about effects).
- In patients with an indication eligible for HSCT, the ASH guideline panel *suggests* using allogeneic transplantation at an earlier age rather than an older age (conditional recommendation, low certainty in the evidence about effects).
    - Recommendations could not be made if an MSD was not available because of the paucity of available data.

    - The impact of age on HSCT outcome may also be affected by the conditioning regimen used.
- The ASH guideline panel *suggests* the use of HLA-identical sibling cord blood when available (and associated with an adequate cord blood cell dose and good viability) over bone marrow (conditional recommendation, very low certainty in the evidence about effects)."

The **Fanconi Anemia Research Fund**, part of the Fanconi Cancer Foundation, published the *Fanconi Anemia Clinical Care Guidelines 5th edition* with the following recommendations for HSCT for the treatment of Fanconi's anemia (Sroka et al. 2020):

- "For patients without a 10/10 or 9/10 matched related donor, 10/10 or 9/10 matched adult unrelated donor and 10-8/10 (or perhaps less) matched umbilical cord blood are associated with good outcomes.
- Transplant without radiation can be successful for patients with Fanconi's anemia.
- Radiation during transplant is clearly associated with increased risk of later cancer in larger series of persons without Fanconi's anemia. More studies are needed to determine if radiation or a radiation-free conditioning protocol increases the risk of cancer in patients with Fanconi's anemia.
- In transplanted Fanconi's anemia patients, development of chronic or acute GVHD increases the risk of later cancer."
- Haploidentical transplant can be a viable option if there are no other donor options available.
- Survival rates following alternate donor transplant continue to improve and outcomes from related and unrelated donors are similar.

The **National Heart, Lung, and Blood Institute (NHLBI) (2014)** published the Evidence-Based Management of Sickle Cell Disease, Expert Panel Report. A section on hematopoietic cell transplantation is included, noting that HSCT is the only therapy for sickle cell disease that has curative potential. The NHLBI recommends that children with sickle cell disease who experience significant, noninfectious complications caused by vaso-occlusion should be considered for HSCT. If full siblings are available, HLA typing should be performed as results are best when performed in children with a sibling donor who is HLA-identical. HSCT is recommended for patients who have experienced significant complications caused by sickle cell disease (e.g., stroke, recurrent episodes of acute chest syndrome or pain). Further research is needed on the identification of clinical or genetic markers that reliably predict an adverse outcome thereby allowing the application of HSCT before significant clinical complications occur. The need for additional research is reiterated for transplantation for those with sickle cell disease.

The **National Marrow Donor Program (NMDP)** has published the following guidance: *Disease-Specific HCT Indications and Outcomes Data; Engraftment; HLA Matching; Patient Eligibility for HCT; Transplant Consultation Timing; and Treatment Before Transplant* ([1-6] 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 |
| **38230** | Bone marrow harvesting for transplantation; allogeneic |
| | **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 |
| **38242** | Allogeneic lymphocyte infusions |
| **38243** | Hematopoietic progenitor cell (HPC); HPC boost |
| | **Histocompatibility and Biopsy Codes** |
| **38221** | Diagnostic bone marrow; biopsy(ies) |
| **38222** | Diagnostic bone marrow; biopsy(ies) and aspiration(s) |
| **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)**

| Code | 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 or pre-and post-transplant care in the global definition |

**CODING DISCLAIMER.** Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

## APPROVAL HISTORY

**06/11/2025** Policy reviewed. Removed numerical HLA matching criteria. Changed definition of engraftment and ANC criteria in coverage policy to align with current guidelines. Removed age stipulation under Sickle Cell/Thalassemia section.

**06/12/2024** New policy created by condensing MCPs 143 and 209 into a single policy. Changes to criteria include clarification that a failed course of immunosuppressive therapy is only for those with aplastic anemia. Haploidentical transplant criteria for aplastic anemia moved from MCP 362 to this policy. IRO Peer Review on June 3, 2024, by a practicing, board-certified physician with specialties in Hematology, Medical Oncology, and Internal Medicine.

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