

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

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

Acute Lymphoblastic Leukemia (ALL)	Hodgkin-Non-Hodgkin Lymphoma
Acute Myeloid Leukemia (AML)	Multiple Myeloma / POEMS Syndrome
Chronic Myeloid Leukemia (CML)	Myelodysplastic Syndrome
Chronic Lymphoblastic Leukemia (CLL)	Myeloproliferative Neoplasms

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 (Chao 2024; Holmberg & Sandmaier 2024; Negrin 2022; Negrin 2025).

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. The hematopoietic stem cells required are obtained from a related or unrelated donor's bone marrow or peripheral blood. For the best outcomes, the stem cell donor is an 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, but not limited to, suitably HLA-matched adult unrelated donors, umbilical cord blood stem cells, and partially HLA-mismatched, or HLA-haploidentical, related donors. This alternative donor source may be especially relevant for minority ethnic groups for which well-matched unrelated donors are less common (NCCN 2025; Fuchs & Luznik 2024).

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 (OS). Haploidentical family members are available much faster than the many months it takes to conduct a nationwide search for unrelated donors. The disadvantage of haploidentical allogeneic HSCT is alloreactivity leading to graft rejection and graft-versus-host disease (GVHD). This was a major problem early in the history of haploidentical HSCT. Graft engineering (depletion of alloreactive T cells to help reduce GVHD) and pharmacologic prophylaxis of GVHD (post-transplantation cyclophosphamide), have reduced some of the risk of graft failure and GVHD (Fuchs & Luznik 2024).

Acute Lymphoblastic Leukemia (ALL) is a heterogeneous hematologic malignancy involving proliferation of lymphoid progenitor cells which invade bone marrow, peripheral blood, and extramedullary locations. ALL occurs in

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both children and adults and is the most common type of cancer in children. The World Health Organization (WHO) classifies ALL as either B- cell lymphoblastic leukemia or T-cell lymphoblastic leukemia. B lymphoblastic leukemia is subdivided by the presence or absence of specific recurrent genetic abnormalities (t(9;22)), MLL rearrangement, t(12;21), hyperdiploidy, hypodiploidy, t(5;14), and t(1;19). Current treatment decisions rely on the immunophenotype (early-pre-B ALL, pre-B ALL, B-cell ALL, or T-cell ALL) and cytogenetics of affected cells (Advani & Aster 2022).

Acute Myeloid Leukemia (AML) is an aggressive blood cell cancer caused by clonal expansion of malignant myeloid blasts in bone marrow, peripheral blood, and other tissues. The leukemic cells interfere with production of normal blood cells, causing weakness, infection, bleeding, and other symptoms and complications. AML is categorized according to the World Health Organization (WHO) classification system based on clinical, morphologic, immunophenotypic, cytogenetic and molecular markers. The five major subcategories of AML include: AML with recurrent genetic abnormalities, AML with myelodysplasia-related features, therapy-related myeloid neoplasm, AML not otherwise specified, and myeloid sarcoma (Kolitz 2025).

Chronic Lymphoblastic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) are identical (i.e., one disease with different manifestation) neoplasms of hematopoietic origin characterized by the accumulation of functionally incompetent lymphocytes. CLL is used when the disease manifests in the blood, bone marrow, lymph nodes, and spleen; whereas SLL is used when the disease is confined primarily to the lymph nodes. CLL/SLL is staged according to two common systems, the Rai and Binet. The Rai system has five stages of disease advancement from 0 through IV. The Binet system is a simplified staging with three stages A through C (A overlaps with Rai 0, I, and II; B with I and II; and C with III and IV). Patients in stages I/II are considered as having intermediate-risk / early-stage disease, and those in stages III/IV as having high-risk / advanced-stage disease. Treatment ranges from periodic observation with supportive treatment of infectious, hemorrhagic, or immunologic complications, to a variety of therapeutic options, including steroids, alkylating agents, purine analogs, combination chemotherapy, monoclonal antibodies, and transplantation.

Donor lymphocyte infusion (DLI) is a form of adoptive immunotherapy and may be requested to induce a graft versus leukemia, or graft versus tumor, response without requiring the recipient to undergo additional high-dose chemotherapy. Donor lymphocytes are collected from the original donor through leukapheresis. The collection of donor lymphocytes is an outpatient procedure for the donor. Lymphocytes are then either infused via vein into the recipient or are frozen for a more clinically appropriate time.

Chronic Myeloid Leukemia (CML) is a myeloproliferative neoplasm characterized by the uncontrolled production of mature and maturing granulocytes. CML is associated with the presence of the Philadelphia chromosome, t(9;22)(q34;q11.2), which creates a BCR-ABL1 fusion gene and production of BCR-ABL1 tyrosine kinase. Exposure to ionizing radiation is the only known risk factor for the development of CML. There are three phases of the disease based mainly on the number of immature blasts in the bone marrow. The chronic phase (CP-CML) lasts a median of 3 years. If left untreated, chronic-phase CML (CP-CML) will typically advance to accelerated-phase CML (AP-CML) or blast-phase CML (BP-CML) within an average timeframe of 3 to 5 years. Conventional-dose regimens used for chronic-phase disease can induce multiple remissions and delay the onset of blast crisis to a median of 4–6 years. However, successive remissions are invariably shorter and more difficult to achieve than their predecessors (Van Etten 2025).

Hodgkin Lymphoma is a lymphoid neoplasm marked by the presence of Reed-Sternberg cells and non-neoplastic inflammatory cells. There are two types of Hodgkin lymphoma, classical and nodular lymphocyte-predominant Hodgkin lymphoma. Most cases are the classical type which includes four subtypes: nodular sclerosing; mixed cellularity; lymphocyte-depleted; lymphocyte-rich classical. Symptoms accompanying classical type tend to be lymphadenopathy, mediastinal mass, fever, night sweats, and weight loss. Nodular lymphocyte-predominant Hodgkin lymphoma typically presents as a chronic asymptomatic swollen peripheral lymph node easily detected on physical exam, with no additional signs or symptoms of cancer at diagnosis. Treatment typically differs from classical Hodgkin lymphoma (Ng et al. 2025; Aster et al. 2023).

Non-Hodgkin Lymphoma is a diverse group of lymphoid tissue malignancies that arise from immature or mature B cells and T cells, and sometimes natural killer cells. There are various subtypes including diffuse large B cell lymphoma, Mantle cell lymphoma, Burkitt's lymphoma, follicular lymphoma, and more. Dependent on the subtype, non-Hodgkin lymphoma can either present insidiously with chronic waxing and waning lymphadenopathy, paired with hepatosplenomegaly and occasionally cytopenia; or the presentation is sudden and aggressive with accompanying rapid mass growth, fever, night sweats, weight loss, and sometimes tumor lysis syndrome (Brown & Freedman 2023;

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Freedman et al. 2024).

Multiple Myeloma is a rare form of cancer characterized by excessive production and improper function of plasma cells found in the bone marrow. Excessive cells may eventually mass together to form a tumor, leading to bone destruction and bone marrow failure. Multiple myeloma refers to cases with multiple tumors present or the bone marrow has greater than 10% plasma cells. Plasma cells play a crucial role in the immune system and secrete a type of antibody called monoclonal proteins (M-proteins). An overproduction of plasma cells leads to unusually high levels of M-proteins. The main symptoms of multiple myeloma may include bone pain (especially in the back and ribs); anemia leading to weakness, fatigue, and lack of pallor; and renal abnormalities. Staging is based on the levels of monoclonal protein (M-protein) in the serum and/or urine, as well as clinical indications such as hemoglobin and serum calcium concentrations, the number of lytic bone lesions, and the presence or absence of renal failure (NORD 2023).

POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) is distinguished by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following (Dispenzieri 2023):

- Osteosclerotic myeloma *
- Castleman disease (angiofollicular lymph node hyperplasia) *
- Increased levels of serum vascular endothelial growth factor (VEGF) *
- Organomegaly
- Endocrinopathy
- Edema
- Typical skin changes
- Papilledema

* Major criteria for diagnosis of POEMS Syndrome

Monoclonal gammopathy of undetermined significance (MGUS) results when monoclonal protein, an abnormal protein, is detected in the blood. While MGUS typically is not problematic, symptoms can include numbness, tingling or weakness. For some patients, MGUS eventually progresses into other types of blood cancer (e.g., multiple myeloma, macroglobulinemia or B-cell lymphoma). Osteosclerotic myeloma is also a form of multiple myeloma. When symptoms other than CRAB (hypercalcemia, renal dysfunction, anemia, or sclerotic bone lesions) develop, consideration of a POEMS syndrome diagnosis should be explored. Patients typically have symptoms similar to classic multiple myeloma; however, instead of the patient having thin and holey bones, osteosclerosis is found (a condition evidenced by abnormal density and hardening of bone) (NORD 2021).

Myelodysplastic syndromes consist of a heterogeneous group of malignant hematopoietic stem cell disorders characterized by abnormal bone marrow and blood cell morphology. Patients with myelodysplastic syndromes have reduced production of red blood cells, platelets, and mature granulocytes that result in symptoms such as anemia, bleeding, fatigue, easy bruising, and increased risk of infection. The median age at diagnosis is approximately 70 years; however, patients as young as 2 years have been reported. The diagnosis of myelodysplastic syndrome is made upon a complete blood count, an evaluation of the bone marrow, and a peripheral smear, with prognosis based on a variety of factors. The Revised International Prognostic Scoring System (IPSS-R) or the Molecular International Prognostic Score System (IPSS-M) should be used to incorporate information on bone marrow blast percentage, karyotype, and cytopenias for the purpose of stratifying the myelodysplastic syndromes into risk groups to guide management. Patients with lower scores are primarily treated with supportive care or low intensity therapies such as azacytidine, decitabine, or immunosuppressive therapy. Patients with a moderate to high scores are primarily treated with combination chemotherapy and/or allogeneic HSCT to alter the disease course. HSCT has been shown to improve overall survival rates in all risk groups (Myers & Corbacioglu 2024; Aster & Stone 2024; ¹⁻²Sekeres & Platzbecker 2024).

Myeloproliferative neoplasms, or myeloproliferative disorders, are an “abnormal proliferation of one or more terminal myeloid cell lines in the peripheral blood” (Thapa et al. 2023). Myeloproliferative neoplasms consist of four types: chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, and primary myelofibrosis. Myeloproliferative neoplasms are characterized by the dysregulated proliferation of myeloid cells including megakaryocytes and myeloid and erythroid progenitors in the bone marrow resulting in ineffective erythropoiesis, the production of cytokines within the marrow microenvironment, and the reactive deposition of fibrous connective tissue (reticulin or collagen) in the bone marrow, often with osteosclerosis. In later fibrotic stages, the peripheral blood

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demonstrates teardrop-shaped red cells (e.g., dacrocytes), nucleated red blood cells, and early myeloid forms (e.g., a triad termed leukoerythroblastosis), and extramedullary hematopoiesis results in hepatomegaly and splenomegaly. Most patients with primary myelofibrosis present with anemia, marked splenomegaly, early satiety, and hypercatabolic symptoms including severe fatigue, low-grade fever, night sweats, bone pain, and weight loss. Management of patients with primary myelofibrosis is determined by the risk of disease progression and estimated overall survival as calculated by prognostic scores. The International Prognostic Scoring System (IPSS), the Dynamic International Prognostic Scoring System (DIPSS) and the Dynamic International Prognostic Scoring System Plus (DIPSS-Plus) score are the three most common scores used for risk stratification. IPSS should be used at time of diagnosis and DIPSS-Plus incorporates karyotyping and is used during the course of treatment. DIPSS can be used if karyotyping is not available. The DIPSS and DIPSS-Plus scoring systems are outlined in the Supplemental Information section. At the current time, allogeneic HSCT constitutes the only treatment modality with a curative potential in primary myelofibrosis. Other treatment modalities are only palliative and include ruxolitinib as first-line therapy for management of disease-related symptoms. Hydroxyurea is considered a first-line therapy for control of hyperproliferation manifestations of myelofibrosis (constitutional symptoms, hepatosplenomegaly, and reduction of leukocytosis and thrombocytosis) (Chao 2024; Thapa et al. 2023; ¹⁻²Tefferi 2023; Tefferi 2025; ¹DynaMed 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).

Acute Lymphoblastic Leukemia

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of acute lymphoblastic leukemia when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
 - a. Complete first remission (CR-1) defined by a bone marrow biopsy that includes normocellular bone marrow with no more than 5% blasts and no signs or symptoms of the disease and any of the following high-risk factors for relapse:
 - i. Children who are < 1 year or > 9 years and adults who are < 35 years
 - ii. Any of the following chromosome abnormalities: t(4;11), t(1;19), t(8;14), deletion of(7q), trisomy 8, 11q23 (MLL) translocation
 - iii. B-cell immunophenotype (i.e., presence of Mature B cell phenotype (Burkitt's lymphoma)
 - iv. Extramedullary disease outside the bone marrow especially affecting central nervous system
 - v. Failure to achieve complete remission within 6 weeks of the start of induction therapy
 - vi. High white blood cell count (WBC) > 50,000 at diagnosis
 - vii. Hypodiploidy: defined as less than 45 chromosomes
 - viii. Minimal residual disease (MRD) positivity following induction
 - ix. Positive Philadelphia chromosome: t(9;22) or BCR-ABL positive
 - b. Second or subsequent complete remission (CR-2) following complete first remission (CR-1) defined by normocellular bone marrow with no more than 5% blasts on bone marrow biopsy and no signs or symptoms of the disease

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- c. Any stage of relapse
2. *Autologous HSCT* may be **considered medically necessary** in Members when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
 - a. Does not have a well-matched allogeneic donor or has medical contraindications to an allogeneic transplantation procedure
 - b. Member is in morphologic and cytogenetic first complete remission (CR-1) at the time of stem cell harvest
 - c. Member has ANY of the following high-risk factors for relapse:
 - i. Children who are < 1 year or > 9 years and adults who are < 35 years
 - ii. Any of the following chromosome abnormalities: t(4;11), t(1;19), t(8;14), deletion of(7q), trisomy 8, 11q23 (MLL) translocation
 - iii. B-cell immunophenotype (i.e., presence of Mature B cell phenotype (Burkitt's lymphoma)
 - iv. Extramedullary disease outside the bone marrow especially affecting central nervous system
 - v. Failure to achieve complete remission within 6 weeks of the start of induction therapy
 - vi. High white blood cell count (WBC) > 50,000 at diagnosis
 - vii. Hypodiploidy: defined as less than 45 chromosomes
 - viii. Minimal residual disease (MRD) positivity following induction
 - ix. Positive Philadelphia chromosome: t(9;22) or BCR-ABL positive
3. *Repeat Allogeneic HSCT* may be **considered medically necessary** in the case of bone marrow relapse**, primary graft failure OR failure to engraft*

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

** NOTE: Bone marrow relapses are defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after a complete remission as indicated by a peripheral blast count of 5,000 or greater ($\geq 5\%$ blasts)

Investigational, Unproven, and/or Not Medically Necessary

1. Autologous HSCT in adults who have refractory ALL or are in second or greater remission
2. A planned tandem/sequential HSCT
3. 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

Acute Myeloid Leukemia

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of acute myeloid leukemia when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
 - a. Adults who are \geq age 18 with ANY of the following:
 - i. History of myelodysplastic syndrome (MDS)
 - ii. Failed induction therapy: presence of leukemia blasts in the blood, bone marrow or any extramedullary site after 4-6 weeks of chemotherapy
 - iii. High white blood cell count (WBC) > 100,000 at diagnosis
 - iv. AML after first relapse
 - v. Extramedullary disease outside the bone marrow especially affecting central nervous system
 - vi. Requiring > one cycle to achieve remission

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- vii. Complete first remission (CR-1)**
 - viii. Adverse to intermediate risk stratification^^
 - b. Children who are \leq age 18 with ANY of the following:
 - i. Children who are < 2 years at diagnosis
 - ii. Failed induction therapy: presence of leukemia blasts in the blood, bone marrow or any extramedullary site after 4-6 weeks of chemotherapy
 - iii. High white blood cell count (WBC) $> 100,000$ at diagnosis
 - iv. AML after first relapse
 - v. Extramedullary disease outside the bone marrow especially affecting central nervous system
 - vi. Requiring $> one$ cycle to achieve remission
 - vii. Abnormality of chromosome 5 or 7
 - viii. Complete first remission (CR-1)*
 - ix. Adverse to intermediate risk stratification^^
 - c. Second or subsequent complete remission (CR-2) following complete first remission defined by bone marrow biopsy including normocellular bone marrow with no more than 5% blasts and no signs or symptoms of the disease
2. *Haploidentical allogeneic HSCT* may be **considered medically necessary** for the treatment of acute myeloid leukemia when there are **no HLA matched sibling or well-matched unrelated donors**, and ALL allogeneic transplant criteria above are met in addition to ALL the following:
- a. Donor is medically, socially, and psychologically fit to donate
 - b. Donors that are < 40 years of age are preferred over donors ≥ 40 years of age
 - c. Absence of major ABO incompatibility between the donor and the 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. The 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 \rightarrow O, A \rightarrow A, B \rightarrow B, or AB \rightarrow AB)
3. *Autologous HSCT* may be **considered medically necessary** for the treatment of acute myeloid leukemia when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
- a. Incomplete first remission (CR-1)
 - b. Absence of a well-matched allogeneic donor OR has medical contraindication to an allogeneic transplantation
 - c. Member is in complete morphologic and cytogenetic complete remission (CR) at the time of stem cell harvest
 - d. Absence of myelodysplastic syndrome (MDS)
4. *Repeat Allogeneic or Autologous HSCT* may be **considered medically necessary** in the case of bone marrow relapse**, primary graft failure OR failure to engraft***

* Complete First Remission (CR-1) (Litzow 2025)			
Parameter	Complete ^a	Partial Remission ^b	No response
Blasts	$< 5\%$ adults $< 10\%$ children	$< 70\%$ ^c	No improvement
Hemoglobin	≥ 12 g/dL adult ≥ 11 g/dL children	≥ 9 g/dL adult & children	No change or less than criteria for partial remission
Granulocytes	$> 200/\text{mm}^3$ adult; $> 1,500/\text{mm}^3$ children	$> 200/\text{mm}^3$ adult; $> 1,500/\text{mm}^3$ children	No change or less than criteria for partial remission

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Platelets	>100,000/mm ³	-	No change or less than criteria for partial remission
Extramedullary disease	Resolved	≥50% reduction	No change
Clinical symptoms	None	Improved	No improvement

^a Complete remission requires that all criteria in this column be fulfilled. ^bPartial remission requires fulfillment of criteria in each row for either complete or partial remission. ^c Achievement of normal myelopoiesis for 2 weeks or longer to >30% of total nucleated cells and a reduction in the number of leukemic cells, lymphocytes and blasts to <70%.

**** NOTE:** Bone marrow relapses are defined as the reappearance of leukemia cells in the bone marrow or peripheral blood after a complete remission as indicated by a peripheral blast count of 5,000 or greater (≥5% blasts)

***** NOTE:** Engraftment is defined as an absolute neutrophil count (ANC) ≥ 0.5 x 10⁹/L (or ≥ 500/mm³) for three consecutive days or three consecutive laboratory values obtained on different days (CIBMTR 2024; NMDP 2022)

^^ Risk Status of AML Based on Cytogenetic and Molecular Factors (³NCI 2025)		
Risk Status	Cytogenetic Factors	Molecular Abnormalities
Favorable Risk	Core binding factor: Inv(16), t(8;21), t(16;16) or t(15;17)	Normal karyotype with an NPM1 variant (in absence of an FLT3 variant), and normal karyotype with double cytosine-cytosine-adenosine-adenosine-thymidine (CCAAT)-enhancer binding protein (C/EBP)-alpha variants.
Intermediate Risk	Patients with normal cytogenetics	Consolidation management should be individualized based on additional molecular markers, patient comorbid factors, and patient preference or, preferably, managed according to a clinical trial.
Adverse Risk	deletion of 5q, 7q, +8, Inv3, t(3;3), t(6;9), abnormality of (17p), t(9;22) Abnormalities of 11q23, excluding t(9;11) a complex or monosomal karyotype, a history of myelodysplasia or antecedent hematologic disorder	Normal cytogenetics with FLT3-ITD variant TP53 variant, RUNX1 variants, ASXL1 variants.

Investigational, Unproven, and/or Not Medically Necessary

1. 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

Chronic Lymphoblastic Leukemia/Small Lymphocytic Lymphoma

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of chronic lymphoblastic leukemia/small lymphocytic lymphoma when ALL MCP 459 Transplant Evaluation criteria are met, in the setting of ONE of the following disease states:
 - a. Relapsed or refractory disease after prior therapy with cBTKi (e.g., ibrutinib, acalabrutinib, zanubrutinib) or ncBTKi-r (e.g., noncovalent reversible BTKi (ncBTKi; pirtobrutinib) and BCL2i- (Venetoclax) containing regimens
 - b. Richter's transformation to clonally related or unknown clonal diffuse large B-cell lymphoma
 - i. *Note:* For Richter transformation that transforms into De Novo or clonally unrelated diffuse large B-cell lymphoma see Non-Hodgkin Lymphoma section
 - ii. *Note:* For Richter transformation that transforms into Classic Hodgkin Lymphoma see Hodgkin Lymphoma section y
 - c. Rai Stage III-IV disease with ANY of the following high-risk factors for relapse:
 - i. High-risk cytogenetics or molecular features (e.g., del(11q) or del(17p)/TP53 mutation; ZAP70, CD38 positivity; unmutated immunoglobulin variable heavy-chain gene mutational status (IGHV)
 - ii. Short initial remission
 - iii. Poor initial response

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iv. Richter's transformation to diffuse large cell lymphoma

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) $\geq 0.5 \times 10^9/L$ (or $\geq 500/mm^3$) 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. HSCT in patients with refractory progressive disease occurring more than 12 months after discontinuation of treatment
2. HSCT in patients with relapsed or refractory CLL after initial purine analogue-based therapy
3. Autologous 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

Chronic Myeloid Leukemia

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of chronic myeloid leukemia when ALL MCP 459 Transplant Evaluation criteria are met, and treatment is intended for ANY of the following:
 - a. No hematologic response* after 6 months of oral TKI (imatinib, dasatinib, nilotinib) therapy or no cytogenetic response^
 - b. Those in cytogenetic relapse at 6, 12, or 18 months, after achieving initial hematologic remission after 3 months of imatinib therapy
 - c. Advanced phase CML at diagnosis or disease progression to accelerated phase while on oral TKI therapy, defined by one or more of the following:
 - i. Peripheral blood myeloblasts $\geq 15\%$ and $< 30\%$
 - ii. Peripheral blood myeloblasts and promyelocytes combined $\geq 30\%$
 - iii. Peripheral blood basophils ≥ 20 percent
 - iv. Platelets $< 100,000/microL$ ($\leq 100 \times 10^9/L$), unrelated to therapy
 - v. Platelets $> 1,000,000/microL$, unresponsive to therapy
 - vi. Progressive splenomegaly and increasing white cell count, unresponsive to therapy
 - vii. Cytogenetic evolution (defined as the development of chromosomal abnormalities in addition to the Philadelphia chromosome)
 - d. Progressing on a TKI to Blast crisis (myeloid or lymphoid), defined by ANY of the following:
 - i. $\geq 30\%$ percent peripheral blood or bone marrow blasts
 - ii. Large foci or clusters of blasts on the bone marrow biopsy
 - iii. Presence of extramedullary blastic infiltrates (e.g., myeloid sarcoma, also known as granulocytic sarcoma or chloroma)
 - e. Intolerance to TKI therapy or TKI resistant disease

* Complete hematologic response (CHR) is defined by (NCCN 2025 v3.2025, p 27):

- Complete normalization of peripheral blood counts with a white blood cell count $< 10,000/microL$ ($< 10 \times 10^9/L$)
- No immature cells, such as myelocytes, promyelocytes, or blasts in peripheral blood
- Platelet count $< 450,000/microL$ ($450 \times 10^9/L$)
- No signs and symptoms of disease with resolution of palpable splenomegaly

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[^] Cytogenetic response is classified according to the percentage of Philadelphia chromosome positive cells (⁷NCCN 2025 v3.2025, p 27):

- Complete cytogenetic response (CCyR): No Ph-positive metaphases
- Major cytogenetic response (MCyR): 0%–35% Ph-positive metaphases
- Partial cytogenetic response (PCyR): 1%–35% Ph-positive metaphases
- Minor cytogenetic response: >35%–65% Ph-positive metaphases

For patients with an inadequate number of metaphases, complete cytogenetic response can also be documented by FISH of blood interphase cell nuclei demonstrating <1 percent BCR-ABL1-positive nuclei of at least 200 nuclei.

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

*NOTE: Engraftment is defined as an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/L$ (or $\geq 500/mm^3$) 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. HSCT in patients with refractory progressive disease occurring more than 12 months after discontinuation of treatment
2. Autologous HSCT
3. 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

Hodgkin/Non-Hodgkin Lymphoma

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of Hodgkin/Non-Hodgkin Lymphoma when ALL MCP 459 Transplant Evaluation criteria are met, and treatment is intended for ONE of the following:
 - a. Diagnosis of Hodgkin Lymphoma with ONE of the following clinical indications:
 - i. Biopsy-proven relapse from primary treatment in less than 12 months
 - ii. Biopsy-proven relapse after autologous transplant
 - iii. Multiple biopsy-proven relapses
 - b. Diagnosis of Non-Hodgkin lymphoma with ONE of the following classifications:
 - i. Diffuse Large B-Cell:
 1. Chemosensitive relapsed disease
 2. Relapsed disease post-autologous transplant
 - ii. Burkitt's Lymphoma (chemosensitive relapsed disease)
 - iii. Follicular Lymphoma as evidenced by ONE of the following:
 1. Histologic transformation to diffuse large B-cell lymphoma
 2. Consolidative therapy for patient in second or third remission
 - iv. Cutaneous T-cell Lymphoma (mycosis fungoides, Sezary Syndrome) that is ONE of the following:
 1. Refractory
 2. Progressive (e.g., Stage IIB, III, or IV)
 - v. Adult T-cell Lymphoma with acute or lymphoma subtype responsive to chemotherapy
 - vi. Mantel Cell (in relapse, needing alternative second-line therapy)
 - vii. T-Cell Prolymphocytic Leukemia (consolidation therapy)
 - viii. Hepatosplenic T Cell Lymphoma (partial or complete response following induction chemotherapy)
 - ix. Other High-Risk Lymphomas at diagnosis

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2. *Autologous HSCT* may be **considered medically necessary** in adults and children when ALL MCP 459 Transplant Evaluation criteria are met, and treatment is intended for ONE of the following:
- Diagnosis of Hodgkin Lymphoma with ONE of the following clinical indications:
 - First relapse in chemosensitive disease
 - Partial remission after radiotherapy for isolated lesions
 - Primary refractory disease
 - Diagnosis of Non-Hodgkin Lymphoma with ONE of the following classifications:
 - Diffuse Large B Cell:
 - Relapsed
 - Treatment refractory or chemosensitive
 - Double or triple cytogenetic rearrangement (MYC and BCL-2 and/or BCL-6) at diagnosis
 - Mantel Cell (partial or complete response following induction chemotherapy OR as consolidation / additional therapy)
 - Burkitt's Lymphoma (relapsed disease)
 - Follicular Lymphoma as evidenced by ONE of the following:
 - Histologic transformation to diffuse large B-cell lymphoma with partial or complete response to treatment
 - Consolidative therapy for patient in second or third remission
 - Relapsed or refractory disease
 - High Grade as evidenced by ONE of the following:
 - C-myc rearrangement at diagnosis
 - Primary induction failure
 - First complete remission (CR-1)
 - First relapse
 - Second complete remission (CR2) or subsequent remission
 - Mature T-Cell as evidence by ONE of the following:
 - First complete remission (CR-1)
 - First relapse
 - Peripheral T Cell (partial or complete response following induction chemotherapy OR as consolidation / additional therapy)
 - Other High-Risk Lymphoma at diagnosis
3. *Haploidentical allogeneic HSCT* may be **considered medically necessary** for the treatment of when there are **no HLA matched sibling or well-matched donors**, and ALL allogeneic transplant criteria above are met in addition to ALL the following:
- Donor is medically, socially, and psychologically fit to donate
 - Donors that are < 40 years of age are preferred over donors ≥ 40 years of age
 - Absence of major ABO incompatibility between the donor and the recipient. Major ABO incompatibilities include:
 - Recipient blood type O: Donor blood type A, B, or AB
 - Recipient blood type A: Donor blood type B or AB
 - Recipient blood type B: Donor blood type A or AB
 - Recipient blood type AB: No major ABO incompatibilities
 - Diagnosis of Hodgkin Lymphoma with ONE of the following clinical indications:
 - Biopsy-proven relapse from primary treatment in less than 12 months
 - Biopsy-proven relapse after autologous transplant
 - Multiple biopsy-proven relapses
 - Matched cytomegalovirus (CMV) IgG serologic status between the donor and the recipient includes ONE of the following:
 - For a recipient who is CMV IgG negative, use a CMV IgG negative donor
 - For a recipient who is CMV IgG positive, use a CMV IgG positive donor
 - Use an ABO compatible donor over a minor ABO incompatible donor (ABO compatible transplants are O→O, A→A, B→B, or AB→AB)

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4. 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) $\geq 0.5 \times 10^9/L$ (or $\geq 500/mm^3$) 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. Planned tandem autologous or allogeneic HSCT for treatment of Hodgkin/Non-Hodgkin Lymphoma
2. Repeat autologous or allogeneic HSCT due to persistent, progressive or relapse for treatment of Hodgkin/Non-Hodgkin Lymphoma
3. 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

Multiple Myeloma / POEMS Syndrome

Medically Necessary

1. *Autologous HSCT* may be **considered medically necessary** for the treatment of **multiple myeloma** when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following:
 - a. Diagnosis of Stage II or III multiple myeloma and ONE of the following:
 - i. A partial response to post induction therapy defined as a 50% decrease either in measurable paraprotein (serum and/or urine) or in bone marrow infiltration sustained for at least 1 month
 - ii. Relapsed disease post induction therapy defined as increased M-proteins in serum and/or urine
 - iii. Refractory disease post induction chemotherapy defined as disease that is unresponsive to post induction chemotherapy
2. *Repeat autologous HSCT* may be **considered medically necessary** for the treatment of **multiple myeloma** when the individual has disease relapse after a durable complete or partial remission following an autologous HSCT
3. *Allogeneic HSCT* may be **considered medically necessary** for the treatment of **multiple myeloma** when the individual has early relapse (less than 24 months) after primary therapy that included an autologous HSCT
4. *Tandem HSCT* may be **considered medically necessary** for the treatment of **multiple myeloma** when ALL the following are met:
 - a. Member has active multiple myeloma
 - b. First and second transplantation are within a 6-month period for either of the following:
 - i. Autologous-autologous tandem HSCT
 - ii. Initial autologous HSCT followed by reduced intensity conditioning allogeneic HSCT
5. *Autologous HSCT* may be **considered medically necessary** for the treatment of **POEMS Syndrome** when ALL MCP 459 Transplant Evaluation criteria are met AND the Member has a diagnosis of disseminated POEMS syndrome defined as diffuse sclerotic lesions or disseminated bone marrow involvement
6. A *second autologous HSCT* may be **considered medically necessary** for the treatment of **responsive POEMS syndrome** that has relapsed after a durable complete or partial remission following an autologous HSCT

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Investigational, Unproven, and/or Not Medically Necessary

1. Hematopoietic stem cell collection, storage, and freezing for a future unplanned transplant, including in utero collection
2. Repeat allogeneic stem cell transplantation due to persistent, progressive or relapsed disease for the treatment of *Multiple Myeloma*
3. Allogeneic and/or tandem HSCT for the treatment of *POEMS Syndrome*

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

Myelodysplastic Syndrome

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of myelodysplastic syndromes when ALL MCP 459 Transplant Evaluation criteria are met, and treatment is intended for ONE of the following:
 - a. Member has an International Prognostic Scoring System – Revised (IPSS-R) score of > 3 (intermediate, high, or very high risk) and/or an International Prognostic Scoring System – Molecular (IPSS-M) score of > 0 to 0.5 (moderate high)
 - b. Myelodysplastic Syndrome with poor prognostic features including ANY of the following:
 - i. Treatment-related myelodysplastic syndrome
 - ii. Refractory cytopenias
 - iii. Adverse cytogenetics and molecular features
 - iv. Transfusion dependence
 - v. Failure of hypomethylating agents or chemotherapy
 - vi. Moderate to severe marrow fibrosis
2. A *subsequent allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** once after the first HSCT has occurred for Members with myelodysplastic syndromes who meet all the above criteria for transplant and have ANY of the following:
 - a. Primary graft failure indicated by no signs of engraftment* by 42 days after the transplant
 - b. Failure to engraft*
 - c. Late relapse (> 18 months after HSCT) as salvage therapy

*NOTE: Engraftment is defined as an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/L$ (or $\geq 500/mm^3$) 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. Autologous HSCT
2. 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

Myeloproliferative Neoplasms / Primary Myelofibrosis

Medically Necessary

1. *Allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** in Members who have an appropriate HLA well-matched donor for the treatment of myeloproliferative neoplasms when ALL MCP 459 Transplant Evaluation criteria are met, in addition to ALL the following criteria:
 - a. ONE of the following:

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- i. For age < 45 years, conventional intensity conditioning allogeneic HSCT is recommended
 - ii. For age > 45 years, reduced intensity conditioning allogeneic HSCT is recommended
 - b. ANY of the following clinical indications (see table in the supplemental information section for additional scoring information) Note: MIPSS-70+ v2.0 is preferred when cytogenetic testing is available, as it incorporates additional prognostic factors. MIPSS-70 remains acceptable when karyotypic data is unavailable. DIPSS-Plus should be used if molecular testing is unavailable, and DIPSS should only be used when both molecular and cytogenetic testing are unavailable
 - i. High risk disease defined as ONE of the following:
 1. Dynamic International Prognostic Scoring System (DIPSS) score of 5-6 points
 2. Dynamic International Prognostic Scoring System – Plus (DIPSS-Plus) score of 4-6 points
 3. Mutation-enhanced International Prognostic Scoring System-70 (MIPSS-70) score \geq 5 points
 4. Mutation and Karyotype-enhanced International Prognostic Scoring System-70+ Version 2.0 (MIPSS-70+ v2.0) score \geq 5 points
 - ii. Intermediate risk disease defined as ONE of the following:
 1. DIPSS score of 1-2 points for intermediate-1 risk (INT-1)
 2. DIPSS score of 3-4 points for intermediate-2 risk (INT-2)
 3. DIPSS-Plus score of 1 point for intermediate-1 risk (INT-1)
 4. DIPSS-Plus score of 2-3 points for intermediate-2-risk (INT-2)
 5. MIPSS-70 score of 2-4 points
 6. MIPSS-70+ v2.0 score of 3-4 points
 - iii. Any myeloproliferative neoplasm or primary myelofibrosis disease with poor prognostic features including ANY of the following:
 1. Dependent on transfusions of red blood cells
 2. Dependent on transfusions of platelets or has frequent infarctions
 3. Has an absolute neutrophil count < 1000/mm³
 4. Resistant to conservative therapy with poor initial response or at progression of disease
2. A *subsequent allogeneic HSCT* (ablative or non-myeloablative) may be **considered medically necessary** once after the first prior HSCT has occurred for Members with any myeloproliferative neoplasm or primary myelofibrosis disease who meet ALL the above criteria for transplant and have ANY of the following:
 - a. Primary graft failure indicated by no signs of engraftment* by 42 days after the transplant
 - b. Failure to engraft*
 - c. Late relapse (> 18 months after HSCT) as salvage therapy

*NOTE: Engraftment is defined as an absolute neutrophil count (ANC) $\geq 0.5 \times 10^9/L$ (or $\geq 500/mm^3$) 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. Autologous HSCT
2. 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

Acute Lymphoblastic Leukemia

Non-Randomized Studies, Retrospective Reviews and Other Evidence

Bader et al. (2024) published the nonrandomized section of the FORUM study, a large, prospective, international, multicenter phase 3 trial designed to evaluate conditioning strategies for allogeneic hematopoietic stem cell transplantation (HSCT) in pediatric patients with high-risk acute lymphoblastic leukemia (ALL). The study consists of both randomized and nonrandomized components. In the randomized portion, children aged 4 years and older were assigned to either total body irradiation (TBI) with etoposide (Eto) or chemotherapy-based conditioning alone before HSCT. However, the nonrandomized part—published by Bader et al. focused on younger children under 4 years old, who were allocated to chemotherapy-only conditioning across 88 centers in 21 countries.

To minimize the long-term adverse effects associated with TBI in younger patients, the study evaluated two TBI-free conditioning regimens: fludarabine (Flu) and thiotepa (Thio), combined with either busulfan (Bu) or treosulfan (Treo). Between 2013 and 2021, 191 children underwent transplantation and were followed for a median of three years. The three-year overall survival (OS) rate was 63% in the Flu/Thio/Bu group and 76% in the Flu/Thio/Treo group, with no statistically significant difference. Three-year event-free survival (EFS) was similar between both groups (52% vs. 51%). (Relapse remained the primary cause of treatment failure, while nonrelapse mortality (NRM) was low across both regimens. Graft-versus-host disease (GVHD) rates varied, with grade >1 acute GVHD occurring more frequently in the Flu/Thio/Bu group (29%) compared to Flu/Thio/Treo (17%). Severe grade 3/4 GVHD rates were similar between the two groups (10% vs. 9%). Chronic GVHD incidence at three years was also low in both regimens.

In conclusion, both chemotherapy-based conditioning approaches were well tolerated, and nonrelapse mortality was minimal. However, relapse remains a major challenge in ensuring long-term treatment success for young children undergoing HSCT. This nonrandomized part of the international, multicenter FORUM trial showed that chemotherapeutic conditioning with either Flu/Thio/Bu or Flu/Thio/Treo allows for HSCT in **children under four years** old with high-risk ALL, while maintaining a low complication rate. Further prospective trials are required and planned to reduce the risk of leukemia recurrence and improve survival in this vulnerable young population.

Acute Myelogenous Leukemia

Randomized Controlled Trials

Stelljes et al. (2024) conducted a phase 3, non-inferiority trial to evaluate whether high-dose cytarabine-based salvage chemotherapy before allogeneic HSCT improves survival in relapsed or poorly responsive AML. 281 patients (aged 18–75) were randomly assigned to immediate HSCT (disease control, n=140) or remission induction with chemotherapy before HSCT (n=141). The study aimed to show non-inferiority of disease control compared to remission induction using a 5% margin and a 2.5% allowable statistical error. The primary endpoint was complete remission by day 56 post-transplantation. In the disease control group, patients proceeded to HSCT immediately with optional low-dose cytarabine or single-dose mitoxantrone (10 mg/m²), followed by sequential conditioning. In the remission induction group, patients received one course of salvage chemotherapy (high-dose cytarabine 3 g/m² or 1 g/m² for older/comorbid patients, twice daily on days 1–3, plus mitoxantrone 10 mg/m² on days 3–5). All patients underwent HSCT regardless of remission status. Treatment success was 83% (116/140) in disease control vs. 79% (112/141) in remission induction (p=0.036 for non-inferiority). Among per-protocol patients, rates were 84% (116/138) vs. 81% (109/134) (p=0.047), with no statistically significant advantage as confidence intervals overlapped zero. Disease control patients had fewer severe non-hematological adverse events (21% vs. 61%, p<0.0001) and spent less time hospitalized before HSCT (median 15 vs. 42 days, p<0.0001). Mortality rates were similar, with two patients in each group dying from AML progression and two additional deaths from treatment-related complications in remission induction. These findings suggest watchful waiting with immediate HSCT may be a viable alternative for fit AML patients with a stem cell donor, reducing toxicity risks. Further randomized trials are needed to refine optimal pre-transplant strategies.

Systematic Reviews and Meta-Analyses

Masetti et al. (2022) conducted a meta-analysis of studies comparing allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission (CR-1) with chemotherapy alone in high-risk pediatric acute myeloid leukemia (AML). Nine studies were included in the meta-analysis with a total of 1448 patients; 522 patients in

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the allo-HSCT group and 926 in the chemotherapy group. Outcomes measured included overall survival (OS), reduced relapse risk (RR), and disease-free survival (DFS). The allo-HSCT group showed significantly improved overall survival ($p = 0.0006$). Two of the nine studies reported RR with a total of 606 patients. The RR was significantly high in the chemotherapy group compared to the allo-HSCT group ($p = 0.006$). DFS was reported in three studies with a total of 861 patients. The results showed improved DFS in the allo-HSCT group ($p = 0.0001$). A limitation of this study is the follow up period as allo-HSCT can be complicated by severe long-term toxicity and salvage rate after relapse is lower in transplanted patients. Another limitation is the differences in chemotherapy protocols and consolidation strategies in the chemotherapy groups. The analysis concluded that allo-HSCT offers significant improvement in OS and DFS for high-risk pediatric AML in CR-1.

Kharfan-Dabaja et al. (2022) completed a systematic review and meta-analysis were performed to assess the role of a second allogeneic hematopoietic cell transplantation (allo-HSCT) in patients with AML. Twelve studies ($n=1586$ patients) involved a mixed population of patients in both pediatric and adult age groups and 8 studies ($n=1186$ patients) restricted to the adult age group were included in the review. Studies were included if they included > 10 patients, were published in full manuscript form, and evaluated the use of a second allo-HSCT for the sole purpose of treating relapsed AML. Outcomes measured include complete hematologic remission (CR), overall survival (OS), progression-free/disease-free survival (PFS/DFS), acute and chronic graft-versus-host disease, non-relapse mortality (NRM), and relapse. In the mixed population group ($n=126$) the CR rate was 47%. In the adult population group ($n=190$) the CR rate was 67%. The OS rates for the mixed population group ($n=1524$) was 28% and 34% in the adult population ($n=1186$). PFS/DFS rates in the mixed population group ($n=419$) was 27% and 30% in the adult population group ($n=1117$). Acute GVHD rates were 35% and 29% in the mixed population group ($n=104$) and adult population group ($n=951$), respectively. Chronic GVHD rates were 27% in the mixed population group ($n=104$) and 58% in the adult population group ($n=398$). In the mixed population group ($n = 1253$), the NRM rate was 40% and in the adult population group ($n=1149$), the NRM rate was 27%. The relapse rate in the mixed population group ($n=314$) was 40% and 51% in the adult population group ($n=1157$). The analysis concluded that a second allo-HSCT is an acceptable treatment choice for AML patients relapsing after a first allo-HSCT.

Chronic Myelogenous Leukemia

Systematic Reviews and Meta-Analyses

Yassine et al. (2022) performed a systematic review and meta-analysis to determine the efficacy of allogeneic HSCT in patients with TKI-resistant chronic phase CML (CP-CML). The meta-analysis included 9 studies with a total of 439 patients. Patients were stratified based on age groups determined by the researchers. Patients were placed in the pediatric group if they were < 18 years of age. Patients ≥ 18 years of age were placed into the adult group. Some of the studies included in the meta-analysis either did not group patients according to age or used overlapping age groups. Patients in those studies were placed into a separate "mixed/unclear population" group. The primary goals of the study were participant characteristics, clinical outcomes based on benefits, progression-free survival (PFS), disease-free survival (DFS), complete remission (CR), molecular response (MR), NRM, relapse, acute GVHD, and chronic GVHD. Stratification of the included studies resulted in 3 studies ($n=200$ patients) for the adult group, 1 study ($n=28$ patients) for the pediatric group, and 5 studies ($n=211$) for the mixed/unclear population group. The pooled outcomes based on benefits for adults was 84%, pediatrics was 91%, and the mixed/unclear population was 76%. PFS was only reported in studies stratified into the mixed/unclear population group. The pooled PFS rates for the mixed/unclear population was 82%. The pooled DFS rates for adults and the mixed/unclear population was 66% and 47% respectively. CR was only reported in 1 study stratified to the adult population and was 56%. The pooled MR rates for adults and the mixed/unclear population was 88% and 89% respectively. The pooled NRM rates for adults and the mixed/unclear population was 20% and 28% respectively. The pooled relapse rates for adults and the mixed/unclear population were 19% and 27% respectively. Acute and chronic GVHD rates were only reported in studies stratified to the mixed/unclear population and were 46% and 51% respectively. Limitations of the study included the inability of researchers to compare outcomes to regimen intensity and outcomes could not be analyzed separately for patients with TKI resistance versus TKI intolerance.

Non-randomized Studies, Retrospective Reviews and Other Evidence

Masouridi-Levrat et al. (2022) completed a prospective study that included 383 patients to determine if prior treatment with a second-generation TKI (2GTKI) before allogeneic HSCT influenced engraftment and non-relapse mortality (NRM) rates. Secondary outcomes measured included rates of acute and chronic GVHD and hepatic sinusoidal obstruction syndrome (SOS). Patients were placed into groups that received dasatinib ($n=155$), nilotinib ($n=64$), or sequential treatment of dasatinib and nilotinib with or without bosutinib and/or ponatinib ($n=164$). Most patients ($n=306$)

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had imatinib as the primary TKI. Median follow-up time after allogeneic HSCT was 37 months. The disease status at the start of the 2GTKI was reported for 265 patients: 123 were in chronic phase 1 (CP1), 67 were in advanced phase (AP) or > CP1, and 75 were in blast crisis (BC). The overall disease status at the time of allogeneic HSCT was reported for 361 patients: 139 were in CP1, 163 in AP or > CP1, and 59 were in BC. Engraftment was able to be evaluated in 379 patients with 350 achieving engraftment, 10 experiencing primary graft failure, and 19 experiencing secondary graft failure. Overall NRM was 18% at 12-months and 24% at 5-years following allogeneic HSCT. Acute GVHD was evaluable in 347 patients with approximately 34% of patients experiencing grade II-IV acute GVHD at a median time of 0.9 months. Chronic GVHD was evaluable in 314 patients with an incidence rate of 60% by the 5-year mark. Median time to chronic GVHD was 5.7 months. Disease relapse occurred in 29% of patients at 2-years and 36% at 5-years. Overall survival (OS) at 2-years was 65.4% and 56% at 5-years. SOS occurred in 6 cases with most of those cases occurring in the dasatinib group (n=5). The SOS rate was 2% in this study which is much lower than previously reported rates of 25% in other studies. Researchers noted an advanced disease stage at the start of 2GTKI and allogeneic HSCT had a negative impact on OS and relapse-free survival rates. OS rates at 5-years were 67% for CP1, 57% for AP or > CP1, and 37% for BC. Researchers reported that allogeneic HSCT could be considered prior to a third line TKI therapy in CP1 due to transplantation rates appear better with pre-transplantation 2GTKI treatment.

Niederwieser and Nicolaus Kröger (2022) published an educational offering titled Transplantation in CML in the TKI era: who, when, and how ? in Hematology, American Society of Hematology Education Program. Advancements in chronic myeloid leukemia (CML) treatment necessitate continuous reassessment of when curative stem cell transplantation (HSCT) is appropriate. Tyrosine kinase inhibitors (TKIs) have significantly reduced the reliance on HSCT, but certain patients remain candidates for transplantation. For those in chronic-phase (chP) CML, initial therapy should start with first- or second-generation TKIs, with ongoing monitoring following ELN or NCCN guidelines. Patients exhibiting high-risk additional cytogenetic abnormalities (ACAs)—which predict poorer TKI responses and increased progression risk—should be evaluated for HSCT. Individuals classified as having resistant disease (NCCN) or treatment failure (ELN) are also considered for transplantation. Those who fail second-generation TKIs and show inadequate response to third-generation TKIs within three months should be assessed for HSCT. Selecting an HLA-identical related or fully matched unrelated donor is crucial, with the conditioning regimen tailored to the patient's age and comorbidities. Patients in accelerated-phase (AP) and blast-phase (BC) CML should initiate intensive chemotherapy (IC), potentially combined with TKIs, before undergoing HSCT. In more advanced-phase (AdP) CML, TKIs typically provide only temporary benefit, and HSCT outcomes are suboptimal unless pretransplant therapy is incorporated. Thus, transitioning these patients to chronic-phase CML via TKIs—either alone in AP or combined with intensive chemotherapy in BC—before proceeding with HSCT is recommended. Posttransplant monitoring with quantitative polymerase chain reaction testing is essential for guiding prophylactic or preemptive TKI treatment, with or without donor lymphocyte infusions (DLIs), to optimize outcomes.

Hodgkin and Non-Hodgkin Lymphoma
Systematic reviews and Meta-analyses

Ahmed et al. (2025) completed a meta-analysis to evaluate the effectiveness and safety of autologous hematopoietic stem cell transplantation (AHSCT) in managing malignant lymphoma following high-dose chemotherapy. A systematic literature review was conducted from February 2017 to August 2024, comparing AHSCT to standard chemotherapy outcomes. The study analyzed 896 patients who underwent AHSCT versus 1,229 patients in the control group receiving conventional chemotherapy. Patients receiving AHSCT demonstrated a significantly higher survival rate compared to standard chemotherapy (Odds Ratio: 2.23, 95% CI [1.54–3.22], $P < 0.0001$). AHSCT recipients showed enhanced disease control, with a progression-free survival odds (PFS) ratio of 2.70 (95% CI [1.86–3.92], $P < 0.0001$). AHSCT led to higher complete and partial remission rates, improving long-term outcomes. The authors found that AHSCT may outperform alternative therapies, but further research is necessary to refine treatment protocols and ensure its widespread clinical application.

Liu et al. (2023) conducted a systematic review and meta-analysis evaluating the efficacy of autologous hematopoietic stem cell transplantation versus chemotherapy or allogeneic hematopoietic stem cell transplantation for follicular lymphoma. A total of 13 studies were included, seven of which compared auto-HSCT with conventional chemotherapy and the other six compared allo-HSCT with auto-HSCT. After analysis, the authors concluded that auto-HSCT improved overall survival, progression-free survival, and event-free survival compared with conventional chemotherapy without auto-HSCT.

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Singh et al. (2022) conducted a meta-analysis analyzing allogeneic HSCT in T-cell lymphoma. A total of 22 studies were analyzed for a total of 888 patients. The patient population was comprised of 40% had peripheral T-cell lymphoma not otherwise specified, 15% had angioimmunoblastic T-cell lymphoma, 21% had anaplastic large cell lymphoma, 5% had cutaneous T-cell lymphoma, and 19% had other histologic subtypes. The results compiled revealed that at two-, three- and five-year post HSCT transplant, overall survival was 57, 54 and 51%, respectively; progression-free survival was 45, 50 and 45%, respectively; non-relapse mortality was 9, 29 and 29%, respectively; relapse rate was 30, 28 and 29%, respectively. This study shows that allo-HSCT provides durable remission in T cell lymphoma.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Ida et al. (2021) conducted a retrospective cohort study on 74 consecutive patients who underwent autologous (n = 23) or allogeneic (n = 51) HSCT. With a median follow-up of 5.8 years among survivors, the 5-year probability of progression-free survival was 64% after autologous HSCT and 55% after allogeneic HSCT (p = 0.21), with a 5-year cumulative incidence of non-relapse mortality of 0% after autologous HSCT and 9.5% after allogeneic HSCT (p = 0.062). The 5-year cumulative incidence of disease progression was similar between autologous and allogeneic HSCT (36% vs. 36%, respectively, p = 0.88). Disease progression was the major cause of treatment failure after both types of HSCT leading the authors to conclude that further strategies are needed to reduce the risk of disease progression.

Multiple Myeloma / POEMS Syndrome

Systematic Reviews and Meta-Analyses

Ludwig et al. (2025) completed a meta-analysis to evaluate the comparative effectiveness of allogeneic stem cell transplantation (allo-HSCT) versus repeat autologous stem cell transplantation (auto-HSCT) in patients with multiple myeloma who relapsed after a first-line auto-HSCT. The study analyzed individual patient data from 815 patients across two major registries—the Japan Society for Hematopoietic Stem Cell Transplantation and the Center for International Blood & Marrow Transplant Research (CIBMTR)—alongside five smaller studies using digitized Kaplan-Meier survival curves. Results indicate statistically superior progression-free survival (PFS) and overall survival (OS) for repeat auto-HSCT compared to allo-HSCT across multiple datasets. Specifically, median PFS was 11.2 months vs. 3.9 months (p < .001), and median OS was 35.1 months vs. 14.1 months (p < .001), favoring auto-HSCT. Despite historical thought suggesting allo-HSCT might offer superior disease control, this analysis demonstrates that the intensity of allo-HSCT does not translate into better survival outcomes due to its higher risks of graft-versus-host disease (GVHD) and infectious complications. While prior studies suggested potential benefits of an auto-allo approach for newly diagnosed high-risk patients, the authors argue that allo-HSCT is no longer recommended in either relapsed or newly diagnosed multiple myeloma. This aligns with the European Myeloma Network-European Hematology Association guidelines, which have removed allo-HSCT as a viable treatment option. Although some patients may benefit from a graft-versus-myeloma effect, the overall disadvantages of allo-HSCT outweigh its potential benefits in relapsed settings. Key limitations of this study include small sample sizes in some datasets, retrospective analysis, and the absence of information on salvage treatments post-transplant. The findings are particularly relevant given that modern immune therapies (CAR-T cells, bispecific antibodies, ADCs) have largely replaced allo-HSCT in regions with access to novel treatments. While more than 200 allo-HSCT procedures were still reported in 2022, a prospective randomized study comparing allo-HSCT with conventional chemotherapy has recently been activated. Ultimately, this analysis reinforces auto-HSCT as the preferred approach in relapsed multiple myeloma, particularly in regions with limited access to novel therapies.

Khorochkov et al. (2021) completed a systematic review with the goal of determining circumstances that an allogeneic HSCT approach is either feasible, preferred, and/or cautionary in patients with multiple myeloma. The review included 16 moderate- to high-quality observational and randomized controlled trials. Overall findings suggest that autologous HSCT combined with high-dose pharmacotherapy is the first-line treatment for newly diagnosed patients that are transplant eligible. Findings also suggest that allogeneic HSCT may benefit high-risk patients, particularly those with resistance to therapeutics. One study by Bryant et al. (2020) included in the review sought to observe the effects of pre-treatment variables on the success of allogeneic HSCT. The most important adverse variable found in that study was that a pre-salvage stage II or III on the International Staging System being associated with relapse and poorer survival. Combined autologous and allogeneic HSCT was shown “to enhance survival but not necessarily outcomes” and was also associated with fewer occurrences of relapse when compared to single or tandem autologous HSCT. Findings also suggest that patients who responded to pre-salvage therapy saw a benefit to progression-free and overall survival when radioimmunotherapy combined with reduced-intensity conditioning was used before allogeneic HSCT. Patients older than 55 years of age were typically associated with worse outcomes due to graft-versus-host disease. It is suggested that the care team evaluate pre-transplant factors including high-risk cytogenetics, age, and pre-salvage

therapy International Staging System criteria before creating a treatment approach tailored to each individual patient.

Costa et al. (2020) completed a meta-analysis comparing the long-term survival of patients with multiple myeloma receiving tandem autologous HSCT versus autologous-allogeneic HSCT. The analysis included 5 trials with a total of 1338 patients. A total of 899 patients were included in the tandem autologous group and 439 patients were included in the autologous-allogeneic group. The primary outcomes of the meta-analysis included overall survival (OS) and progression-free survival (PFS). Secondary outcomes were non-relapse mortality (NRM), cumulative incidence of relapse or progression, and post-relapse survival. Overall results showed a lower risk of NRM in the tandem autologous HSCT group (6.9% at 5 years and 8.3% at 10 years) compared to the autologous-allogeneic group (17.4% at 5 years and 19.7% at 10 years). However, the risk of relapse or progression was higher in the tandem autologous group (69.7% at 5 years and 77.2% at 10 years) than the autologous-allogeneic group (52.4% at 5 years and 61.6% at 10 years). PFS rates at 5 years were 23.4% and 14.4% for 10 years in the tandem autologous group versus 30.1% at 5 years and 18.7% for the autologous-allogeneic group, indicating that patients in the autologous-allogeneic group had improved PFS. OS for the tandem autologous group at 5 years was 59.8% and 36.4% at 10 years compared to 62.3% at 5 years and 44.1% at 10 years for the autologous-allogeneic group, indicating that patients in the autologous-allogeneic group had improved OS. Post-relapse survival was improved in the autologous-allogeneic group with survival rates of 51.1% at 5 years compared to 37.0% for the tandem autologous group.

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Li et al. (2024) conducted a single center retrospective analysis on the long-term outcomes of newly diagnosed POEMS patients treated with autologous HSCT. A total of 239 patients were included in the analysis with the primary outcome being dual hematologic and vascular endothelial growth factor complete responses. Median follow up was 94 months with a 5-year overall survival rate of 92.8%, and 72% 5-year time to next-line treatment (TTNT) rate. Hematologic complete response and vascular endothelial growth factor (VEGF) complete response were 57.3% and 68.6%, respectively, with 90.5% of patients achieving an overall clinical response. Patients achieving hematologic complete response or VEGF complete response had better survival outcomes compared to non-complete response patients, with a further benefit of a median TTNT of 129 months in patients with dual hematologic and VEGF complete responses. This analysis led the authors to conclude that HSCT offered excellent long term survival rates in patients newly diagnosed with POEMS syndrome.

Kook et al. (2024) conducted a retrospective analysis on the long-term outcomes of POEMS patients who received HSCT across eight institutions in South Korea between 2000 and 2022. A total of 84 patients were included in the analysis. Response to treatment was assessed clinically, hematologically, and biochemically. Clinical response was measured as either clinical improvement or no response/clinical progression. Hematologic response was placed into five categories: 1. Complete Response: defined as negative results for bone marrow and negative immunofixation analysis of serum and urine. 2. Very Good Partial Response: defined as a 90% reduction in monoclonal protein or immunofixation positivity, if monoclonal protein was at least 0.5 g/dL at baseline. 3. Partial Response: defined as a 50% reduction in monoclonal protein or immunofixation-positivity if the baseline monoclonal protein level was at least 1.0 g/dL. 4. No Response: defined as conditions that did not fulfill the above criteria. 5. Progression: defined as the re-emergence of serum/urine monoclonal protein if it were undetectable or increased by 25% from the lowest post-treatment value. Biochemical response was measured by assessing the plasma VEGF levels and placing them into five categories: 1. Complete Remission: defined as normalization of levels. 2. Partial Response: defined as > 50% reduction in serum VEGF levels. 3. No Response: defined as not fulfilling the above criteria. 4. Not Evaluable: defined as initial serum VEGF level not raised/not evaluated. 5. Progression: defined as persistent serum VEGF level elevation by more than that of 2 recordings from a previously normal result or persistent serum VEGF level rise by > 50% from the lowest post-treatment value of more than 2 recordings. Of the 84 patients assessed in the study, 75 were treated at the institution where they were diagnosed and were included in the outcome analysis. Six patients (8.0%) received local radiotherapy alone, 17 (22.7%) received chemotherapy alone, 9 (12.0%) underwent both chemotherapy and local radiotherapy, and 43 (57.3%) underwent upfront autologous HSCT. Of the 43 patients who underwent upfront autologous HSCT, 31 (41.3%) received it without previous induction chemotherapy. In the autologous HSCT cohort VEGF responses were detected in 19 patients with the following breakdown of categories: 14 (73.7%) achieved complete response, 3 patients (15.8%) achieved partial response, 1 (5.3%) remained stable disease, and 1 (5.3%) patient showed no response. A hematological response was observed in 38 patients with the following breakdown of categories: 25 (65.8%) achieved a complete response, 9 (23.7%) achieved a very good partial response, and 4 (10.5%) achieved a partial response. The overall clinical improvement rate was 87.2%. Eight patients (18.6%) died, 5 (11.6%) from transplant-related mortality, with the only factor showing a tendency towards increased transplant related mortality

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being aged > 50 years. Subgroup analysis of the 43 patients who received upfront autologous HSCT showed that there was a tendency of poor overall survival in patients with eGFR < 30 mL/min/1.73 m² than in patients with eGFR > 30 mL/min/1.73 m² (P = 0.078), and a diagnosis year > 2014 was associated with a trend for longer progression-free survival (p = 0.056). The authors concluded that the progression towards plasma cell-targeting treatments and the introduction of autologous HSCT have enhanced the overall prognosis of POEMS syndrome.

Kansagra et al. (2022) conducted a retrospective analysis comparing outcomes in patients with POEMS syndrome versus Multiple Myeloma who underwent autologous HSCT, utilizing data from the Center for International Blood and Marrow Transplant Research between 2008 – 2018. A total of 331 POEMS patients from 92 centers were identified and analyzed. Five-year outcomes were superior among patients with POEMS syndrome compared with Multiple Myeloma where the 5-year progression-free survival (72.2% vs 34.5%; p = 0.001) and 5-year overall survival (90.9% vs 71%; p = 0.001). Consistent with existing data the only factor that decreased overall survival was age of > 60 years (hazard ratio, 2.6; 95% CI, 1.2-5.6; p = 0.0148) at the time of autologous HSCT. There were no significant predictors for relapse, non-relapse mortality, and progression-free survival. Of 331 POEMS patients, 16 (5%) patients developed second primary malignancies, including 4 (1.2%) myeloid malignancies and 12 (3.6%) new solid tumors, comparable to Multiple Myeloma with 2.8 % hematologic second primary malignancies of 2.8% and 4.2% solid tumor second primary malignancies. Study limitations included inability to assess important clinical factors such as VEGF, lung function, and imaging characteristics due to missing data from various institutions. Overall, the analysis revealed autologous HSCT had better long-term safety and outcome results in POEMS patients versus those with Multiple Myeloma, which was to be expected. The authors conclude that this pooled data analysis can provide a benchmark and aid in clinical decision making.

Myelodysplastic Syndromes

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Kröger (2025) published a review article on the treatment of high-risk myelodysplastic syndromes. Allogeneic HSCT remains the only curative treatment for high-risk myelodysplastic syndrome (HR-MDS) and is recommended for carefully selected patients due to its therapy-related risks. Optimal transplant timing varies based on prognostic scoring systems, with immediate transplantation improving outcomes for patients with high or very high IPSS-R scores, while lower-risk patients may benefit from delayed transplant. Molecular and cytogenetic factors significantly influence post-transplant outcomes, with mutations such as TP53, RUNX1, and ASXL1 linked to higher relapse and mortality risk. Donor selection plays a crucial role, with matched sibling donors showing better survival, although haploidentical HSCT with post-transplant cyclophosphamide offers comparable results. Conditioning regimen choice impacts survival, with myeloablative approaches reducing relapse rates but increasing non-relapse mortality, while treosulfan-based reduced-intensity regimens may improve outcomes. HSCT is also recommended for lower-risk MDS patients experiencing progressive disease, severe cytopenias, or treatment failure. Despite poorer HSCT outcomes in TP53-mutated patients, research suggests transplantation still improves survival compared to non-transplant approaches. Lastly, pre-transplant therapy is advised for MDS patients with ≥10% blasts, but its impact on survival remains uncertain, highlighting the need for further prospective studies.

Tentori et. al (2024) completed a retrospective cohort study incorporating a decision analysis model to evaluate the optimal timing of allogeneic hematopoietic stem-cell transplantation (HSCT) in myelodysplastic syndrome (MDS). Allogeneic HSCT remains the only curative treatment for high-risk MDS (HR-MDS) and is recommended for carefully selected patients due to its therapy-related risks. Optimal transplant timing varies based on prognostic scoring systems, with immediate transplantation improving outcomes for patients with high or very high IPSS-R scores, while lower-risk patients may benefit from delayed transplant. Molecular and cytogenetic factors significantly influence post-transplant outcomes, with mutations such as TP53, RUNX1, and ASXL1 linked to higher relapse and mortality risk. Donor selection plays a crucial role, with matched sibling donors showing better survival, although haploidentical HSCT with post-transplant cyclophosphamide offers comparable results. Conditioning regimen choice impacts survival, with myeloablative approaches reducing relapse rates but increasing non-relapse mortality, while treosulfan-based reduced-intensity regimens may improve outcomes. HSCT is also recommended for lower-risk MDS patients experiencing progressive disease, severe cytopenias, or treatment failure. Despite poorer HSCT outcomes in TP53-mutated patients, research suggests transplantation still improves survival compared to non-transplant approaches. Lastly, pre-transplant therapy is advised for MDS patients with ≥10% blasts, but its impact on survival remains uncertain, highlighting the need for further prospective studies.

Shimomura et al. (2021) conducted an evaluation study to analyze epidemiological data and identify prognostic factors

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for adolescents and young adults undergoing allogeneic HSCT, as HSCT is the only curative treatment for MDS in this population. Six hundred and forty-five patients were selected from patients enrolled in a multicenter prospective registry for HSCT from 2000 to 2015. Survival rates were estimated using the Kaplan–Meier method. Prognostic factors were identified using the multivariable Cox proportional hazards model. The 3-year overall survival rate was 71.2% (95% confidence interval [CI]: 67.4–74.6%). In multivariable analysis, active disease status (adjusted hazard ratio: 1.54, 95% CI: 1.09–2.18, $p = 0.016$), poor cytogenetic risk (1.62, 1.12–2.36, $p = 0.011$), poor performance status (2.01, 1.13–3.56, $p = 0.016$), HLA-matched unrelated donors (2.23, 1.39–3.59, $p < 0.001$), HLA-mismatched unrelated donors (2.16, 1.09–4.28, $p = 0.027$), and cord blood transplantation (2.44, 1.43–4.17, $p = 0.001$) were significantly associated with poor 3-year overall survival.

Yoo et al. (2020) conducted a single center retrospective study analyzing the outcomes of allogeneic HSCT for childhood MDS. Thirty-six patients (low-grade MDS, 24; advanced myelodysplastic syndrome, 12) were included in the study, having received HSCT at the Asan Medical Center over two different decades. Outcomes were analyzed according to disease status, conditioning regimen, various donor types, and period of HSCT. During a median follow-up of 5.6 (range, 1.4–21.1) years, the probability of overall survival and failure-free survival was 77% and 69%, respectively. The cumulative incidence of transplantation-related mortality was 12%. Comparable outcomes were observed for HSCT from haploidentical family donors vs. HLA-identical donors (transplantation-related mortality, 10% vs. 14%, $p = 0.837$; overall survival 86% vs. 79%, $p = 0.625$) making the feasible outcomes of haploidentical HSCT an attractive alternative in the future procedures.

Zhou et al. (2020) conducted an evaluation study to analyze the outcomes post – HSCT in patients with hypoplastic myelodysplastic syndrome. Between September 2013 and October 2019, a total of 20 consecutive patients with hypoplastic myelodysplastic syndrome and 1 patient with clonal cytopenia of undetermined significance who underwent allogeneic HSCT were enrolled in this study. The donor sources included 9 MSDs, 2 matched unrelated donors, 4 mismatched unrelated donors and 6 haploidentical donors. The median time for myeloid engraftment was 11 days (range 9–17 days), and for platelet engraftment was 10 days (range 7–17 days). The cumulative incidence of myeloid and platelet recovery was $95.2 \pm 6.0\%$ and $90.5 \pm 7.3\%$, respectively, $40.0 \pm 11.3\%$ for grades II–III acute GVHD, $36.8 \pm 11.5\%$ for chronic GVHD and $23.8 \pm 9.6\%$ for non-relapse mortality. No patients experienced relapse. Sixteen surviving patients were followed up for a median of 1113 days (range 110–2305 days), and the overall survival and relapse-free survival rates were both $72.7 \pm 10.6\%$. The conclusion of this limited retrospective analysis suggests that patients with hypoplastic myelodysplastic syndrome have a favorable survival after allogeneic HSCT.

Myeloproliferative Neoplasms/Primary Myelofibrosis

Systematic Reviews and Meta-Analyses

Bewersdorf et al. (2021) completed a systematic review and meta-analysis to determine the safety and efficacy of allogeneic HSCT for primary myelofibrosis. A total of 43 studies with 8739 patients were included in the meta-analysis. The primary outcomes assessed were OS, non-relapse mortality (NRM), relapse-free survival (RFS), progression-free survival (PFS), incidence of acute and chronic GVHD, and incidence of graft failure. The outcomes for OS, NRM, RFS, and PFS were reported at 1-year, 2-year, and 5-year intervals based on the data available for each interval. The overall survival was 66.7% at 1-year, 64.4% at 2-years, and 55.0% at 5-years and was reported by 15, 21, and 22 studies, respectively. The NRM was 25.9% at 1-year, 29.7% at 2-years, and 30.5% at 5-years and was reported by 19, 12, and 10 studies, respectively. The RFS was 65.3% at 1-year, 56.2% at 2-years, and 53.6% at 5-years and was reported by 7 studies for all intervals. The PFS was 56.9% at 1-year, 50.6% at 2-years, and 43.5% at 5-years and was reported by 10 studies. It is important to note that not all studies reported RFS and PFS at all timepoints and researchers had to rely on each study's definition of RFS and PFS. The incidence of acute and chronic GVHD was reported in 36 and 32 studies respectively with 26 studies only reporting grade II–IV GVHD. Acute GVHD was reported in 44.0% of patients overall with 15.2% of patients developing grade III or IV GVHD. Chronic GVHD was reported in 46.5% of patients overall with 26.1% of patients developing extensive, moderate, or severe chronic GVHD. The overall incidence of graft failure was 10.6%. The rate of primary graft failure was 7.3% and secondary graft failure was 5.9%. Researchers were unable to quantitatively assess adverse events other than acute or chronic GVHD. Researchers were also unable to stratify outcomes based on DIPSS. However, they noted that the survival outcomes reported in their analysis were in-line with other studies, indicating that allogeneic HSCT “should be considered for eligible patients with higher-risk myelofibrosis.”

Non-Randomized Studies, Retrospective Reviews, and Other Evidence

Choudhary et al. (2023) completed an observational, retrospective study at a single tertiary care center in India. The

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study included a total of 15 patients with a median age of 52 years (range 5-64 years) undergoing allogeneic HSCT for myelofibrosis. Primary outcomes measured included overall survival and disease-free survival. Secondary outcomes measured included acute and chronic GVHD, graft failure, and cytomegalovirus reactivation. Scores from both the DIPSS and the hematopoietic cell transplantation-specific co-morbidity index were used to assess risk prior to transplantation. Stem cells were HLA-matched with related, haploidentical, and unrelated donors. Participants received antimicrobial prophylaxis in the form of fluconazole, acyclovir, and co-trimoxazole. For this study, "engraftment was defined as an ANC $> 500/\mu\text{L}$ for three consecutive days and a platelet count $> 20,000/\mu\text{L}$ for 7 days after the last platelet transfusion." All patients receiving MSD transplants received a reduced intensity conditioning regimen. All patients received cyclosporine A and methotrexate for GVHD prophylaxis. Patients receiving haploidentical HSCT received intravenous cyclophosphamide and oral tacrolimus and mycophenolate post-transplant for GVHD prophylaxis. Prior to transplant, "eight patients were in the high-risk DIPSS category, and seven were in the intermediate-risk category." Twelve patients received an MSD transplant, 2 received haploidentical transplant, and 1 received a matched unrelated donor transplant. Median follow-up was 364 days with a range from 7-2,815 days. There were 10 patients ≤ 55 years of age and 5 patients > 55 years of age. Overall survival was 60% ($n=9$). OS for the intermediate-2 risk was 100% ($n=7$) and high-risk was 25% ($n=2$). Overall survival based on age was similar with ≤ 55 years ($n=6$) and > 55 years ($n=3$) both being 60%. Univariate analysis results of risk factors showed a higher overall survival for the intermediate-risk group compared to the high-risk group. Overall disease-free survival was 60% ($n=9$). Approximately 27% ($n=4$) of all patients developed acute GVHD and 27% ($n=4$) developed chronic GVHD. No patients experienced graft failure. Only one patient developed cytomegalovirus reactivation. Approximately 40% ($n=6$) of patients included in the study died, with 5 of those deaths related to sepsis and 1 related to GVHD. The 5 deaths related to sepsis occurred before engraftment.

National and Specialty Organizations

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 $\geq 500/\text{mm}^3$ (or $\geq 0.5 \times 10^9/\text{L}$) 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 $\geq 500/\text{mm}^3$. 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 $500/\text{mm}^3$, 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 $\geq 0.5 \times 10^9/\text{L}$ ($500/\text{mm}^3$). 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 $\geq 0.5 \times 10^9/\text{L}$ ($500/\text{mm}^3$).

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 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 2023 ASTCT guidelines (Kanate et al. 2023) provide an updated focus on immune effector cell therapy (IECT) due to rapid advancements in chimeric antigen receptor T cell (CAR-T) therapy and multiple new FDA approvals since 2020. However, the indications for autologous and allogeneic hematopoietic stem cell transplantation (HSCT) remain unchanged, and the reader is directed to the previous 2020 guideline for HSCT recommendations.

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Chronic Phase-Chronic Myelogenous Leukemia (CP-CML) (Kanate et al. 2020)

- Allogeneic HSCT is recommended I early CP-CML
- Autologous HSCT is not recommended in clinical practice for any stage of CML based on available evidence

Multiple myeloma (Dhakal et al. 2022)

- Early autologous transplantation is recommended as consolidation therapy in eligible, newly diagnosed myeloma patients after 4-6 cycles of induction therapy
- Early autologous transplantation is recommended in MM patients with high-risk cytogenetics [t (4;14); t (14;16); t (14;20)], 1p deletion, 1q gain/amplification and 17p deletion in the absence of clinical trial
- Outside of clinical trial, tandem autologous transplantation is not recommended in standard risk myeloma patients after induction
- Autologous transplantation is recommended in first relapse for patients who have not received transplant as first-line therapy
- Salvage second autologous transplantation is recommended in patients who were in remission for at least 36 months with maintenance and 18 months in the absence of maintenance
- Allogeneic transplantation is recommended in relapsed and/or refractory setting in clinical trial

The National Marrow Donor Program (NMDP):

Acute lymphoblastic leukemia (ALL) (¹NMDP)

"Allogeneic hematopoietic cell transplantation (HSCT) is a better treatment option for patients with ALL in first complete remission (CR1) compared to autologous transplantation or chemotherapy. Patients with standard-risk ALL have better survival outcomes than those with high-risk ALL".

Acute myeloid leukemia (AML) (²NMDP)

"Patients with AML transplanted while in first or second complete remission have significantly better outcomes than patients transplanted with advanced disease. This is true whether the patient is undergoing matched related or matched unrelated HSCT."

Chronic lymphocytic leukemia (CLL) (³NMDP)

"Allogeneic HSCT remains the only curative option for patients with CLL. Approximately 80% of transplants in CLL are allogeneic transplants."

Chronic myeloid leukemia (CML) (⁴NMDP)

"Allogeneic hematopoietic cell transplantation (HSCT) is no longer considered first-line treatment for adults with CML due to evidence of significant clinical benefit for patients receiving BCR-ABL1 tyrosine kinase inhibitors (TKIs)."

Hodgkin lymphoma (HL) (⁵NMDP) / Non-Hodgkin lymphoma (NHL) (⁶NMDP)

"Hematopoietic cell transplantation (HSCT), often autologous but occasionally allogeneic, is a treatment option for recurrent disease. Allogeneic HSCT outcomes in patients with relapsed/refractory HL have significantly improved over time."

"Most hematopoietic cell transplantation (HSCT) performed for NHL is autologous, but in some cases, physicians may perform allogeneic HSCT for particularly high-risk relapsed or refractory disease."

Multiple Myeloma (⁷NMDP)

"MM is the most common indication for hematopoietic cell transplantation (HSCT) in the United States. Approximately 96% of transplants in patients with MM are autologous transplants."

Myelodysplastic syndromes (MDS) (⁸NMDP)

"More MDS patients are now eligible for allogeneic hematopoietic cell transplantation (HSCT) than ever before. The development of reduced-intensity conditioning regimens makes HSCT which is the only potentially curative treatment option, more feasible for older patients."

Myeloproliferative neoplasms (MPN) (⁹NMDP)

"MPNs have been treated with conservative strategies over the years, but autologous HSCT is an option that can prolong survival."

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The **National Comprehensive Cancer Network (NCCN)** published the following Clinical Practice Guidelines in Oncology:

Acute Lymphoblastic Leukemia (1v 3.2024)

The guideline outlines algorithms for induction and consolidation therapy in Ph+B-ALL (p.14), Ph-B-ALL (p.16), and T-ALL (p.18), as well as for relapsed or refractory cases (p.20). These therapies are stratified based on age and the presence or absence of significant comorbidities. Allogeneic HSCT is integrated into different parts of the treatment algorithm, depending on the specific leukemia subtype. Participation in clinical trials is incorporated as an option within the treatment induction algorithm for Ph+B-ALL, Ph-B-ALL, and T-ALL. For relapsed or refractory disease, clinical trials also serve as a potential pathway within the treatment framework.

Acute Myeloid Leukemia (2NCCN v 2.2025)

The guideline provides algorithms for induction, consolidation therapy, and relapse management in Acute Promyelocytic Leukemia (APL) (p.15-20) and Acute Myeloid Leukemia (AML) (p.30-42). For APL, treatment approaches are categorized by risk level, with low-risk patients defined as those with WBC counts $\leq 10 \times 10^9/L$ and high-risk patients with WBC counts $> 10 \times 10^9/L$. Hematopoietic stem-cell transplantation (HSCT) is introduced in the relapse therapy algorithm (2NCCN 2025, p.20)

For AML, therapies are stratified into favorable, intermediate, and poor/adverse risk groups. HSCT is included in multiple treatment pathways:

- Follow-up and reinduction after cytarabine-based induction (p.34)
- Follow-up after lower-intensity induction therapy (p.38)
- Consolidation therapy (p.39)
- Surveillance and management of relapsed/refractory disease post-consolidation (p.42)

Clinical trials also serve as a potential pathway within the treatment framework.

Chronic Myeloid Leukemia (7NCCN, v 3.2025)

The guideline recommends consideration of allogeneic bone marrow transplant for treatment of CML for individuals with high-disease risk score upon diagnosis. Since response rates with TKIs have been favorable as an initial treatment option (first- and second-line therapies) for CP-CML, HSCT is no longer recommended as a first-line treatment option for CP-CML (p.39). Recommendations for allogeneic HSCT include (p.55):

- Those who have BP-CML at diagnosis (very rare)
- Those patients with disease progression to AP-CML or BP-CML while on TKI therapy
- Those patients with CP-CML that is resistant and/or intolerant to all available TKIs

Patients with AP-CML and BP-CML should consider participating in clinical trials and undergoing assessment for allogeneic HCT (p.54).

Allogeneic hematopoietic stem-cell transplantation (HSCT) offers a potential cure for patients with chronic myeloid leukemia (CML). Recent advancements, including expanded access to alternative donor sources (such as unrelated donors and cord blood), enhanced HLA testing for more precise donor matching, and the adoption of reduced-intensity conditioning regimens—have contributed to better transplant outcomes (p.55).

Hodgkin Lymphoma (4NCCN, v 2.2025)

The guideline recommends HSCT for:

- Allogeneic HSCT within the second-line therapy for classic Hodgkin lymphoma suspected relapse after ≥ 3 months (p.31)
- Allogeneic HSCT with a category 3 recommendation for select patients with relapsed or refractory disease (p.95)
- Autologous or allogeneic HSCT is an option for patients with FDG-PET–positive refractory HL (Deauville 5) that is responsive to RT alone or to subsequent systemic therapy, with or without RT disease (p.95)

Peripheral T-Cell Lymphomas (6NCCN, v1.2025)

- Autologous HSCT is preferred for first relapse if disease remains chemo-sensitive and is used as consolidation therapy after remission with first line chemotherapy (p.12-13)
- Allogeneic HSCT is considered for high-risk patients, early relapse or refractory disease (p.14)

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B-Cell Lymphomas (⁵NCCN, v2.2025)

- Allogeneic HSCT may be appropriate for patients with:
 - Classic Follicular Lymphoma (p.23)
 - Marginal zone lymphomas (p.47)
 - Mantel cell lymphoma (p.54)
 - Diffuse large B-cell lymphoma (p. 67, 68, 73)
 - Histologic transformation of Indolent Lymphomas to DLBCL (p.86)
 - Burkitt lymphoma (p.93)
- High-dose therapy with autologous stem cell rescue (HDT/ASCR) may be appropriate for patients with:
 - Classic follicular lymphoma (p.22)
 - Marginal zone lymphomas (p.46-47)
 - Mantel cell lymphoma (p.52-57)
 - Diffuse large B-cell lymphoma (p.64-73)
 - Histologic transformation of Indolent Lymphomas to DLBCL (p. 85-87)
 - Burkitt lymphoma (p.91-96)

Multiple myeloma (³NCCN v2.2025):

- Autologous HSCT is the standard of care following primary induction therapy (p.68)
- A second cycle of a tandem transplant (within six months of the initial autologous HSCT) may be considered for patients who achieve only a partial response or have stable disease after their first HSCT (p.13)
- For patients treated with or without prior transplant, allogeneic HSCT is a recommended option for transplant candidate with relapse or progressive disease (p.14)

Myelodysplastic syndromes (⁸NCCN v2.2025):

- Select patients with very low, low, and intermediate risk disease based on IPSS-R scoring *and* clinically significant cytopenia(s) *and* clinically relevant thrombocytopenia or neutropenia should be considered for treatment with allogeneic HSCT if there is disease progression or no response to treatment with azacytidine, decitabine, or oral decitabine and cedazuridine and there is no *IDH1* mutation (p.12).
- Select patients with very low, low, and intermediate risk disease based on IPSS-R scoring *and* “symptomatic anemia with no del(5q) ± other cytogenetic abnormalities with ring sideroblasts < 15% (or ring sideroblasts < 5% with an *SF3B1* mutation) *and* a serum EPO > 500 mU/mL with poor probability to respond to immunosuppressive therapy *and* no response within 6 cycles of azacytidine or 4 cycles of decitabine or oral decitabine and cedazuridine or lenalidomide or intolerance *and* no *IDH1* mutation should be considered for allogeneic HSCT” (p.14).
- “Patients with IPSS Intermediate-1, IPSS-R Intermediate, and WHO-Based Prognostic Scoring System Intermediate-Risk myelodysplastic syndromes with severe cytopenias would also be considered candidates for HSCT. Matched sibling, unrelated donor, haploidentical donor, or cord blood donor, including standard and reduced-intensity preparative approaches, may be considered” (p.12).

Myeloproliferative neoplasms (including myelofibrosis) (¹⁰NCCN v1.2025)

Indicate that “allogeneic HSCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.” (p.20). These guidelines include recommendations for allogeneic HSCT and classify the following by prognostic risk model (MIPSS-70, MIPSS-70+ v. 2.0, DIPSS, or DIPSS-Plus):

- Lower-risk asymptomatic patients should be observed and/or included in a clinical trial. Lower-risk symptomatic patients should receive ruxolitinib, peginterferon alfa-2a, or hydroxyurea (if cytoreduction would be symptomatically beneficial). Patients with thrombocytopenia or complex cytogenetics should be evaluated for allogeneic HSCT (p.10).
- Higher risk patients are treated based on platelet count. Those with a platelet count < 50 x 10⁹/L and not a transplant candidate should receive pacritinib and/or be considered for inclusion in a clinical trial. Those with a platelet count ≥ 50x10⁹/L and not a transplant candidate should receive ruxolitinib, fedratinib, pacritinib or momelotinib and/or be considered for inclusion in a clinical trial. Those that are a transplant candidate should receive allogeneic HSCT regardless of platelet count (p.11).

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- Patients with accelerated or blast phase myelofibrosis should have a bone marrow workup and evaluation completed. Those that are a transplant candidate should be included in a clinical trial and complete induction therapy (hypomethylating agents ± JAK inhibitors, intensive induction chemotherapy, venetoclax-based regimens.) followed by allogeneic HSCT (for patients in remission) (p.30).

The **National Cancer Institute (NCI)** published the following guidelines:

Chronic Myelogenous Leukemia (²NCI 2025)

- Recommend considering allogeneic HSCT early in the chronic phase in patients younger than 60 years of age with an identical twin or with HLA-matched siblings despite the procedure being associated with considerable morbidity and mortality.
- Recommend allogeneic HSCT as the preferred choice of treatment for patients that are intolerant of or have a poor response to TKI therapy, certain patients that have a T315I mutation, and certain patients in the blastic phase. Progressively worse outcomes have been noted when using allogeneic HSCT in the accelerated and blast phases).

Childhood myelodysplastic neoplasms (¹NCI 2025):

- “Allogeneic HSCT is considered the optimal approach to treatment for pediatric patients with myelodysplastic syndrome.
- Although matched sibling donor transplant is preferred, similar survival has been noted with well-matched, unrelated cord blood and haploidentical approaches.
- Because survival after HSCT is improved in children with early forms of myelodysplastic syndromes (refractory anemia), transplant before progression to late myelodysplastic syndrome or acute myeloid leukemia should be considered. HSCT should especially be considered when transfusions or other treatments are required, as is usually the case in patients with severe symptomatic cytopenias.”

Myelodysplastic syndromes (⁴NCI 2024):

- Allogeneic HSCT is the only potentially curative treatment for myelodysplastic syndromes.
- Although HSCT represents the only treatment modality with curative potential, the relatively high morbidity and mortality of this approach limits its use. A decision analysis predating approval of azacitidine, in patients with a median age younger than 50 years, suggested optimal survival when transplant was delayed until disease progression for lower-risk patients but implemented at diagnosis for higher-risk patients.
- Allogeneic HSCT with reduced intensity conditioning has extended transplantation as a possible modality for treatment of older patients.”
- Survival rates are inferior in patients with higher IPSS scores.
- Advanced disease staging and the use of reduced intensity conditioning have been associated with an increased risk of disease relapse

The **European Leukemia Net (ELN)** and **European Society for Blood and Marrow Transplantation (EBMT)** published recommendations for HSCT in *primary myelofibrosis*. They make the following recommendations for patient selection (Kröger et al. 2024):

- “Patients with primary myelofibrosis and an intermediate-2 or high-risk DIPSS score, or a high-risk mutation-enhanced IPSS for patients younger than 70 years (MIPSS70) or MIPSS70+ score, and a low or intermediate risk myelofibrosis transplant scoring system (MTSS) score.
- Patients with secondary myelofibrosis and a high or intermediate-2 secondary myelofibrosis prognostic model score.
- Patients with primary myelofibrosis and an intermediate-1 risk DIPSS score, or intermediate risk MIPSS70 or MIPSS70+ score, with low risk MTSS score, balancing patient preferences, actual treatment options, including clinical trials, and other risk features (i.e., TP53 mutations).
- Patients over 70 years of age can be offered allogeneic HSCT on an individual basis, balancing patient preferences and disease-associated and patient-associated features.”

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The **EBMT** and **ELN** also make the following recommendations for allogeneic HSCT:

- “Immediate for patients with intermediate-2-risk and high-risk DIPSS score, whereas allogeneic HSCT can be delayed for low-risk or intermediate-1-risk disease.
- Transplantation-eligible patients on JAK inhibitors should be assessed for response and after 6 months of therapy patients falling into the high-risk category of the response to ruxolitinib after 6 months (RR6) model should receive timely evaluation for transplantation.
- In case of splenomegaly response (less than 5 cm below lower costal margin), proceed with allogeneic HSCT; in other circumstances, second-line options are recommended (alternative JAK inhibitors or novel agents, splenectomy, or splenic irradiation), particularly when spleen is palpable more than 15 cm below the lower costal margin.
- Patients with increased peripheral blood blasts (up to 10%) and those with accelerated phase or blast phase disease are not excluded from allogeneic HSCT and should be referred for timely evaluation.
- Patients in chronic phase with less than 10% blasts in peripheral blood or bone marrow do not require any additional therapy directed at blast reduction before transplantation.
- Splanchnic vein thrombosis is not necessarily a contraindication to allogeneic HSCT—in these patients thrombosis should be evaluated for portal hypertension and for liver cirrhosis; pre-transplantation interventions, if effective, might revert the contraindication to transplantation.
- HLA-matched sibling donors remain the preferred donor type, except when the potential donor is deemed too old or has comorbidities that will exclude them.
- In the absence of an HLA-matched sibling or HLA-matched unrelated donor, alternative donor sources should be considered: outcomes are similar for haploidentical HSCT and 7/8 matched HSCT from an unrelated donor; cord blood transplantation is generally not recommended.
- Peripheral blood is the recommended stem-cell source for HLA-matched sibling and unrelated donor transplants, and preliminary data suggest that it might also be for haploidentical transplantation using post-transplantation cyclophosphamide (PTCY)
- A high dose of CD34+ stem cells ($>7.0 \times 10^6$ cells per kg) is recommended for HLA-matched sibling and unrelated donor transplants; due to a scarcity of data, a preferred stem-cell dose cannot be recommended for haploidentical transplants.
- Reduced intensity conditioning and myeloablative conditioning are both valid options.
- For older patients or those with clinically significant comorbidities, or both, a reduced intensity conditioning regimen is more appropriate, whereas for younger patients with a good performance status, a myeloablative conditioning regimen can be selected.
- Current data suggest no benefit to adjusting intensity on the basis of genomic risk.
- Data suggest that the majority of patients who relapse more than 5 years post-transplantation can be successfully salvaged by second allogeneic HSCT.
- Patients who relapse within 1 year or have early graft failure are poor second transplant candidates.”

The **EBMT** and **ELN** also make the following recommendations for prevention of graft failure and the use of donor lymphocyte infusions:

- Primary graft failure “needs to be identified early (before day +28) and requires a fast decision of whether to proceed with a second transplantation.
- Prevention of primary graft failure includes the preferential use of an HLA-matched donor, a high dose of CD34+ cells at the time of transplantation, and the control of bulky splenomegaly.
- A finding that indicates potential molecular relapse should be confirmed by a consecutive analysis within 28 days.
- Pre-emptive therapy with donor lymphocyte infusion should be initiated after cessation of immunosuppression at the stage of persistent MRD and pursued until complete remission or MRD clearance is achieved; in case of molecular or haematological relapse, donor lymphocyte infusion is indicated.
- Prophylactic donor lymphocyte infusion is currently not recommended.”

The **National Institute for Health and Care Excellence (NICE)** has published recommendations for *myelofibrosis-related splenomegaly or symptoms*. Both recommendations state that allogeneic HSCT “is the only potential curative treatment available, but it is unsuitable for many people with myelofibrosis” as individuals must be fit enough for HSCT treatment (NICE 2024; NICE 2016). Momelotinib (NICE 2024) and ruxolitinib (NICE 2016) are viable treatment options to treat disease-related splenomegaly or symptoms in individuals with intermediate-2 or high-risk disease.

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CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	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 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 of 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.

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APPROVAL HISTORY

- 06/11/2025** Policy reviewed. Removed numerical HLA matching criteria. Updated definition of engraftment and ANC criteria in coverage policy. Additional changes have been made to align with current guidelines under the following sections: ALL, AML, CLL/Small Lymphocytic Lymphoma, CML, Myelodysplastic Syndrome, and Myeloproliferative Neoplasms / Primary Myelofibrosis. IRO Peer Review on May 27, 2025, by a practicing physician board certified in Pathology - Hematology, Internal Medicine, Medical Oncology.
- 06/12/2024** New policy comprised of retired MCPs 118 (Acute Lymphoblastic Leukemia), 119 (Acute Myeloid Leukemia), 187 (Chronic Myeloid Leukemia), 188 Chronic Lymphocytic Leukemia, 122 (Hodgkin/Non-Hodgkin Lymphoma), 122 (Multiple Myeloma) to condense HSCT for Blood Cancers. IRO Peer Reviewed on May 28, 2024, by a practicing physician board certified in Medical Oncology and Internal Medicine. IRO Peer Reviewed on June 3, 2024, by a practicing physician board certified in Hematology, Medical Oncology, and Internal Medicine.

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