Medical Coverage Policy

Effective Date.....11/15/2023
Next Review Date.....8/15/2024
Coverage Policy Number..... 0533

Stem Cell Transplantation: Blood Cancers

Table of Contents

Related Coverage Resources

Cell-Based Therapy for Cardiac and Peripheral Arterial Disease
Donor Lymphocyte Infusion and Hematopoietic Progenitor Cell (HPC) Boost
Stem Cell Transplantation: Non-cancer Disorders
Stem Cell Transplantation: Solid Tumors
Transplantation Donor Charges
Umbilical Cord Blood Banking

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Overview

This Coverage Policy addresses hematopoietic stem cell transplantation (HSCT) for blood cancers such as leukemias, lymphomas and myeloma.

Coverage Policy

Coverage for hematopoietic stem cell transplantation (HSCT) varies across plans. Refer to the customer's benefit plan document for coverage details.

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Acute Lymphoblastic Leukemia (ALL)	**Allogeneic hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of acute lymphoblastic leukemia (ALL) when ANY of the following criteria are met:** • failed induction therapy • second or subsequent remission • B-cell lineage ALL with marrow relapse while on treatment or within six months of completing treatment • T-cell lineage ALL in first or subsequent remission • first remission with poor prognosis or high risk features* **A second allogeneic HSCT is considered medically necessary for the treatment of ALL when relapsed disease occurs more than six months after first allogeneic HSCT.** **A tandem/sequential HSCT for the treatment of ALL is considered experimental, investigational or unproven.** **HSCT for the treatment of ALL is considered not medically necessary when ANY of the following conditions are present:** • active central nervous system (CNS) involvement • presence of any significant comorbid medical or psychiatric illness which would significantly compromise the clinical care and chances of survival • advanced age in an adult *See Appendix A
Acute Myeloid Leukemia (AML)	**Allogeneic HSCT is considered medically necessary for the treatment of acute myeloid leukemia (AML) when ANY of the following criteria is met:** • first remission for an adverse-risk or intermediate-risk* individual • second or subsequent remission • failed induction • no induction treatment and any of the following:

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	➢ antecedent hematological disease ➢ treatment-related secondary AML **A second allogeneic HSCT is considered medically necessary for the treatment of AML when BOTH of the following criteria are met:** • relapse of disease occurring more than six months after first allogeneic HSCT • second or subsequent remission **Allogeneic HSCT is considered medically necessary for the treatment of blastic plasmacytoid dendritic cell neoplasm following complete remission.** **Autologous HSCT is considered medically necessary for the treatment of AML when allogeneic HSCT is not available or is not appropriate and EITHER of the following criteria is met:** • first remission for a favorable/intermediate risk* individual • second or subsequent remission **Tandem HSCT is considered experimental, investigational or unproven for the treatment of AML** *See Appendix B
Amyloidosis (systemic light-chain)	**Autologous HSCT is considered medically necessary for the treatment of amyloidosis (systemic light-chain) in the absence of severe or multiple comorbidities that would increase risk of poor result or death.** **A second autologous HSCT for the treatment of recurrent or refractory amyloidosis (systemic light-chain) is considered experimental, investigational or unproven.** **The following procedures for the treatment of amyloidosis (systemic light-chain) are considered experimental, investigational or unproven:** • tandem autologous HSCT • allogeneic HSCT
Chronic Lymphocytic Leukemia (CLL)	**Allogeneic HSCT is considered medically necessary for the treatment of chronic lymphocytic leukemia (CLL) that is not responsive to standard therapy.**

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Chronic Myeloid Leukemia (CML)	**Allogeneic HSCT is considered medically necessary for the treatment of chronic myeloid leukemia (CML) in ANY of the following:** • hematologic remission not reached after three months of tyrosine kinase inhibitor (TKI) therapy • no cytogenetic response or those in cytogenetic relapse at 6, 12, or 18 months after achieving initial hematologic remission after three months of TKI therapy • molecular remission not reached by 12 months of TKI therapy • disease progression on TKI therapy to accelerated phase or blast crisis • an individual who is not a candidate for TKI therapy **Autologous HSCT for the treatment of CML is considered experimental, investigational or unproven.**
Chronic Myelomonocytic Leukemia (CMML)	**Allogeneic HSCT is considered medically necessary for the treatment of chronic myelomonocytic leukemia (CMML).** **Autologous HSCT for the treatment of CMML is considered experimental, investigational or unproven.**
Hodgkin Lymphoma	**Autologous HSCT is considered medically necessary for the treatment of refractory, primary progressive or recurrent Hodgkin lymphoma.** **Allogeneic HSCT is considered medically necessary for the treatment of refractory, primary progressive, or recurrent Hodgkin lymphoma when the individual is not a candidate for autologous HSCT or in the setting of a failed autologous transplant.**
Juvenile Myelomonocytic Leukemia (JMML)	**Allogeneic HSCT is considered medically necessary for the treatment of juvenile myelomonocytic leukemia (JMML).** **Autologous HSCT for the treatment of JMML is considered experimental, investigational or unproven.**
Multiple Myeloma (MM)	**Autologous HSCT for the treatment of active (i.e., symptomatic) multiple myeloma (MM) is considered medically necessary.** **A second autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary for EITHER of the following:** • as a tandem autologous HSCT following autologous HSCT • in an individual with progressive disease following a previous autologous HSCT

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
Myelodysplastic Syndromes	**Allogeneic HSCT is considered medically necessary for the treatment of an individual with intermediate- or high-risk* myelodysplastic syndrome (MDS).** *according to the Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes Risk Assessment
Myelofibrosis	**Allogeneic HSCT is considered medically necessary for the treatment of myelofibrosis for symptoms that persist, or worsen despite standard supportive care.** **Autologous HSCT is considered experimental, investigational or unproven for the treatment of myelofibrosis.**
Non-Hodgkin Lymphoma (NHL)	**Autologous HSCT is considered medically necessary for the treatment of an adult with stage II - IV or relapsed non-Hodgkin lymphoma (NHL).** **Allogeneic HSCT is considered medically necessary for the treatment of an adult with stage II - IV or relapsed non-Hodgkin lymphoma (NHL) who is not a candidate for autologous HSCT.** **Allogeneic or autologous HSCT as medically necessary for the treatment of a child with recurrent NHL with chemosensitive disease.** **The following procedures for the treatment of NHL are considered experimental, investigational or unproven:** • autologous OR allogeneic HSCT for stage I disease in an adult • tandem autologous OR allogeneic HSCT in an adult or a child (For primary CNS lymphoma, see CP 0534 Stem Cell Transplantation: Solid Tumors)
POEMS Syndrome	**Autologous HSCT is considered medically necessary for the treatment of POEMS syndrome.**
Primary Central Nervous System (CNS) Lymphoma	Refer to CP 0534 Stem Cell Transplantation: Solid Tumors.
Systemic Mastocytosis	**Allogeneic hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of advanced / aggressive systemic mastocytosis.**

General Background

Hematopoietic stem cell transplantation (HSCT), also called hematopoietic cell transplantation (HCT) or stem cell transplant, is a type of treatment for cancer (and a few other conditions as well). Bone marrow produces all of the different cells that make up the blood, such as red blood cells, white blood cells, and platelets. All of the cells of the immune system are also made in the bone marrow. All of these cells develop from a type of precursor cell found in the bone marrow, called a "hematopoietic stem cell." Hematopoietic stem cells are found in the peripheral blood and the bone marrow; therefore stem cells can be collected or harvested from either location.

Some of the most effective treatments for cancer, such as chemotherapy and radiation, are toxic to the bone marrow. In general, the higher the dose, the more toxic the effects on the bone marrow. After the treatment, a healthy supply of stem cells is reintroduced, or transplanted. The transplanted cells then reestablish the blood cell production process in the bone marrow. HSCT is a method of replacing immature blood-forming cells in the bone marrow that have been destroyed by drugs, radiation, or disease. It may be autologous (i.e., using a person's own stem cells) or allogeneic (i.e., using stem cells donated by someone else).

- Autologous transplant — In autologous transplantation, an individual's own hematopoietic stem cells are removed before the high dose chemotherapy or radiation is given, and they are then frozen for storage and later use. After chemotherapy or radiation is complete, the harvested cells are thawed and returned to the individual, like a transfusion.
- Allogeneic transplant — In allogeneic transplantation, the hematopoietic stem cells come from a donor, ideally a brother or sister with a similar genetic makeup. If an individual does not have a suitably matched sibling, an unrelated person with a similar genetic makeup may be used. Under some circumstances, a parent or child who is only half-matched can also be used; this is termed a haploidentical transplant. In other circumstances, umbilical cord blood may be used in an umbilical cord blood transplant.
- Myeloablative transplant — A myeloablative transplantation uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells.
- Non-myeloablative transplant — A non-myeloablative transplantation, sometimes referred to as reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. The idea is to minimize up front toxicity by using lower doses of intensive therapy, while retaining the immune graft versus tumor effect. This approach may be recommended for a variety of reasons including age, type of disease, other medical issues, or prior therapies.

Racial disparities
The American Society for Transplantation and Cellular Therapy (ASTCT) and the National Marrow Donor Program (NMDP) have formed the ACCESS Initiative to address and reduce barriers to hematopoietic cell transplantation (HCT) and cellular therapy (CT) in an effort to ensure equal access and outcomes for all patients in need.

- In addition to cellular therapy physicians, the initiative includes program administrators, health policy and health equity experts, health service researchers, participants from commercial payer organizations, and federal stakeholders.
- The ACCESS Initiative incorporates a comprehensive approach to reduce HCT/CT-related access barriers and resultant inferior outcomes. The inaugural ASTCT-NMDP ACCESS Workshop was held in Washington, DC on July 28 and 29, 2022, wherein committee members met to discuss and to define goals for 3 focus areas: awareness, poverty, and racial and ethnic inequity. The goals include:

  - Increasing awareness among community physicians of disease indications for HCT/CT and providing education for patients and caregivers on HCT/HCT availability, clinical trials, and support services available for them.
  - Identifying HCT/CT recipients at high risk of adverse outcomes due to socioeconomic adversity and developing patient-, center-, and policy-related initiatives to improve these patients' access and survival.
  - Improving equity in access and outcomes for all HCT/CT recipients, regardless of race or ethnicity, by working with HCT/CT centers to address the gap in knowledge of these patient populations and provide accurate data on the sociodemographic characteristics of patients in their regions.
- Ultimately, publications and policy changes based upon committee efforts would be laudable (Auletta, et al., 2022; National Marrow Donor Program).

Landry (2021) conducted a systematic review of the literature which included 17 publications that evaluated racial disparities and access to SCT (11 retrospective cohort studies, one literature review, 3 cross-sectional studies, and 2 focus group samplings).

- In 2014, the Affordable Care Act (ACA) became fully implemented. This expansion of coverage for uninsured or underinsured has led to approximately 40% of SCT procedures performed in the United States now reimbursed by governmental payers.
- Eight of the included studies evaluating access to SCT were performed after 2014.
  - Three of these studies specifically evaluated utilization and found that ethnic minorities with multiple myeloma, ALL, AML, and AL amyloidosis are still underutilizing SCT, with significant differences in referral and time to referral for Blacks.
- Eight retrospective reviews found substantial variation in access to SCT by ethnic minorities (Black, Hispanic, or Asian) when compared to their Caucasian counterparts.
- Thirteen publications found racial disparities in either overall survival, progression free survival, treatment related mortality, relapse, or combinations of these outcomes.
- The author stated that "While variation in overall mortality between ethnic minorities and white patients has traditionally been attributed to decreased utilization of stem cell transplant, our review revealed that discouragement of potential donors, differences in treatment failure and/or transplant rejection, and overall stigmatization and mistrust of the medical profession likely play significant roles in continued, worse outcomes seen in minority patients."

Majhail et al. (2012) reviewed published literature and noted disparities by race exist in three areas related to HCT: donor availability, access to HCT and outcomes of HCT. About 70% of patients who need allogeneic HCT do not have a matched sibling and must rely on unrelated donors or umbilical cord blood (UCB). African-Americans/Blacks have a lower likelihood of finding an unrelated donor. The probability of finding a match within the National Marrow Donor Program's (NMDP) Be The Match Registry is estimated to be 0.93 for Whites, 0.82 for Hispanics, 0.77 for Asian Americans and 0.58 for Blacks. Whites constitute nearly 74% donors in the registry, whereas the representation of Hispanics (10%), Blacks (7%) and Asians (7%) is less frequent.

Contraindications
Many factors affect the outcome of a tissue transplantation; the selection process is designed to obtain the best result for each individual. The presence of any significant comorbid conditions which would significantly compromise clinical care and chances of survival is a contraindication to transplant. Relative contraindications for HSCT include (but are not limited to):

- poor cardiac function (ejection fraction less than 35%)
- poor liver function (bilirubin greater than 2.0 mg/dL and transaminases greater than two times normal), unless related to disease

- poor renal function (creatinine clearance less than 50 mL/min) (not applicable for most auto transplants)
- poor pulmonary function (diffusion capacity less than 50% of predicted) human immunodeficiency virus (HIV) if not controlled or active hepatitis B, hepatitis C or human T-cell lymphotrophic virus type 1(HTLV-1)
- Karnofsky rating less than 60% and/or Eastern Cooperative Oncology Group (ECOG) performance status greater than two

Blood Cancers
Most blood cancers start in the bone marrow where blood is produced. Stem cells in bone marrow mature and develop into three types of blood cells: red blood cells, white blood cells, or platelets. In most blood cancers, the normal blood cell development process is interrupted by uncontrolled growth of an abnormal type of blood cell.

There are three main types of blood cancers:

- Leukemia, a type of cancer found in blood and bone marrow, is caused by the rapid production of abnormal white blood cells. The high number of abnormal white blood cells are not able to fight infection, and they impair the ability of the bone marrow to produce red blood cells and platelets. Leukemia can be either acute or chronic. Chronic leukemia progresses more slowly than acute leukemia, which requires immediate treatment. Leukemia is also classified as lymphoblastic/lymphocytic or myeloid/myelogenous. Lymphocytic/Lymphoblastic leukemia refers to abnormal cell growth in the marrow cells that become lymphocytes, a type of white blood cell that plays a role in the immune system. In myeloid leukemia, abnormal cell growth occurs in the marrow cells that mature into red blood cells, white blood cells, and platelets.
- Lymphoma is a type of blood cancer that affects the lymphatic system, which removes excess fluids from the body and produces immune cells. Lymphocytes are a type of white blood cell that fight infection. Abnormal lymphocytes become lymphoma cells, which multiply and collect in lymph nodes and other tissues. Over time, these cancerous cells impair the immune system. Lymphomas are divided into two categories:

    - Non-Hodgkin lymphoma: Non-Hodgkin's lymphomas are the most common. There are about 61 known types of non-Hodgkin lymphoma. About 85 percent of non-Hodgkin's lymphomas diagnosed in the U.S. are B-cell lymphomas, which means they originated from this type of cell. B-cell lymphomas grow quickly (high-grade) or slowly (low-grade). There are over a dozen types of B-cell non-Hodgkin lymphomas. The rest are T cell lymphomas, named after a different cancerous white blood cell, or lymphocyte.
    - Hodgkin lymphoma: The Hodgkin's lymphomas are the rarest types of the disease and are characterized by Reed-Sternberg cells. There are six different subtypes of Hodgkin's lymphoma.

- Myeloma (multiple myeloma) is a cancer of the plasma cells. Because myeloma frequently occurs at many sites in the bone marrow, it is often referred to as 'multiple myeloma' (MM). Plasma cells are white blood cells that produce disease- and infection-fighting antibodies. The plasma cells make an abnormal protein (antibody) known by several different names, including monoclonal immunoglobulin, monoclonal protein (M-protein), M-spike, or paraprotein.

  There are other plasma cell disorders that also have abnormal plasma cells but do not meet the criteria to be called active multiple myeloma. These other plasma cell disorders include but are not limited to:

- Smoldering multiple myeloma (SMM)
- Light chain amyloidosis.
- POEMS syndrome

Myelodysplastic Syndromes (MDS) are conditions that can occur when the blood-forming cells in the bone marrow become abnormal (dysplastic). There are several different types of MDS, based on how many types of blood cells are affected and other factors.

Myelofibrosis is considered a myeloproliferative neoplasm. Three other disorders are commonly classified as MPNs: chronic myeloid leukemia, essential thrombocythemia and polycythemia vera. Also called primary myelofibrosis (PMF) or idiopathic myelofibrosis, it is characterized by replacement of the bone marrow by fibrous scar tissue, which reduces the ability of the marrow to produce red blood cells.

POEMS (Polyneuropathy, organomegaly, endocrinopathy, M- protein, skin changes) syndrome is a rare plasma cell disorder characterized by demyelinating peripheral neuropathy and clonal plasma cell proliferation. It can be mistaken for chronic inflammatory demyelinating polyneuropathy. The clinical manifestations of POEMS syndrome can be debilitating; therefore, early diagnosis is essential (Khouri, et al., 2021).

Systemic mastocytosis (SM) is no longer considered a subgroup of myeloproliferative neoplasms, but is considered a distinct disease category. It results from a clonal, neoplastic proliferation of morphologically and immunophenotypically abnormal mast cells (MC) that accumulate in one or more organ systems. The clinical presentation of mastocytosis is heterogeneous, ranging from skin-limited disease (cutaneous mastocytosis, CM), particularly in pediatric cases where the majority have disease-onset within the first 2 years of life and commonly experience spontaneous regression of skin lesions at puberty, to a more aggressive variant with extra-cutaneous involvement (systemic mastocytosis, SM) that may be associated with multiorgan dysfunction/failure and shortened survival, that is generally seen in adult patients (Pardanani, et al., 2023).

Professional Societies/Organizations
The table below includes information and recommendations from the following sources:

1. The American Society for Transplantation and Cellular Therapy (ASTCT) (formerly known as the American Society for Blood and Marrow Transplantation [ASBMT]) Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy (Kanate, et al., 2020).

2. The National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Note that all recommendations are category 2A unless otherwise stated.

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td>Acute Lymphoblastic/ Leukemia (ALL)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)
<table><tr><th>Children (<18 years)</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr><tr><td>Acute lymphoblastic leukemia</td><td>N</td><td>N</td></tr></table></td></tr>
</table>

Cancer	

CR1, standard risk		
Acute lymphoblastic leukemia CR1, high risk	S	N
Acute lymphoblastic leukemia CR2	S	N
Acute lymphoblastic leukemia CR3+	C	N
Acute lymphoblastic leukemia Not in remission *Used in clinical practice but associated with high failure rates; hence, recommend clinical trial enrollment and nontransplant strategies when available.	C *	N

Adults	Allogeneic HCT	Autologous HCT
Acute lymphoblastic leukemia CR1, standard risk	S	N
Acute lymphoblastic leukemia CR1, high risk	S	N
Acute lymphoblastic leukemia CR2	S	N
Acute lymphoblastic leukemia CR3+	S	N
Acute lymphoblastic leukemia Not in remission *Used in clinical practice but associated with high failure rates; hence, recommend clinical trial enrollment and nontransplant strategies when available.	S*	N

NCCN GUIDELINES™ Acute Lymphoblastic Leukemia (V.1.2022, April 4, 2022)

Principles of Systemic Therapy
Treatment of Adults ≥65 years or Adults with Substantial Comorbidities

- For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic stem cell transplant (SCT) may be appropriate (ALL-D, 9 of 10).

Overview of Treatment Phases in ALL Management
Hematopoietic Stem Cell Transplantation
As part of postremission consolidative therapy, the decision to proceed with allogeneic/autologous HCT or prolonged maintenance are mutually exclusive approaches in ALL therapy. Each case will need to be individualized based on disease setting and features. Allogeneic HCT is more likely to be a primary part of post-consolidative therapy in AYA and adult patients with evidence of high-risk features (including Ph-positivity, Ph-like disease, or persistent MRD). Notably, while younger patients may experience lower transplant-related mortality, older age is by itself not a contraindication. For this reason, HLA typing and bone marrow transplant referral should be considered for all newly diagnosed and relapsed

Cancer	
	transplant-naïve patients to facilitate timely donor identification, and ultimately allogeneic transplant if warranted. (MS-13) <u>NCCN Recommendations for Ph-Positive ALL</u> AYA and Adult Patients with Ph-Positive ALL The panel recommends that Ph-positive ALL AYA and adult patients less than 65 years of age and no substantial comorbidities be treated in a clinical trial, when possible. Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support. The optimal time for a patient to receive allogeneic HCT is unclear; however, proceeding to allogenic HCT with MRD is not optimal and additional therapy is recommended to eliminate MRD before transplant. In cases of persistent or rising MRD, consolidation therapy options may include blinatumomab (B-ALL) with or without TKI, or continuation of multiagent chemotherapy or corticosteroid combined with a TKI. In younger AYA patients (aged ≤21 years), emerging data suggest that allogeneic HCT may not confer an advantage over chemotherapy combined with TKIs. Allogeneic HCT may be useful in appropriate candidates with MRD negativity, while considering post-HCT TKI following consolidation therapy. (MS-25, 26) Patients with Relapsed/Refractory Ph-Positive B-ALL For all patients with R/R Ph-positive B-ALL, participation in a clinical trial is preferred. If transplant-naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucel or brexucabtagene autoleucel is unclear. (MS-26, 27) <u>NCCN Recommendations for Ph-Negative ALL</u> AYA Patients with Ph-Negative ALL The panel recommends that AYA patients with Ph-negative ALL (regardless of risk group) be treated in a clinical trial, where possible. (MS-43) For patients experiencing a CR following initial induction therapy, monitoring for MRD should be initiated (see NCCN Recommendations for MRD Assessment). If the resulting MRD status is negative, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate. Consolidation with allogeneic HCT may also be considered, especially if the patient has high-risk features. If the MRD status is positive, blinatumomab (for B-ALL) is recommended or allogeneic HCT may be considered. Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. If the MRD status is unknown, allogeneic HCT is recommended,

Cancer	
	especially if the patient has high-risk features, although MRD retesting should be considered at first available opportunity. A continuation of multiagent chemotherapy may also be considered, and MRD assessments should be performed at the earliest subsequent opportunity. In all cases, the optimal timing of HCT is unclear. Adult Patients with Ph-Negative ALL For adult patients with Ph-negative ALL, the panel recommends treatment in a clinical trial, where possible. For relatively fit patients (aged <65 years without substantial comorbidities), the recommended treatment approach is similar to that for AYA patients. For patients experiencing a CR after initial induction therapy, monitoring for MRD should be initiated (see NCCN Recommendations for MRD Assessment). If the resulting MRD status is negative, continuation of the multiagent chemotherapy protocol for consolidation and maintenance is recommended. Consolidation with allogeneic HCT may also be considered, especially if the patient has high-risk features. The effect of WBC counts on prognosis in adult patients with ALL is less firmly established than in pediatric populations. If the MRD status is positive, blinatumomab (for B-ALL) is recommended or allogeneic HCT may be considered. After blinatumomab treatment, consolidative therapy with allogeneic HCT should be considered. If the MRD status is unknown, allogeneic HCT is recommended, especially if the patient has high-risk features. A continuation of multiagent chemotherapy may also be considered. In all cases, the optimal timing of HCT is unclear. (MS-44) Patients with Relapsed/Refractory Ph-Negative B-ALL For patients with R/R Ph-negative B-ALL, the approach to second-line treatment may depend on the duration of the initial response. If transplant-naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucel or brexucabtagene autoleucel is unclear. (MS-45) <u>NCCN Recommendations for Evaluation and Treatment of Extramedullary Involvement</u> Does not address HCT. **<u>NCCN GUIDELINES™ Pediatric Acute Lymphoblastic Leukemia (V.2.2023 — March 10, 2023)</u>** NCCN Principles of Hematopoietic stem cell transplant are listed on pages PEDALL-J, and provide detailed indications for: • HCT (B-cell) in First Remission • HCT (B-cell) in Non-First Remission Settings • HCT (T-cell) <u>NCCN Recommendations for Ph-Negative or Ph-Like ALL</u>

Cancer	
	Front-Line Management: The panel recommends that pediatric and AYA patients with Ph-negative or Ph-like ALL be treated in a clinical trial when possible. In all cases, HCT may be considered as part of consolidation or maintenance therapy. However, the role of allogeneic HCT following tisagenlecleucel is unclear. (MS-26, 27) R/R Management: For pediatric and AYA patients with Ph-negative or Ph-like ALL experiencing early or late first relapse, the panel recommends initial treatment with systemic therapy. (MS-27) <u>NCCN Recommendations for Ph-Positive ALL</u> Front-Line Management: The panel recommends that pediatric and AYA patients with Ph-positive ALL be treated in a clinical trial that incorporates TKIs when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy and a TKI. As an alternative for maintenance, HCT may be considered. Of note, HCT is not required but may be considered for Ph-positive ALL in CR1. R/R Management: The NCCN Panel recommendations for pediatric and AYA patients with R/R Ph-positive ALL are similar to what has been summarized for R/R Ph-negative or Ph-like ALL.(MS-30) <u>NCCN Recommendations for T-ALL</u> Front-Line Management: The panel recommends that pediatric and AYA patients with T-ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are treated with chemotherapy. Patients who have very-high-risk features may continue chemotherapy or pursue alternative therapy and consider HCT as part of consolidation therapy. However, it is recommended that additional therapy be given to achieve MRD negativity prior to HCT. (MS-32) R/R Management: For pediatric and AYA patients with T-ALL experiencing first relapse, the panel recommends initial treatment with clinical trial or chemotherapy. If patients experience CR2, consolidation therapy with chemotherapy should be continued with HCT. (MS-32) <u>NCCN Recommendations for Infant ALL</u> Front-Line Management: The panel recommends that infant patients with ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are treated with Interfant-based chemotherapy. In all cases, HCT may be considered as part of consolidation or maintenance therapy.

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>R/R Management: The NCCN Panel recommendations for infant patients with R/R ALL are similar to what has been summarized for R/R Ph-negative or Ph-like ALL. (MS-34, 35)

<u>NCCN GUIDELINES™ Adolescent and Young Adult (AYA) Oncology (V.3.2023 — January 9, 2023)</u>

Hematopoietic Stem Cell Transplant
HSCT is a potentially curative treatment option for an increasing number of AYA patients with leukemias and lymphomas. Graft-versus-host disease (GVHD), chronic immunosuppression, and gonadal dysfunction in males and females related to high-dose conditioning chemotherapy and RT are the major post-transplant complications associated with HSCT. Chronic GVHD has been identified as the leading cause of non-relapse mortality in HSCT survivors. AYA patients are at a higher risk of developing chronic GVHD than younger children.
HSCT survivors are also at increased risk for late complications, which include recurrent infections, secondary cancers, cardiac dysfunction, growth failure, weight loss, neurocognitive delay, and other end-organ dysfunction.
Allogeneic HSCT survivors irradiated at 30 years or younger are at higher risk of developing secondary solid cancers.
Findings highlight the increasingly recognized need for long-term follow-up care that incorporates screening and surveillance of AYA survivors of HSCT. (MS-9)

<u>NCCN GUIDELINES™ Older Adult Oncology (V.1.2023 — February 14, 2023)</u>
A recommended assessment tool is the Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI).</td></tr>
<tr><td>Acute Myeloid Leukemia (AML)

(also referred to as acute myelogenous leukemia)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

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<tr><td>Acute myeloid leukemia
CR1, intermediate risk</td><td>C</td><td>N</td></tr>
<tr><td>Acute myeloid leukemia
CR1, high risk</td><td>S</td><td>N</td></tr>
<tr><td>Acute myeloid leukemia
CR2+</td><td>S</td><td>N</td></tr>
<tr><td>Acute myeloid leukemia
Not in remission</td><td>S</td><td>N</td></tr>
<tr><td>Acute promyelocytic leukemia
Relapse</td><td>R</td><td>R</td></tr>
</table>
</td></tr>
</table>

Cancer	

Adults	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia CR1, low risk	N	C
Acute myeloid leukemia CR1, intermediate risk	S	C
Acute myeloid leukemia CR1, high risk	S	N
Acute myeloid leukemia CR2	S	C
Acute myeloid leukemia CR3+	S	N
Acute myeloid leukemia Not in remission	S	N
Acute myeloid leukemia Therapy-related, CR1	S	N
Acute promyelocytic leukemia CR1	N	N
Acute promyelocytic leukemia CR2, molecular remission	C	S
Acute promyelocytic leukemia CR2, not in molecular remission	S	N
Acute promyelocytic leukemia CR3+	C	N
Acute promyelocytic leukemia Not in remission	C	N
Acute promyelocytic leukemia Relapse after autologous transplant	C	N
Blastic plasmacytoid dendritic cell neoplasm	R	R

American Society of Transplantation and Cellular Therapy (Tarlock 2022)
Hematopoietic Cell Transplantation in the Treatment of Pediatric Acute Myelogenous Leukemia and Myelodysplastic Syndromes: Guidelines from the American Society of Transplantation and Cellular Therapy

- Should children with favorable risk cytogenetic and molecular lesions (CBF, NPM1, CEBPA bZip) undergo HCT in first complete remission (CR1), even if measurable residual disease (MRD) positive (+) at first end of induction (EOI)? Recommendation = No
- Should children with FLT3-ITD undergo HCT in CR1? Recommendation = Yes
- Should children with high-risk cytomolecular abnormalities undergo HCT in CR1? Recommendation = Yes
- Should children who are MRD+ by flow cytometry at EOI and no other risk-stratifying lesion be considered for HCT in CR1? Recommendation = Yes

Cancer	
	• Should children with primary induction failure or refractory disease after 2-3 cycles of chemotherapy be considered for allogenic HCT, even if not in CR1? Recommendation = Yes • Should children who relapse be offered HCT following attempts to obtain second complete remission (CR2)? Recommendation = Yes • Should HCT be considered for Down syndrome (DS)-AML in certain situations of relapsed or highly refractory disease with careful consideration of its limitations and toxicity risk? Recommendation = Yes • Should patients with relapsed or refractory extramedullary disease (EMD) be considered for HCT with boost radiation to sites of persistent disease with conditioning? Recommendation = Yes • Should HCT in CR1 be offered for acute promyelocytic leukemia (PML)? Recommendation = No • Should auto-HCT be offered in relapsed acute promyelocytic leukemia after induction of CR2 and PML-RARa PCR-negative? Recommendation = Yes **American Society of Transplantation and Cellular Therapy** (Dholaria 2021) Hematopoietic Cell Transplantation in the Treatment of Newly Diagnosed Adult Acute Myeloid Leukemia: An Evidence-Based Review from the American Society of Transplantation and Cellular Therapy. • Should unfavorable-risk* patients undergo allo-HCT in CR1? Recommendation = Yes • Should intermediate-risk* patients undergo allo-HCT in CR1? Recommendation = Yes • Should favorable-risk* patients undergo allo-HCT in CR1? Recommendation = No (CBF-AML with KIT mutation may be considered for allo-HCT in CR1.) • Is there any role of secondary mutational abnormalities in selecting a patient for allo-HCT? Recommendation = Unclear • Should the presence of MRD at the end of induction therapy be considered an indication to offer allo-HCT? Recommendation = Yes • Should AML with induction failure undergo allo-HCT? Recommendation = Unclear • Should secondary AML undergo allo-HCT in CR1? Recommendation = Yes • Should therapy-related AML undergo allo-HCT in CR1? Recommendation = Yes (Except therapy-related AML with favorable karyotype [inv(16); t(8;21); t(15;17)]) • Should patients ≥60 years undergo allo-HCT in CR1? Recommendation = Yes • Is auto-HCT a good alternative to chemotherapy consolidation in patients who are not eligible for allo-HCT? Recommendation = Yes (Favorable-risk or intermediate-risk with MRD—) * Risk stratification by European Leukemia Net 2017 guidelines. **NCCN GUIDELINES™ Acute Myeloid Leukemia (V.3.2023 — April 5, 2023)**

Cancer	
	NCCN Recommendations The NCCN AML Panel strongly encourages enrollment in a clinical trial for treatment induction of younger patients (aged <60 years) with AML. (MS-34) HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity conditioning (RIC) allogeneic HCT from a matched sibling or an alternative donor, which constitutes the best option for long-term disease control. (MS-35) CBF Cytogenetic Translocations and MRD Negative There are insufficient data to evaluate the use of allogeneic HCT in first remission for patients with AML who are MRD negative and have favorable-risk cytogenetics outside of a clinical trial. (MS-40) Intermediate-Risk Cytogenetics and/or Molecular Abnormalities Including MRD Positive The panel members agree that transplant-based options (either matched sibling or alternate donor allogeneic HCT) or 3 to 4 cycles of HiDAC affords a lower risk of relapse and a somewhat higher DFS when given as consolidation for patients with intermediate-risk cytogenetics. The role of autologous HCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. While autologous HCT is still incorporated into the clinical trial design in Europe, the consensus of the NCCN AML Panel was that autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. (MS-40) Treatment-Related Disease Other than CBF and/or Unfavorable Cytogenetics and/or Molecular Abnormalities The panel strongly recommends clinical trials as standard therapy for patients with poor prognostic features, which include FLT3-ITD abnormalities in the setting of otherwise NK-AML, high WBC (>50,000/mcL) at diagnosis, or adverse cytogenetics/molecular markers as well as secondary and therapy-related AML. If remission is observed, consolidation therapy is recommended, and strong consideration should be given to allogeneic HCT with matched sibling or alternative donor (including umbilical cord blood products) as part of consolidation strategy. (MS-41) NCCN Recommendations Similar to recommendations for adults younger than 60 years, the NCCN AML Panel encourages enrollment in a clinical trial for treatment induction of patients aged ≥60 years with AML. (MS-49) NCCN Recommendations Previous Intensive Therapy

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>For patients who had previously received intensive therapy, a marrow to document remission status upon hematologic recovery should be performed after 4 to 6 weeks. If a CR is observed, a clinical trial is recommended. Other postremission or maintenance therapy recommendations include but are not limited to allogeneic HCT. (MS-52)
For patients who experience induction failure, a clinical trial, low-intensity therapy (azacitidine, decitabine), allogeneic HCT (preferably in the context of a clinical trial), therapies for R/R disease (see Management of Relapsed/Refractory AML), or best supportive care are recommended treatment options. (MS-53)

Previous Lower-Intensity Therapy
For patients who previously received lower-intensity therapy, a marrow to document remission status upon hematologic recovery should be performed, with the timing dependent on the therapy used. If a response is observed, allogeneic HCT may be considered for select patients. (MS-53)

<u>NCCN Recommendations</u>

The NCCN AML Panel recommends enrollment in a clinical trial for the management of Relapsed/Refractory AML as a strongly preferred option. Other options include targeted therapy or chemotherapy followed by allogeneic HCT.

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)
Due to the rarity of BPDCN, there have been limited established standardized therapeutic approaches. HCT seems to generate durable remissions, especially if given in first CR. (MS-68)
NCCN Recommendations: With all treatment options, if CR is observed, allogeneic HCT or autologous HCT should be considered.(MS-69)</td></tr>
<tr><td>Amyloidosis</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Amyloid light chain amyloidosis</td><td>N</td><td>S</td></tr>
</table>

<u>NCCN GUIDELINES™ Systemic Light chain Amyloidosis (V.2.2023 — November 28, 2022)</u>

All patients with newly diagnosed systemic light chain amyloidosis (SLCA) should be assessed for autologous HCT eligibility. Those with low tumor burden can proceed to receive HCT immediately. Those who are not eligible for HCT due to high tumor burden may receive systemic therapy first, and their eligibility for transplant may be assessed after initiating systemic therapy based on improvements in functional status and/or organ response. The NCCN panel members recommend that treatment of SLCA should be in the context of a clinical trial when</td></tr>
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<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>possible, because data are insufficient to identify optimal treatment of the underlying plasma cell disorder. (MS-5)</td></tr>
<tr><td>Chronic Lymphocytic Leukemia (CLL)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Chronic lymphocytic leukemia
High risk, 1st or greater remission</td><td>S</td><td>N</td></tr>
<tr><td>Chronic lymphocytic leukemia
T-cell prolymphocytic leukemia</td><td>S</td><td>R</td></tr>
<tr><td>Chronic lymphocytic leukemia
B-cell, prolymphocytic leukemia</td><td>R</td><td>R</td></tr>
<tr><td>Chronic lymphocytic leukemia
Transformation to high grade lymphoma</td><td>C</td><td>S</td></tr>
<tr><td>Hairy cell leukemia
First remission</td><td>N</td><td>N</td></tr>
<tr><td>Hairy cell leukemia
Second remission</td><td>N</td><td>N</td></tr>
<tr><td>Hairy cell leukemia
≥ third remission or refractory disease</td><td>R</td><td>N</td></tr>
</table>

<u>NCCN GUIDELINES™ Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (V.2.2023 — January 25, 2023)</u>

Indications for Allogeneic HCT
Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule inhibitor therapy in patients without significant comorbidities. HCT-specific comorbidity index (HCT-CI) could be used for the assessment of comorbidities prior to HCT and to predict the risks of non-relapse mortality and the probabilities of survival after HCT.
For patients with CLL/SLL with del(17p) or TP53 mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if CK (≥3 abnormalities) is present. However, available data suggest that CK (≥5 abnormalities) is associated with inferior OS and EFS following allogeneic HCT with reduced-intensity conditioning in patients with high-risk interphase cytogenetics. (MS-21, 22)

<u>NCCN GUIDELINES™ Hairy Cell Leukemia (V.1.2023 — August 30, 2022)</u>
Does not address Hematopoietic Stem Cell Transplantation</td></tr>
<tr><td>Chronic Myeloid Leukemia (CML)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</td></tr>
</table>

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<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>
<table>
<tr><th>Children (<18 years)</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Accelerated phase</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Blast phase</td><td>C</td><td>N</td></tr>
</table>
<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 1, TKI intolerant</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 1, TKI refractory</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 2+</td><td>S</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Accelerated phase</td><td>S</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Blast phase</td><td>S</td><td>N</td></tr>
</table>
<u>NCCN GUIDELINES™ Chronic Myeloid Leukemia (V.2.2023 — April 13, 2023)</u>

Allogeneic Hematopoietic Cell Transplant
Allogeneic HCT is a potentially curative treatment for patients with CML. Ongoing advances in alternative donor sources (such as unrelated donors and cord blood), more accurate HLA testing for a stringent selection of unrelated matched donors, and the use of reduced-intensity conditioning regimens have improved outcomes following allogeneic HCT.
Allogeneic HCT is an appropriate treatment option for the very rare patients presenting with BP-CML at diagnosis, patients with disease that is resistant to TKIs, patients with progression to AP-CML or BP-CML while on TKI therapy, and patients with CML that is resistant and/or intolerant to all TKIs.
The potential use of allogeneic HCT must be tied to faithful monitoring of disease, since the major potential pitfall in delaying transplantation is "missing" the chronic phase interval. (MS-22)
</td></tr>
<tr><td>Chronic Myelomonocytic Leukemia (CMML)</td><td>See Myelodysplastic Syndromes</td></tr>
<tr><td>Hodgkin Lymphoma</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</td></tr>
</table>

Cancer	

Children (<18 years)	Allogeneic HCT	Autologous HCT
Hodgkin lymphoma CR1	N	N
Hodgkin lymphoma Primary refractory, sensitive	N	C
Hodgkin lymphoma Primary refractory, resistant	C	N
Hodgkin lymphoma First relapse, sensitive	N	S
Hodgkin lymphoma First relapse, resistant	C	N
Hodgkin lymphoma Second or greater relapse	C	C

Adults	Allogeneic HCT	Autologous HCT
Hodgkin lymphoma CR1 (PET negative)	N	N
Hodgkin lymphoma Primary refractory, sensitive	C	S
Hodgkin lymphoma Primary refractory, resistant	C	N
Hodgkin lymphoma First relapse, sensitive	S	S
Hodgkin lymphoma First relapse, resistant	C	N
Hodgkin lymphoma Second or greater relapse	S	S
Hodgkin lymphoma Relapse after autologous transplant	S	N

NCCN GUIDELINES™ Hodgkin Lymphoma (V.2.2023 — November 8, 2022)

NCCN Recommendations for Refractory CHL

Histologic confirmation with biopsy is recommended before initiating treatment for refractory disease. Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or systemic therapy with or without RT. Conventional-dose second-line systemic therapy may precede HDT/ASCR. RT should be strongly considered for selected sites of relapse that have not been previously irradiated. In radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR.

Second-line systemic therapy followed by response assessment with FDG-PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should proceed to HDT/ASCR with or without RT (category 1). Observation with or without RT can be considered, if HDT/ASCR is contraindicated. Maintenance therapy with BV can be considered for patients with high risk of relapse as defined by the AETHERA trial

Cancer	
	(defined as those having primary refractory disease, duration of first CR <1 year, or relapse with extranodal or advanced-stage disease). An alternative regimen with or without RT or RT alone is recommended for patients with a Deauville score of 4 or 5 after second-line systemic therapy. Autologous or allogenic HCT following additional therapy may be considered in these patients. Another approach for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT, followed by maintenance therapy with BV for patients with a high risk of relapse. The panel has included allogeneic HCT with a category 3 recommendation for select patients with relapsed or refractory disease. Autologous or allogeneic HCT 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. (MS-26, 27) NCCN Recommendations for Relapsed CHL Most patients require second-line systemic therapy followed by RT or HDT/ASCR with or without ISRT. (MS-27) Summary Second-line systemic therapy followed by HDT/ASCR with or without RT is recommended for patients with relapsed or refractory CHL. Maintenance therapy with BV (for 1 year) following HDT/ASCR can be considered for patients with high risk of relapse. (MS-28) **NCCN GUIDELINES™ Pediatric Hodgkin Lymphoma (V.2.2023 — March 9, 2023)** NCCN Recommendations for Low-Risk CHL For patients with stage IA, IIA, and IB CHL (with or without bulky disease; no E-lesions), the panel recommends enrollment in an ongoing clinical trial or treatment according to EuroNet-PHL-C1 (a category 1 recommendation) as the preferred strategies. (MS-8) NCCN Recommendations for Intermediate-Risk CHL For patients with stage IA/IIA CHL (with bulky disease; with or without E-lesions), IB CHL (with or without bulky disease or E-lesions), IIB CHL (no bulky disease; with or without E-lesions), and IIIA CHL, the panel recommends enrollment in an ongoing clinical trial or treatment according to AHOD0031 or EuroNet-PHL-C1 as the preferred strategies. (MS-10) NCCN Recommendations for High-Risk CHL For patients with stage IIB, IIIA, IIIB, and IV CHL, the panel recommends enrollment in an ongoing clinical trial or treatment with Bv-AVE-PC according to AHOD1331 or treatment according to EuroNet-PHL-C1 as the preferred strategies. (MS-12) NCCN Recommendations for Relapsed or Refractory CHL Histologic confirmation with biopsy is recommended before initiating treatment for relapsed or refractory disease given the risk for transformation and high false-positive rate of FDG-PET/CT. If the biopsy

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>is negative, the panel recommends either observation with short-interval follow-up or additional workup if there is a high index of suspicion. If the biopsy is positive, the panel recommends enrollment in a clinical trial if available, and referral to or consulting with a center of expertise, as several options exist for the treatment of R/R disease and there is a lack of data to support one regimen over another.
Typically, patients are treated with re-induction therapies, and after an FDG-PET/CT or FDG-PET/MRI assessment, if metabolic CR is observed (Deauville score ≤3), treatment can be followed up with HDT/ASCR with or without ISRT and with or without maintenance therapy. In general, RT is performed as consolidation after transplant. If a metabolic CR is not achieved, RT may be used before transplant. (MS-15)

<u>NCCN Recommendations for Stage IA NLPHL with Complete Resection Confirmed by FDG-PET/CT</u>
For patients with stage IA NLPHL with complete resection confirmed by FDG-PET/CT, the panel recommends enrollment in an ongoing clinical trial or observation as the preferred strategies. (MS-16)

<u>NCCN Recommendations for Stage IA or IIA NLPHL with Incomplete Resection and Non-Bulky</u>
For patients with stage IA or IIA NLPHL with incomplete resection and non-bulky disease, the panel recommends enrollment in an ongoing clinical trial, AVPC x 3 cycles (category 1 recommendation), or CVbP with or without rituximab as preferred strategies. An FDA-approved biosimilar is an acceptable substitute for rituximab. (MS-17)

<u>NCCN GUIDELINES™ Cancer in People with HIV (V.1.2023 — December 20, 2022)</u>

Management of Hodgkin Lymphoma in 'People with HIV' (PWH)
Autologous stem cell transplantation also appears to be safe and effective in PWH who have recurrent/relapsed Hodgkin lymphoma. (MS-15)
Allogeneic HCT also appears to be safe in this population (PWH with acute leukemia, myelodysplasia, or lymphoma) (MS-16)</td></tr>
<tr><td>Juvenile Myelomonocytic Leukemia (JMML)</td><td>See Myelodysplastic Syndromes</td></tr>
<tr><td>Multiple Myeloma (MM)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myeloma, initial response</td><td>D</td><td>S</td></tr>
<tr><td>Myeloma, sensitive relapse</td><td>S</td><td>S</td></tr>
<tr><td>Myeloma, refractory</td><td>C</td><td>C</td></tr>
</table>
</td></tr>
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Cancer	

Plasma cell disorders, Relapse after autologous transplant	C	C
Plasma cell leukemia	S	C

NCCN GUIDELINES™ Multiple Myeloma (V. 3.2023 — December 8, 2022)

Transplant Eligibility
All patients are assessed to determine eligibility for HCT. The NCCN Panel recommends that all patients eligible for HCT should be referred for evaluation by HCT center and hematopoietic stem cells (for at least two transplants, in younger patients) should be harvested. High-dose therapy with hematopoietic stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with MM. The types of HCT may be single autologous HCT, a tandem HCT (a planned second course of high-dose therapy and HCT within 6 months of the first course), or an allogeneic HCT.

The NCCN Guidelines for Multiple Myeloma indicate that all types of HCT are appropriate in different clinical settings. In general, all candidates for high-dose chemotherapy must have sufficient hepatic, renal, pulmonary, and cardiac function. However, renal dysfunction is not an absolute contraindication to transplant. (MS-20, 21)

Autologous Hematopoietic Cell Transplantation
Autologous HCT results in high response rates and remains the standard of care after primary therapy for eligible patients.
According to the NCCN Guidelines, for transplant-eligible patients autologous HCT is the preferred option after primary induction therapy while a delayed HCT after early stem cell collection and storage is appropriate as well. (category 1) A repeat HCT can be considered for treatment of progressive/refractory disease after primary treatment in patients with prolonged response to initial HCT. (MS-21)

Tandem Hematopoietic Cell Transplantation
Tandem HCT refers to a planned second course of high-dose therapy and HCT within 6 months of the first course.
The NCCN Multiple Myeloma Panel recommends collecting enough hematopoietic stem cells for at least one HCT in all eligible patients, and for 2 transplants in the younger patients if tandem transplant or salvage transplant would be considered. According to the NCCN Multiple Myeloma Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT and is an option for patients who do not achieve at least a VGPR after the first autologous HCT and those with high-risk features. (MS-22, 23)
A second autologous HCT can be considered at the time of disease relapse.
According to the NCCN Multiple Myeloma Panel, repeat autologous HCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding HCT and documented progression. (MS-23)

Cancer	
	According to the NCCN Multiple Myeloma Panel, repeat autologous HCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding HCT and documented progression. (MS-24) Allogeneic Hematopoietic Cell Transplantation Allogeneic HCT includes either myeloablative or nonmyeloablative (ie, "mini" transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Non myeloablative transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between myeloablative and nonmyeloablative transplants relates to the chemotherapy regimen used. There is ongoing interest in myeloablative allogeneic HCT, particularly given the lack of a significant cure rate for single or tandem autologous HCT. (MS-24) **American Society for Transplantation and Cellular Therapy (ASTCT) 2022 Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma (Dhakal, et al., 2022)** The following are 2022 Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments in the First-Line Setting for MM: 1. The panel recommends early autologous transplantation as a consolidation therapy in eligible, newly diagnosed myeloma patients after 4-6 cycles of induction (Grade: A*) 2. The panel recommends mobilization and storage of peripheral blood stem cells in newly diagnosed myeloma patients not undergoing autologous transplantation after first line of therapy for future use as a treatment at first relapse (Grade: B) 3. The panel does not recommend using MRD testing to guide use of autologous transplantation after induction therapy in myeloma, outside the setting of a clinical trial (Grade:C) 4. The panel does not recommend age as the only selection factor when considering autologous transplantation in myeloma (Grade: B) 5. In the absence of clinical trial, the panel recommends early autologous transplantation in myeloma patients with high-risk cytogenetics [t (4;14); t (14;16); t (14;20)], 1p deletion, 1q gain/amplification and 17p deletion (Grade: B) 6. The panel does not recommend tandem autologous transplantation in standard risk myeloma patients after induction, outside in the setting of a clinical trial (Grade: B) 7. The panel does not recommend routine multiagent consolidation therapy in patients in very good partial response or better after

Cancer	
	autologous transplantation outside the setting of clinical trial (Grade: B) 8. The panel does not recommend consolidation with CAR-T cell therapy in patients after first line therapy outside the setting of clinical trial (Grade: C) 9. The panel recommends lenalidomide maintenance after autologous transplantation in standard risk patients unless contraindicated (Grade: A) 10. The panel recommends bortezomib and lenalidomide maintenance or clinical trial after autologous transplantation in high-risk patients (Grade: B) 11. The panel does not recommend allogeneic transplantation except in the context of clinical trial (Grade: C) 12. The panel does not recommend tandem autologous-allogeneic transplantation except in the context of clinical trial (Grade: C) 13. The panel recommends dose adjusted melphalan in patients with renal impairment including on dialysis, >70 years and KPS<80 (Grade: B) 14. The panel recommends treating primary plasma cell leukemia similar to high-risk myeloma in the absence of clinical trial (Grade: B) The following are 2022 Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments for <u>RR MM</u>: 1. The panel recommends autologous transplantation in first relapse in patients who have not received transplant as a first-line therapy (Grade: A) 2. The panel recommends consideration of autologous transplantation in patients with primary refractory disease (Grade: C) 3. The panel recommends salvage second autologous transplantation in patients who were in remission for (at least) 36 months with maintenance and 18 months in the absence of maintenance (Grade: B) 4. The panel recommends CAR-T cell therapy after 4 or more prior lines of therapy (Grade: A) 5. The panel recommends clinical trial, if possible after CAR failures (Grade: B) 6. The panel encourages allogeneic transplantation in relapsed and/or refractory setting only in the context of clinical trial (Grade: B) *A: There is good research-based evidence to support the recommendation. B: There is fair research-based evidence to support the recommendation. C: The recommendation is based on expert opinion and panel consensus. X: There is evidence of harm from this intervention. (ASTCT/ Dhakal, et al., 2022)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td>Myelodysplastic Syndromes</td><td>
<u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)
<table>
<tr><th>Children (<18 years)</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myelodysplastic syndromes (MDS) Low risk</td><td>C</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes High risk</td><td>S</td><td>N</td></tr>
<tr><td>Juvenile myelomonocytic leukemia</td><td>S</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes Therapy related</td><td>S</td><td>N</td></tr>
</table>
<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myelodysplastic syndromes Low/intermediate – 1 risk</td><td>C</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes Intermediate-2/high risk</td><td>S</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes Therapy-related, CR1</td><td>S</td><td>N</td></tr>
</table>
<u>American Society for Transplantation and Cellular Therapy</u>
<u>(DeFilipp, 2023)</u>
<u>Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines</u>

Should allogeneic HCT routinely be offered early for advanced (IPSS intermediate-2 [int-2] and high risk) (int-2/high) de novo MDS? Recommendation = Yes
Should allogeneic HCT routinely be offered early for lower risk (intermediate-1) (low/int-1) de novo MDS? Recommendation = No
Should eligibility for HCT in MDS be limited by age? Recommendation = No
Should eligibility for HCT in MDS be limited by comorbidity? Recommendation = Unclear
Should HCT be offered for patients with therapy-related MDS? Recommendation = Yes
Should patients be assessed for chromosomal anomalies and somatic mutations prior to HCT? Recommendation = Yes
Should HCT be offered for patients with high-risk cytogenetic or molecular disease? Recommendation = Yes
Should patients with MDS receive disease-directed therapy prior to HCT? Recommendation = Unclear

<u>NCCN GUIDELINES™ Myelodysplastic Syndromes (V.1.2023 — September 12, 2022)</u>
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</table>

Cancer	
	Myelodysplastic/Myeloproliferative Neoplasms The category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) was added to the 2008 update of the WHO classification of myeloid neoplasms. This category includes chronic myelomonocytic leukemia (CMML); atypical chronic myeloid leukemia (aCML), BCR-ABL1 negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features. The management of CMML depends on the characteristics of the patient's disease and is typically focused on supportive care and cytoreductive therapy.38 Patients who are asymptomatic with low-risk disease may be observed until disease progression. In patients with CMML-1 and CMML-2, hypomethylating agents (HMAs), decitabine and azacitidine (AzaC) have demonstrated efficacy, and emerging data suggest utility of ruxolitinib in this context. Patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias, and high transfusion burden are candidates for hematopoietic stem cell transplantation (HCT).(MS-5) Allogeneic HCT is the only treatment modality that can induce long-term remissions in aCML. HMAs and/or ruxolitinib and/or allogeneic HCT may be considered for patients with BCR-ABL negative aCML. Allogeneic HCT is the main treatment option for JMML. (MS-6) High-Intensity Therapy High-intensity therapy includes intensive induction chemotherapy or HCT. (MS-33) Therapy for Higher-Risk Disease (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High) Treatment for higher-risk patients is dependent on whether they are possible candidates for intensive therapy (eg, allogeneic HCT, intensive chemotherapy). For patients who are transplant candidates, an HLA-matched sibling or HLA-matched unrelated donor can be considered. Results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is generally the strategy in older individuals. (MS-38) **NCCN GUIDELINES™ Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (V. 1.2023 — May 19, 2023 ~~1.2022, April 14, 2022~~)** Myeloid/Lymphoid Neoplasms with Eosinophilia and *PDGFRA* or *PDGFRB* Rearrangement Durable remissions are only rarely achieved with induction chemotherapy or allogeneic hematopoietic cell transplant (HCT). (MS-12)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>Myeloid/Lymphoid Neoplasms with Eosinophilia and FGFR1 or JAK2 or ABL1 or FLT3 Rearrangement
MLN-Eo with the above-mentioned TK fusion gene rearrangements are generally associated with an aggressive clinical course, relapse, or disease progression to blast phase and allogeneic HCT is the only potentially curative option. (MS-13)</td></tr>
<tr><td>Myelofibrosis</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table>
<tr><th>Adults
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myelofibrosis and myeloproliferative diseases, Primary, low risk</td><td>C</td><td>N</td></tr>
<tr><td>Myelofibrosis and myeloproliferative diseases, Primary, intermediate/high risk</td><td>C</td><td>N</td></tr>
<tr><td>Myelofibrosis and myeloproliferative diseases, Secondary</td><td>C</td><td>N</td></tr>
<tr><td>Myelofibrosis and myeloproliferative diseases, Hypereosinophilic syndromes, refractory</td><td>R</td><td>N</td></tr>
</table>

<u>NCCN GUIDELINES™Myeloproliferative Neoplasms (V.1.2023 — May 19, 2023)</u>

Allogeneic HCT is the only potentially curative treatment option resulting in long-term remissions for patients with MF. (MS-19)

Lower-Risk MF
Patients with asymptomatic lower-risk MF should be observed and monitored for signs and symptoms of disease progression with MPN-SAF TSS (MPN-10). Enrollment in a clinical trial is also an option. (MS-22)

Higher-Risk MF
Evaluation for allogeneic HCT is recommended for all patients with higher-risk MF and allogeneic HCT is recommended for patients who meet transplant eligibility criteria. (MS-23)

Disease Progression to Advanced Phase or Transformation to Acute Myeloid Leukemia
Allogeneic HCT remains the only curative option resulting in long-term disease control in selected transplant-eligible patients who achieve a CR to induction chemotherapy. (MS-30)</td></tr>
<tr><td>Non-Hodgkin Lymphoma (NHL)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)</td></tr>
</table>

Cancer	

Children (<18 years)	Allogeneic HCT	Autologous HCT
Anaplastic large cell lymphoma CR1	N	N
Anaplastic large cell lymphoma Primary refractory, sensitive	C	C
Anaplastic large cell lymphoma Primary refractory, resistant	C	N
Anaplastic large cell lymphoma First relapse, sensitive	C	C
Anaplastic large cell lymphoma First relapse, resistant	C	N
Anaplastic large cell lymphoma Second or greater relapse	C	C
Burkitt lymphoma (BL) First remission	N	N
Burkitt lymphoma First or greater relapse, sensitive	C	C
Burkitt lymphoma First or greater relapse, resistant	C	N
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR1, standard risk	N	N
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR1, high risk	S	N
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR2	S	N
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), CR3+	C	N
Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), Not in remission	C	N
T cell non-Hodgkin lymphoma CR1, standard risk	N	R
T cell non-Hodgkin lymphoma CR1, high risk	R	R
T cell non-Hodgkin lymphoma CR2	S	C
T cell non-Hodgkin lymphoma CR3+	C	C
T cell non-Hodgkin lymphoma Not in remission	C	N

Adults	Allogeneic HCT	Autologous HCT
Burkitt lymphoma (BL) CR1	N	N

Cancer				
		Burkitt lymphoma First or greater relapse, sensitive	C	C
		Burkitt lymphoma First or greater relapse, resistant	C	N
		Burkitt lymphoma Relapse after autologous transplant	C	N
		Cutaneous T cell lymphoma (CTCL) Relapse	S	C
		Diffuse large B cell lymphoma CR 1 (PET negative)	N	N
		Diffuse large B cell lymphoma Primary refractory, sensitive	S	S
		Diffuse large B cell lymphoma Primary refractory, resistant	S	N
		Diffuse large B cell lymphoma First relapse, sensitive	S	S
		Diffuse large B cell lymphoma First relapse, resistant	S	N
		Diffuse large B cell lymphoma Second or greater relapse	S	S
		Diffuse large B cell lymphoma Relapse after autologous transplant	S	N
		Diffuse large B cell lymphoma Plasmablastic lymphoma CR1	R	R
		Diffuse large B cell lymphoma Plasmablastic lymphoma Relapse	R	C
		Follicular lymphoma CR 1	N	N
		Follicular lymphoma Primary refractory, sensitive	N	S
		Follicular lymphoma Primary refractory, resistant	S	N
		Follicular lymphoma First relapse, sensitive (including POD24)	N	S
		Follicular lymphoma First relapse, resistant	S	N
		Follicular lymphoma Second or greater relapse	S	S
		Follicular lymphoma Transformation to high grade lymphoma	C	S
		Follicular lymphoma Relapse after autologous transplant	S	N
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements CR 1 (PET negative)	N	C
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6*	R	C

Cancer					
		rearrangements Primary refractory, sensitive			
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements Primary refractory, resistant	R	N	
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements First relapse, sensitive	R	C	
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements First relapse, resistant	R	N	
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements Second or greater relapse	R	C	
		High-grade B cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements Relapse after autologous transplant	R	N	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia CR 1	N	N	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia Primary refractory, sensitive	N	C	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia Primary refractory, resistant	R	N	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia First or greater relapse, sensitive	C	S	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia First or greater relapse, resistant	R	N	
		Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia Relapse after autologous transplant	C	N	
		Mantle cell lymphoma CR 1/first partial remission	C	S	
		Mantle cell lymphoma Primary refractory, sensitive	S	S	
		Mantle cell lymphoma Primary refractory, resistant	C	N	
		Mantle cell lymphoma First relapse, sensitive	S	S	
		Mantle cell lymphoma First relapse, resistant	C	N	
		Mantle cell lymphoma	S	S	

Cancer	

Second or greater relapse		
Mantle cell lymphoma Relapse after autologous transplant	S	N
T cell lymphoma CR 1/first partial remission	S	S
T cell lymphoma Primary refractory, sensitive	S	S
T cell lymphoma Primary refractory, resistant	C	N
T cell lymphoma First relapse, sensitive	S	S
T cell lymphoma First relapse, resistant	C	N
T cell lymphoma Second or greater relapse	S	C
T cell lymphoma Relapse after autologous transplant	S	N

NCCN GUIDELINES™ B-cell Lymphoma (V.3.2023 — May 11, 2023 ~~4.2022, June 9, 2022~~)

Burkitt Lymphoma
NCCN Recommendations
It is preferred that patients with BL receive treatment at centers with expertise in the management of this highly aggressive disease. Participation in clinical trials is recommended for all patients. CHOP or CHOP-like therapy is not adequate for the treatment of BL The management of patients with B-cell lymphomas with features intermediate between BL and DLBCL (now included in the new category, HGBL, NOS) as well as those patients with double-hit or triple-hit lymphomas (HGBL with translocations of MYC and BCL2 and/or BCL6) has not been well studied. Therefore, these patients are best managed in the context of clinical trials evaluating novel targeted agents. (MS-144) Patients with relapsed or refractory disease should be treated in the context of a clinical trial. Consolidation with high-dose therapy and autologous stem cell rescue
(HDT/ASCR) or allogeneic HCT (if donor available) may be considered for selected patients achieving a CR or PR to second-line therapy. (MS-145)

HIV-Related B-Cell Lymphomas
NCCN Recommendations
The NCCN Guidelines recommend the use of ART and growth factor support along with full-dose chemotherapy with or without rituximab. (MS-153)

Post-Transplant Lymphoproliferative Disorders
NCCN Recommendations
Treatment options for PTLD depend on the histological subtype and should be individualized. RI, if possible, should be a part of the initial treatment approach for all patients with PTLD. Initial management strategies include reduction of calcineurin inhibition (cyclosporin or

Cancer	
	tacrolimus) by 50% and discontinuation of antimetabolic agents (azathioprine or mycophenolate mofetil). (MS-167) Follicular Second-line Consolidation or Extended Dosing HDT/ASCR is an appropriate consolidative therapy for patients with second or third remission. (MS-24) Nodal Marginal Zone Lymphoma Second-line Consolidation or Extended Dosing HDT/ASCR is included as an option for consolidative therapy for patients with disease responding to second-line therapy. Allogeneic hematopoietic cell transplant (HCT) may also be considered for highly selected patients. (MS-64) Histologically Transformed Marginal Zone Lymphoma HDT/ASCR and allogeneic HCT may be reasonable treatment options for selected patients with histologically transformed MZL. (MS-70) Mantle Cell Lymphoma Consolidation After Aggressive Induction Therapy The panel recommends consolidation with HDT/ASCR for eligible patients in CR following induction therapy with aggressive regimens, although no studies have compared maintenance rituximab with HDT/ASCR for patients in first CR. Rituximab maintenance following HDT/ASCR is included with a category 1 recommendation. (MS-86) Allogeneic HCT using reduced-intensity conditioning (RIC) has been evaluated as a consolidation strategy for patients in remission following treatment for relapsed/refractory MCL (MS-92) Diffuse Large B-Cell Lymphoma HDT/ASCR is therefore not routinely recommended. (MS-108) Relapsed or Refractory Disease: Consolidation therapy with HDT/ASCR (category 1 for patients with CR) with or without RT is recommended for patients with CR or PR to second-line therapy, if they are candidates for transplant. (MS-113) Burkitt Lymphoma Relapsed or Refractory Disease Consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR) or allogeneic HCT (if donor available) may be considered for selected patients achieving a CR or PR to second-line therapy. (MS-145) **NCCN GUIDELINES™ Pediatric Aggressive Mature B-Cell Lymphomas (V.1.2023 — April 4, 2023)** Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma Treatment for Relapsed or Refractory Disease Second-line therapy followed by consolidation with autologous or allogeneic HCT (based on response to second-line therapy) is recommended for most patients if they are not enrolled in a clinical trial.

Cancer	
	Most patients with relapsed/refractory disease achieving a CR to second-line therapy should receive an autologous or allogeneic HCT. Patients with a PR to second-line therapy can also receive an autologous or allogeneic HCT. (MS-11) Primary Mediastinal Large B-Cell Lymphoma Treatment for Relapsed/Refractory Disease The management of relapsed/refractory PMBL in both pediatric and adult patients is similar to the management of relapsed/refractory DLBCL - second-line therapy with cross-resistant chemoimmunotherapy regimens followed by autologous HCT. Patients with a CR to second-line therapy should receive an autologous HCT. Allogeneic HCT is not considered an optimal approach. (MS-14) **NCCN GUIDELINES™ Primary Cutaneous Lymphomas (V.1.2023 — January 5, 2023)** Mycosis Fungoides/Sézary Syndrome (MFSS) Allogeneic HCT has a role in a subset of patients with advanced-stage MF and SS who have received multiple lines of therapy. (MS-29) Allogeneic HCT may be considered for appropriate patients with stage IIB–IV disease that is refractory to multiple primary treatment options. Allogeneic HCT is generally reserved for patients with systemic disease and/or extensive skin involvement that is refractory to or progressive after multiple lines of systemic therapy options. (MS-30) **NCCN GUIDELINES™ T-cell Lymphomas (V.1.2023 — January 5, 2023)** Peripheral T-Cell Lymphomas Treatment for Relapsed or Refractory Disease Further data from prospective studies are needed to determine the role of HDT/ASCR and allogeneic HCT in patients with relapsed/refractory PTCL. (MS-17) Second-line systemic therapy followed by consolidation with HDT/ASCR or allogeneic HCT for those with a CR or PR is recommended for patients who are candidates for transplant. (MS-18) Breast Implant-Associated ALCL High-dose therapy followed by autologous HCT could be considered for patients achieving complete response to systemic therapy. (MS-36) T-Cell Large Granular Lymphocytic Leukemia NCCN Recommendations Low-dose methotrexate or cyclophosphamide (with or without corticosteroids) or cyclosporine are included as options for first-line therapy. (MS-44) T-Cell Prolymphocytic Leukemia Data from retrospective studies suggest that allogeneic HCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL. (MS-53)

Cancer	
	NCCN Recommendations Given the poor prognosis associated with T-PLL, the NCCN Guidelines Panel recommends that patients be managed in a clinical trial. In patients who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT.(MS-53, 54) Adult T-Cell Leukemia/Lymphoma Available evidence mostly from retrospective studies suggest that allogeneic HCT may be associated with long term survival in some patients with ATLL, suggesting a contribution of graft-versus-leukemia/lymphoma (GVL) effect. (MS-66) NCCN Recommendations In the NCCN Guidelines, patients with ATLL are classified into four subtypes (chronic, smoldering, acute, and lymphoma) according to the Shimoyama criteria. There are no optimal standard treatment regimens for the management of ATLL. Thus, the NCCN Guidelines Panel recommends enrollment in clinical trials as one of the options for all patients with ATLL. (MS-67) Hepatosplenic T-Cell Lymphoma NCCN Recommendations The optimal treatment approach remains undefined given the absence of data from prospective randomized clinical studies. (MS-78) Consolidation therapy with allogeneic HCT is recommended for eligible patients with complete response or partial response after initial induction therapy or second-line therapy. Consolidation therapy with autologous HCT can be considered if a suitable donor is not available or for patients who are ineligible for allogeneic HCT.(MS-79) Extranodal Natural Killer/T-Cell Lymphomas, Nasal Type Data confirm that hematopoietic stem cell transplant (HSCT) should be considered for consolidation in selected patients with relapsed ENKL (MS-91) NCCN Recommendations Participation in a clinical trial is the preferred option for all patients with ENKL with any stage of disease. (MS-91) There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized. (MS-93) Relapsed/Refractory Disease HCT is an option for eligible patients. Several small case reports have reported favorable long-term outcomes after allogeneic HCT in patients with relapsed/refractory disease. Allogeneic HCT is preferred, if a donor is available. (MS-93) Aggressive NK-Cell Leukemia Allogeneic HCT may be helpful to improve the outcome of patients with ANKL and the panel favors consolidation with allogeneic HCT (over autologous HCT) for patients in first remission. (MS-94)

Cancer	
	NCCN GUIDELINES™ Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma (V. 1.2023 — July 6, 2022) Therapy for Previously Treated WM HCT is also an option for relapsed WM in selected patients. HCT options listed in the NCCN Guidelines for WM/LPL are for high-dose therapy with autologous stem cell rescue. According to the NCCN Panel, myeloablative or non-myeloablative allogeneic HCT may be considered, but in the context of a clinical trial. (MS-13) **American Society of Transplantation and Cellular Therapy (ASTCT) Clinical Practice Recommendations for Transplantation and Cellular Therapies in Mantle Cell Lymphoma (Munshi, et al., 2021)** The following are 2021 Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments in the First-Line Setting for MCL: 1. The panel recommends autologous HCT as consolidation therapy in eligible, newly diagnosed MCL patients (without TP53 mutation or biallelic deletion) in complete remission or partial remission after first-line therapies.(Grade: A*) 2. The panel does not recommend autologous transplantation as consolidation therapy in MCL patients with disease not responsive to most recent antilymphoma therapy. (Grade: B) 3. The panel does not recommend using measurable residual disease (MRD) testing to guide use of autologous transplantation consolidation after first-line therapies in MCL outside the setting of a clinical trial. (Grade: C) 4. The panel does not recommend using MIPI or MIPI-c prognostic score as a criterion determining use of autologous transplantation as consolidation therapy in eligible newly diagnosed MCL patients in first complete remission or partial remission after first-line therapies. (Grade: C) 5. The panel does not recommend allogeneic transplantation consolidation in MCL patients (without TP53 mutation or biallelic deletion), achieving a complete or partial remission after first-line therapies. (Grade: B) 6. The panel does not recommend consolidation with CAR T cell therapy in MCL patients achieving a complete or partial remission after first-line therapies outside the setting of a clinical trial. (Grade: C) 7. If a TP53 mutation (or biallelic deletion) is present, the panel recognizes that outcomes are poor for MCL patients in complete or partial remission after first-line therapies who then undergo autologous transplantation. However, no specific alternative strategy has yet been shown to improve outcomes in such patients. Therefore, the panel recommends considering autologous transplantation consolidation as well as alternative consolidation strategies (eg, CAR T cell therapy or allogeneic

Cancer	
	transplantation), ideally in the context of a clinical trial, for such patients. (Grade: C) The following are 2021 Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR T Cell Treatments for R/R MCL: 1. If a TP53 mutation (or biallelic deletion) is present, the panel does not recommend autologous transplantation in relapsed MCL patients achieving a complete or partial remission after second or subsequent lines of therapy.(Grade: B) 2. The panel recommends both CAR T cell therapy or allogeneic transplant consolidation as acceptable options, in relapsed MCL patients with TP53 mutation (or biallelic deletion) in a complete or partial remission after second or subsequent lines of therapy. (Grade: C) 3. If a TP53 mutation (or biallelic deletion) is present, the panel recommends treatment with CAR T cells in relapsed MCL patients, with disease unresponsive to last antilymphoma therapy. (Grade: B) 4. In relapsed MCL patients, the panel recommends offering CAR T cell therapy before proceeding with allogeneic transplantation. (Grade: C) 5. Regarding timing of CAR T cell application in relapsed MCL patients (without TP53 mutation or biallelic deletion), the panel recommends offering CAR T cell therapy to patients relapsing after (or who are intolerant to) at least one BTK inhibitor. (Grade: B) 6. The panel does not recommend allogeneic transplantation in relapsed MCL patients with disease refractory to most recent antilymphoma treatment. (Grade:B) 7. The panel recommends allogeneic transplantation for eligible relapsed MCL patients who have achieved only a partial remission with a BTK inhibitor in second or subsequent treatment line, particularly in regions without access to CAR T cell therapy or in subjects where such therapy is not feasible. (Grade: B) 8. The panel recommends allogeneic transplantation in eligible MCL patients relapsing/progressing after CAR T cell therapy, if they achieve a complete or partial remission or if they have stable disease with subsequent antilymphoma therapies. (Grade: C) 9. Among eligible MCL patients lacking a TP53 mutation (or biallelic deletion) not undergoing autologous transplant consolidation following first-line therapies, the panel recommends considering autologous transplantation consolidation therapy in patients who have achieved a complete remission after second-line chemoimmunotherapies. (Grade: B) 10. The panel recommends considering allogeneic transplant consolidation in eligible MCL patients who still have detectable disease at 3 or more months following CAR T cell therapy. (Grade: C) *A: There is good research-based evidence to support the recommendation.

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>B: There is fair research-based evidence to support the recommendation.
C: The recommendation is based on expert opinion and panel consensus.
X: There is evidence of harm from this intervention.
(ASTCT/Munshi, et al., 2021)</td></tr>
<tr><td>POEMS Syndrome</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table><tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr><tr><td>POEMS syndrome</td><td>N</td><td>C</td></tr></table>
<u>National Organization for Rare Disorders (NORD):</u>
On a patient information webpage on POEMS Syndrome, NORD states that “There is no standard treatment for POEMS syndrome. Treatment options for patients diagnosed with POEMS syndrome include radiation therapy, chemotherapy, and/or hematopoietic cell transplantation.”</td></tr>
<tr><td>Systemic Mastocytosis</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table><tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr><tr><td>Systemic mastocytosis</td><td>R</td><td>N</td></tr></table>
<u>NCCN GUIDELINES™ Systemic Mastocytosis (V.1.2023 — May 24, 2023)</u>

<u>Allogeneic HCT</u>
Allogeneic HCT has been evaluated in patients with advanced SM and the outcomes are significantly affected by the subtype of SM and the type of conditioning regimen used.
Reduced-intensity conditioning regimens were associated with lower survival than myeloablative conditioning regimens.(MS-18)

Evaluation for allogeneic HCT should be considered for patients with ASM and MCL if there is adequate response to initial treatment with cytoreductive therapy. Among patients with SM-AHN, allogeneic HCT should be considered as part of initial treatment when the AHN component requires HCT. It should also be considered if the SM component presents as advanced SM (and there is adequate response to initial treatment with cytoreductive therapy) or progresses to advanced SM during treatment. Prophylactic anti-mediator drug therapy (corticosteroids, antihistamines, and epinephrine) should be used with the conditioning regimen in all patients. (MS-18)</td></tr>
</table>

American Society for Transplantation and Cellular Therapy (ASTCT 2023)
Evaluation of Children with Malignancies for Blood and Marrow Transplantation: A Report from the ASTCT Committee on Practice Guidelines (Fraint, et al., 2023) states:

> The underlying disease indication for HCT is the main driver of HCT planning and its tempo, donor selection, and preparative evaluation checklists. Allogeneic HCT indications in pediatric malignant disease typically include high-risk acute myeloid leukemia (AML), relapsed or refractory acute lymphoid leukemia (ALL), relapsed or refractory chronic myeloid leukemia, juvenile myelomonocytic leukemia, myelodysplastic syndrome, and some high-risk lymphomas, whereas autologous HCT is indicated for lymphomas and a variety of high-risk solid tumors, with the most common procedure being tandem autologous HCT for high-risk neuroblastoma. These indications have been described in more detail by (Kanate, et al., 2020) an ASTCT Committee on Practice Guidelines Task Force.

Literature Review
ALL: Several randomized controlled trials (RCTs) and case studies have demonstrated improved outcomes with the use of myeloablative conditioning and allogeneic HSCT in subsets of adults with five-year overall survival (OS) rates of 28%–69% (Cornelissen, 2009; Tomblyn, 2009; Goldstone, 2008; Fielding, 2007; Vey, 2007; Oyekunle, 2006). Although variables exist, several studies have demonstrated improved outcomes with the use of myeloablative allogeneic HSCT compared with autologous HSCT or chemotherapy in selected infants and children with ALL (Eckert, 2013; Schrauder, 2006; Balduzzi, 2005; Dalle, 2005; Sanders, 2005; Klingebiel, 2005).

Data are not robust regarding improved overall survival rates for the use of autologous HSCT compared with allogeneic HSCT. However, this therapy may result in improved disease-free survival (DFS) and may be an acceptable treatment option for selected individuals who are ineligible for allogeneic HSCT (Thomas, 2004).

AML: Several randomized controlled trials, meta-analyses and retrospective reviews have demonstrated relapse (RFS)-, disease-free (DFS), and overall (OS) survival benefit with the use of myeloablative allogeneic HSCT in first complete remission for individuals with poor- and intermediate risk AML. No improvement was noted for individuals with good-risk disease (Schetelig, 2015; Li, et al., 2015; Stelljes, 2011; Koreth, 2009; Fagioli, 2008; Gassas, 2008).

Although clinical trial data are limited, non-myeloablative or reduced-intensity conditioning permits the use of allogeneic HSCT for a subset of individuals who may be unable to tolerate the toxic effects of myeloablative chemotherapy prior to allogeneic HSCT (Scott, 2017; Abdul Wahid, 2014; Lioure, 2012; Baron, 2007; Grigg, 2007; Martino, 2007).

Two meta-analyses evaluated the outcomes of autologous HSCT versus chemotherapy in six studies of adult patients with AML in first CR. Patients receiving autologous HSCT had better EFS in both studies; however, there was no difference in OS. The studies did not address the effect in the high-risk population (Levi, 2004; Nathan, 2004).

Amyloidosis (systemic light-chain): Several prospective case series and retrospective studies have demonstrated higher complete response rates in addition to improved outcomes after high-dose chemotherapy and autologous HSCT, in selected subgroups with AL amyloidosis (Chee, 2010; Cibeira, 2011; Sanchorawala, 2007).

CLL: There are scarce randomized controlled trials evaluating the role of allogeneic hematopoietic stem-cell transplantation (HSCT) in chronic lymphocytic leukemia (CLL); however, the evidence

demonstrated by several nonrandomized trials suggests that high-dose allogeneic HSCT may be potentially curative for a select population of patients with CLL based on the long-term survival of some patients who have achieved a complete remission (Moreno, 2005; Oscier, 2004).

Several case series and retrospective studies involving non-myeloablative conditioning and allogeneic HSCT have demonstrated improved remission rates, improved progression-free and overall survival rates at variable time intervals ; Khouri, 2007; Brown, 2006.

Several prospective comparisons have investigated the safety and effectiveness of autologous HSCT for CLL (Reljic, 2015; Magni, 2014; Brion, 2012; Dreger, 2012; Michalett, 2011)

CML: The published, peer-reviewed scientific literature supports the safety and effectiveness of allogeneic HSCT for the treatment of CML in selected individuals. Although it remains a research interest, improved outcomes have not been demonstrated for autologous HSCT compared with conventional chemotherapy in individuals with CML and the role of autologous HSCT has not been established for this indication (Hehlman, 2008; Kebriaei, 2007)

CMML/JMML: Data from randomized controlled clinical trials are lacking; however, several prospective and retrospective studies have demonstrated improved overall survival (OS) with myeloablative allogeneic HSCT (Symeonidis, 2015; Yabe, 2014; Park, 2013).

Hodgkin Lymphoma: Rancea et al. (2013) published a Cochrane review regarding the effectiveness of high-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. The authors included three randomized controlled open-label trials with 14 publications, assessing 398 patients. Data from this systematic review suggest a survival benefit for patients with relapsed or refractory HL after first-line therapy in those treated with HDCT followed by ASCT compared to patients treated with conventional chemotherapy.

A systematic review and meta-analysis published by Rashidi et al. (2016) reported autologous HSCT outcomes of 38 studies (42 reports) involving 1850 patients. The primary endpoints were six-month, one-year, two-year and three-year relapse-free survival (RFS) and overall survival (OS). The pooled estimates for RFS were 77%, 50%, 37% and 31% at six months and one, two and three years, respectively. The corresponding outcomes for OS were 83%, 68%, 58% and 50%, respectively. Data suggests that non-durable remissions are a major shortcoming of allogeneic HSCT in Hodgkin lymphoma.

Multiple Myeloma: Allogeneic HSCT may include the use of a myeloablative or nonmyeloablative conditioning regimen (Kuruvilla, 2007; Kennedy, 2006; Rotta, 2008). Although autologous HSCT is not curative, studies demonstrate an improvement in complete response rates and prolongation of median overall survival (OS) by approximately 12 months (Giralt, 2009; Barlogie, 2006 [a-c]). Several randomized controlled trials have demonstrated improved response rates and overall survival (OS) rates with the use of tandem compared with single autologous transplantation (Kumar, 2009; Bruno, 2007).

Myelodysplastic Syndromes: Allogeneic HSCT offers the potential for long-term disease-free survival (DFS), and is a component of the standard of care for individuals with good performance status and no significant comorbidity for individuals with de novo and secondary myelodysplastic syndromes (Alessandrino, 2008; Kebriaei, 2005). Autologous HSCT may be appropriate in a carefully selected subset of individuals who achieve complete remission following induction chemotherapy and in whom suitable autologous stem-cells can be collected (Alessandrino, 2002; Kroger, 2006 de Witte, 2007).

Myelofibrosis: Allo-HSCT remains an important curative option for patients with PMF. When assessing a PMF patient for transplantation, focus should be placed on: (1) pre-transplant symptom burden and quality of life, (2) age, (3) comorbidities, (4) disease-specific factors, (5) functional status, and (6) availability of related donors. Unfortunately, despite the dramatic improvements in transplantation over the years, many patients with PMF who undergo transplant evaluation are considered ineligible due to age, comorbidities, or other factors and should be considered for clinical trial or symptom-directed therapies (Wolfe, et al., 2022).

Non-Hodgkin Lymphoma: The peer-reviewed published scientific literature supports the safety and effectiveness of high-dose chemotherapy with autologous HSCT as a standard treatment option for selected adults with aggressive or advanced indolent, aggressive or recurrent chemosensitive disease. There is a clear survival benefit for compared with conventional chemotherapy (Song, 2007; Oyan, 2006). Although pediatric data are not robust, there is evidence in the published peer-reviewed scientific literature supporting improvement in overall survival (OS) with autologous HSCT compared with standard chemotherapy for the treatment of stage II, stage III or stage IV NHL (Won, 2006; Sandlund, 2002).

Although data are not robust, myeloablative allogeneic HSCT is considered an acceptable treatment option for selected adults and children with NHL (Kim, 2006; Laudi, 2006; Kasamon, 2005). Non-myeloablative allogeneic HSCT may result in improved OS and is considered an acceptable treatment option for selected adults with NHL (Tomblyn , 2011; Rezvani, 2008; Vigouroux, 2007).

POEMS Syndrome: POEMS (Polyneuropathy, organomegaly, endocrinopathy, M- protein, skin changes) syndrome is a rare plasma cell disorder. Jurczyszyn et al. (2022) retrospectively reported on a multi-country registry of 108 patients with POEMS.A total of 15 hematology centers from 9 countries from the period of 1992 to 2019 were included in the analysis. Median follow up was 2.6 years. High dose chemotherapy with autologous stem cell transplant (ASCT) was incorporated into front line treatment in 25 patients (30%). Fifty-two percent ASCT patients achieved complete remission/very good partial remissions (CR/VGPR), compared to 35% in the non-ASCT group (p=.003). The authors concluded that proteasome inhibitors (PI) as single agents, the combination of a proteasome inhibitors with immunomodulatory agents (IMiDs), and ASCT all demonstrate high responses and should be considered standard options for a newly diagnosed POEMS patient.

Systemic Mastocytosis: Systemic mastocytosis (SM) results from a clonal proliferation of abnormal mast cells (MC) in extra-cutaneous organs. Broadly, patients either have indolent/smoldering SM (ISM/SSM) or advanced SM, including aggressive SM (ASM), SM with associated myeloid neoplasm (SM-AMN), and mast cell leukemia. Identification of poor-risk mutations (i.e., *ASXL1, RUNX1, SRSF2, NRAS*) further refines the risk stratification. Treatment goals for ISM patients are primarily directed towards anaphylaxis prevention/symptom control/osteoporosis treatment. Patients with advanced SM frequently need MC cytoreductive therapy to ameliorate disease-related organ dysfunction. Tyrosine kinase inhibitors (TKI) (midostaurin, avapritinib) have changed the treatment landscape in SM. While deep biochemical, histological and molecular responses have been documented with avapritinib treatment, its efficacy as monotherapy against a multimutated AMN disease component in SM-AMN patients remains unclear. Cladribine continues to have a role for MC debulking, whereas interferon-α has a diminishing role in the TKI era. Treatment of SM-AMN primarily targets the AMN component, particularly if an aggressive disease such as acute leukemia is present. Allogeneic stem cell transplant has a role in such patients. Imatinib has a therapeutic role only in the rare patient with an imatinib-sensitive KIT mutation (Pardanani, et al., 2023).

American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No relevant statements.

Use Outside of the US
The European Society for Medical Oncology has published numerous Haematological Malignancies Practice Guidelines.

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	STEM CELL Transplantation (Formerly 110.8.1)	1/27/16
LCD		Numerous	

Note: Please review the current Medicare Policy for the most up-to-date information.
(NCD = National Coverage Determination; LCD = Local Coverage Determination)

Appendix A

Acute Lymphoblastic Leukemia (ALL) High-risk Features
National Comprehensive Cancer Network® Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (Version 1.2023 — May 31, 2023)

	B-ALL	T-ALL
Age	>35 years	>35 years
White blood cell (WBC) count	>30 x 10^9 /L	>100 x 10^9 /L
Phenotype	N/A	ETP-ALL
Cytogenetics/ Molecular risk group	• Hypodiploidy (<44 chromosomes) [There are other results that are not < 44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hypodiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Hypodiploid ALL is also often associated with *TP53* loss of function mutations and Li-Fraumeni syndrome.] • *TP53* mutation • *KMT2A* rearranged (t[4;11] or others) • *IgH* rearranged [Includes *IGH::IL3* rearrangement.] • *HLF* rearranged • *ZNF384* rearranged • *MEF2D* rearranged • *MYC* rearranged • *BCR::ABL1*-like (Philadelphia chromosome [Ph]-like) ALL ➢ JAK-STAT (*CRLF2r, EPORr, JAK1/2/3r, TYK2r*, mutations of *SH2B3, IL7R, JAK1/2/3*)	*RAS/PTEN* mutation and/or *NOTCH1/FBXW7* wild type

	B-ALL	T-ALL
	➢ ABL class (rearrangements of *ABL1, ABL2, PDGFRA, PDGFRB, FGFR*) ➢ Other (*NTRKr, FLT3r, LYNr, PTK2Br*) • *PAX5alt* • t(9;22)(q34;q11.2): *BCR::ABL1* [Interphase FISH for the detection of *BCR::ABL1* transcript on blood granulocytes is recommended to differentiate between de novo blast phase chronic myeloid leukemia (BP-CML) and de novo Ph-positive ALL.] with *IKZF1* plus [*IKZF1* deletions with co-occurring deletions in *CDKN2A, CDKN2B, PAX5*, or *PAR1* in the absence of *ERG* deletion, which are called *IKZF1* plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL.] and/or antecedent chronic myeloid leukemia. • Intrachromosomal amplification of chromosome 21 (iAMP21) • Alterations of *IKZF1* [*IKZF1* deletions with co-occurring deletions in *CDKN2A, CDKN2B, PAX5*, or *PAR1* in the absence of *ERG* deletion, which are called *IKZF1* plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL.] [Emerging evidence suggests DUX4r ALL is favorable. Additionally in cases of *DUX4r, IKZF1* alterations do not confer poor prognosis.] • Complex karyotype (5 or more chromosomal abnormalities)	

Appendix B

2022 European LeukemiaNet (ELN) Acute Myeloid Leukemia (AML) Risk Classification by genetics at initial diagnosis (Dohner, et al., 2022)

[Risk Categories are mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.]

Favorable Risk Category

- t(8;21)(q22;q22.1)/*RUNX1-RUNX1T1* [Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.]
- inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ *CBFB::MYH11* [Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.]
- Mutated *NPM1* [AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk] without *FLT3*-ITD
- bZIP in-frame mutated *CEBPA* [Only in-frame mutations affecting the basic leucine zipper (bZIP) region of *CEBPA,* irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.]

Intermediate Risk Category

- Mutated *NPM1* [AML with *NPM1* mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk] with *FLT3*-ITD
- Wild-type *NPM1* with *FLT3*-ITD [without adverse-risk genetic lesions]
- t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* [The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.]
- Cytogenetic and/or molecular abnormalities not classified as favorable or adverse

Adverse Risk Category

- t(6;9)(p23.3;q34.1)/*DEK::NUP214*
- t(v;11q23.3)/*KMT2A*-rearranged [Excluding *KMT2A* partial tandem duplication (PTD).]
- t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
- t(8;16)(p11.2;p13.3)/*KAT6A*::*CREBBP*
- inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)*
- t(3q26.2;v)/*MECOM(EVI1)*-rearranged
- −5 or del(5q); −7; −17/abn(17p)
- Complex karyotype [complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.], Monosomal karyotype [monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML].
- Mutated *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1*, and/or *ZRSR2* [For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.]
- Mutated *TP53* [*TP53* mutation at a variant allele fraction of at least 10%, irrespective of the *TP53* allelic status (mono- or biallelic mutation); *TP53* mutations are significantly associated with AML with complex and monosomal karyotype.]

Coding Information

Notes:

1. This list of codes may not be all-inclusive.
2. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT®* Codes	**Description**
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
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

CPT®* Codes	Description
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
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
38242	Allogeneic lymphocyte infusions

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

References

1. American Cancer Society. A-Z index. Accessed June 2023. Available at URL address: https://www.cancer.org/cancer/types.html

2. American Society for Transplantation and Cellular Therapy (ASTCT) Practice Guidelines. Accessed June 2023. Available at URL address: https://www.astct.org/learn/practice-guidelines https://learn.astct.org/products/indications-for-hematopoietic-cell-transplantation-and-immune-effector-cell-therapy-guidelines-from-the-american-society-for-transplantation-and-cellular-therapy (See Kanate, et al., 2020)

3. American Society of Hematology. ASH Clinical Practice Guidelines. Accessed June 2023. Available at URL address: https://www.hematology.org/education/clinicians/guidelines-and-quality-care/clinical-practice-guidelines https://www.hematology.org/education/clinicians/guidelines-and-quality-care/other-clinical-guidelines

4. Auletta JJ, Sandmaier BM, Jensen E, Majhail NS, Knutson J, ACCESS Workshop Team, et al. The ASTCT-NMDP ACCESS Initiative: A Collaboration to Address and Sustain Equal

Outcomes for All across the Hematopoietic Cell Transplantation and Cellular Therapy Ecosystem. Transplant Cell Ther. 2022 Dec;28(12):802-809.

5. Centers for Medicare & Medicaid Services (CMS). National Coverage Determinations (NCDs). NCD for STEM CELL Transplantation (Formerly 110.8.1) (110.23). Accessed June 2023. Available at URL address: https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=366&ncdver=1&keyword=STEM%20CELL&keywordType=starts&areaId=all&docType=NCD&contractOption=all&sortBy=relevance&bc=1

6. Centers for Medicare & Medicaid Services (CMS). Local Coverage Determinations (LCDs). MCD Search. Accessed June 2023. Available at URL address: https://www.cms.gov/medicare-coverage-database/search.aspx

7. European Society for Medical Oncology. ESMO Clinical Practice Guidelines. Accessed June 2023. Available at URL address: https://www.esmo.org/Guidelines

8. Fraint E, Abdel-Azim H, Bhatt NS, Broglie L, Chattha A, et al. Evaluation of Children with Malignancies for Blood and Marrow Transplantation: A Report from the ASTCT Committee on Practice Guidelines. Transplant Cell Ther. 2023 May;29(5):293-301.

9. Kanate AS, Majhail NS, Savani BN, Bredeson C, Champlin RE, Crawford S, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020;26(7):1247-1256.

10. Landry I. Racial disparities in hematopoietic stem cell transplant: a systematic review of the literature. Stem Cell Investig. 2021 Dec 14;8:24.

11. Majhail NS, Farnia SH, Carpenter PA, Champlin RE, Crawford S, Marks DI, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015 Nov;21(11):1863-1869.

12. Majhail NS, Nayyar S, Santibañez ME, Murphy EA, Denzen EM. Racial disparities in hematopoietic cell transplantation in the United States. Bone Marrow Transplant. 2012 Nov;47(11):1385-90.

13. Mayo Clinic. Patient Care & Health Information. Diseases and Conditions. Accessed June 2023. Available at URL address: https://www.mayoclinic.org

14. National Cancer Institute (NCI). Cancer Types. Physician Data Query (PDQ®) Health Professional Version. Accessed June 2023. Available at URL address: https://www.cancer.gov/types

15. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Treatment by Cancer Type. Accessed June 2023. Available at URL address: https://www.nccn.org/guidelines/category_1

16. National Comprehensive Cancer Network® (NCCN). NCCN GUIDELINES™ Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network. Supportive Care. Hematopoietic Cell Transplantation (HCT) (Version 1.2023 — March 31, 2023). Accessed June 2023. Available at URL address: https://www.nccn.org/guidelines/category_3

17. National Marrow Donor Program. Diseases treatable by transplants. Accessed June 2023. Available at URL address: https://bethematch.org/transplant-basics/how-transplants-work/

18. National Marrow Donor Program. Newsroom. ACCESS Initiative Strives to End Access and Outcome Disparities Across The Hematopoietic Cell Transplantation and Cellular Therapy Ecosystem. Feb 2023. Accessed July 2023. Available at URL address: https://network.bethematchclinical.org/news/newsroom/access-initiative-strives-to-end-access-and-outcome-disparities-across-the-hematopoietic-cell-transplantation-and-cellular-therapy-ecosystem/

Acute Lymphocytic/Lymphoblastic Leukemia (ALL)

1. Balduzzi A, Valsecchi MG, Uderzo C, De Lorenzo P, Klingebiel T, Peters C, et al. Chemotherapy versus allogeneic transplantation for very-high-risk childhood acute lymphoblastic leukaemia in first complete remission: comparison by genetic randomisation in an international prospective study. Lancet. 2005 Aug 20-26;366(9486):365-42.

2. Cornelissen JJ, van der Holt B, Verhoef GE, van't Veer MB, van Oers MH, Schouten HC, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. Blood. 2009 Feb 5;113(6):1375-82.

3. Dalle JH, Moghrabi A, Rousseau P, Leclerc JM, Barrette S, Bernstein ML, et al. Second induction in pediatric patients with recurrent acute lymphoid leukemia using DFCI-ALL protocols. J Pediatr Hematol Oncol. 2005 Feb;27(2):73-9.

4. DeFilipp Z, Advani AS, Bachanova V, Cassaday RD, Deangelo DJ, et al. Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2019;25(11):2113-2123.

5. Eckert C, Henze G, Seeger K, Hagedorn N, Mann G, Panzer-Grümayer R, et al. Use of allogeneic hematopoietic stem-cell transplantation based on minimal residual disease response improves outcomes for children with relapsed acute lymphoblastic leukemia in the intermediate-risk group. J Clin Oncol. 2013 Jul 20;31(21):2736-42.

6. Fielding AK, Richards SM, Chopra R, Lazarus HM, Litzow MR, Buck G, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. Blood. 2007 Feb 1;109(3):944-50.

7. Goldstone AH, Richards SM, Lazarus HM, Tallman MS, Buck G, Fielding AK, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. 2008 Feb 15;111(4):1827-33.

8. Klingebiel T, Lang P, Schumm M, Koehl U, Bader P, Schwabe D, et al. Experiences with haploidentical stem cell transplantation in children with acute lymphoblastic leukemia. Pathol Biol (Paris). 2005 Apr;53(3):159-61.

9. Oyekunle AA, Kroger N, Zabelina T, Ayuk F, Schieder H, Renges H, et al. Allogeneic stem cell transplantation in patients with refractory acute leukemia: a long-term follow-up. Bone Marrow Transplant. 2006 Jan;37(1):45-50.

10. Sanders JE, Im HJ, Hoffmeister PA, Gooley TA, Woolfrey AE, Carpenter PA, et al. Allogeneic hematopoietic cell transplantation for infants with acute lymphoblastic leukemia. Blood. 2005 May 1;105(9):3749-56.

11. Schrauder A, Reiter A, Gadner H, Niethammer D, Klingebiel T, Kremens B, et al. Superiority of allogeneic hematopoietic stem-cell transplantation compared with chemotherapy alone in high-risk childhood T-cell acute lymphoblastic leukemia: results from ALL-BFM 90 and 95. J Clin Oncol. 2006 Dec 20;24(36):5742-9

12. Thomas X, Boiron JM, Huguet F, Dombret H, Bradstock K, Vey N, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 Trial. J Clin Oncol. 2004 Oct 15;22(20):4075-86.

13. Tomblyn MB, Arora M, Baker KS, Blazar BR, Brunstein CG, Burns LJ, et al. Myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia: analysis of graft sources and long-term outcome. J Clin Oncol. 2009 Aug 1;27(22):3634-41.

14. Vey N, Thomas X, Picard C, Kovascovicz T, Charin C, Cayeula JM, et al. Allogeneic stem cell transplantation improves the outcome of adults with t(1;19)/E2A-PBX1 and t(4;11)/MLL-AF4 positive B-cell acute lymphoblastic leukemia: results of the prospective multicenter LALA-94 study. Leukemia. 2006 Dec;20(12):2155-61.

Acute Myeloid Leukemia (AML)

1. Abdul Wahid SF, Ismail NA, Mohd-Idris MR, Jamaluddin FW, Tumian N, Sze-Wei EY, et al. Comparison of reduced-intensity and myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and acute lymphoblastic leukemia: a meta-analysis. Stem Cells Dev. 2014 Nov 1;23(21):2535-52.

2. Baron F, Storb R. Hematopoietic cell transplantation after reduced-intensity conditioning for older adults with acute myeloid leukemia in complete remission. Curr Opin Hematol. 2007 Mar;14(2):145-51.

3. Dholaria B, Savani BN, Hamilton BK, Oran B, Liu HD, et al. Hematopoietic Cell Transplantation in the Treatment of Newly Diagnosed Adult Acute Myeloid Leukemia: An Evidence-Based Review from the American Society of Transplantation and Cellular Therapy. Transplant Cell Ther. 2021 Jan;27(1):6-20.

4. Dohner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022 Sep 22;140(12):1345-1377.

5. Fagioli F, Zecca ML, Locatelli F, Lanino E, Uderzo C, Di Bartolomeo P et al. Allogeneic stem cell transplantation for children with acute myeloid leukemia in second complete remission. J Pediatr Hematol Oncol. 2008 Aug;30(8):575-83.

6. Gassas A, Ishagi MK, Afzal S, Finkelstein-Shechter T, Dupuis A, Doyle J. A comparison of the outcomes of children with acute myelogenous leukemia in either first or second

complete remission (CR1 vs CR2) following allogeneic hematopoietic stem cell transplant at a single transplant center. Bone Marrow Transplant. 2008 Jun;41(11):941-5.

7. Grigg AP, Gibson J, Bardy PG, Reynolds J, Shuttleworth P, Koelmeyer RL, et al. A prospective multicenter trial of peripheral blood stem cell sibling allografts for acute myeloid leukemia in first complete remission using fludarabine-cyclophosphamide reduced intensity conditioning. Biol Blood Marrow Transplant. 2007 May; 13(5):560-7.

8. Koreth J, Schlenk R, Kopecky KJ, Honda S, Sierra J, Djulbegovic BJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009 Jun 10;301(22):2349-61.

9. Levi I, Grotto I, Yerushalmi R, Ben-Bassat I, Shpilberg O. Meta-analysis of autologous bone marrow transplantation versus chemotherapy in adult patients with acute myeloid leukemia in first remission. Leuk Res. 2004 Jun;28(6):605-12.

10. Li D, Wang L, Zhu H, Dou L, Liu D, Fu L, et al. Efficacy of Allogeneic Hematopoietic Stem Cell Transplantation in Intermediate-Risk Acute Myeloid Leukemia Adult Patients in First Complete Remission: A Meta-Analysis of Prospective Studies. PLoS One. 2015 Jul 21;10(7):e0132620.

11. Lioure B, Béné MC, Pigneux A, Huynh A, Chevallier P, Fegueux N, et al. Early matched sibling hematopoietic cell transplantation for adult AML in first remission using an age-adapted strategy: long-term results of a prospective GOELAMS study. Blood. 2012 Mar 22;119(12):2943-8.

12. Martino R, Valcarcel D, Brunet S, Sureda A, Sierra J. Comparable non-relapse mortality and survival after HLA-identical sibling blood stem cell transplantation with reduced or conventional-intensity preparative regimens for high-risk myelodysplasia or acute myeloid leukemia in first remission. Bone Marrow Transplant. 2008 Jan;41(1):33-8.

13. Nathan PC, Sung L, Crump M, Beyene J. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a meta-analysis. J Natl Cancer Inst. 2004 Jan 7;96(1):38-45.

14. Schetelig J, Schaich M, Schäfer-Eckart K, Hänel M, Aulitzky WE, Einsele H, et al. Hematopoietic cell transplantation in patients with intermediate and high-risk AML: results from the randomized Study Alliance Leukemia (SAL) AML 2003 trial.Leukemia. 2015 May;29(5):1060-8.

15. Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2017 Apr 10;35(11):1154-1161.

16. Sekeres MA, Guyatt G, Abel G, Alibhai S, Altman JK, et al. American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020 Aug 11;4(15):3528-3549.

17. Stelljes M, Beelen DW, Braess J, Sauerland MC, Heinecke A, Berning B, et al. Allogeneic transplantation as post-remission therapy for cytogenetically high-risk acute myeloid leukemia: landmark analysis from a single prospective multicenter trial. Haematologica. 2011 Jul;96(7):972-9.

18. Tarlock K, Sulis ML, Chewning JH, Pollard JA, Cooper T, et al. Hematopoietic Cell Transplantation in the Treatment of Pediatric Acute Myelogenous Leukemia and Myelodysplastic Syndromes: Guidelines from the American Society of Transplantation and Cellular Therapy. Transplant Cell Ther. 2022 Sep;28(9):530-545.

Amyloidosis (systemic light-chain)

1. Chee CE, Dispenzieri A, Gertz MA. Amyloidosis and POEMS syndrome. Expert Opin Pharmacother. 2010 Jun;11(9):1501-14.

2. Cibeira MT, Sanchorawala V, Seldin DC, Quillen K, Berk JL, Dember LM, et al. Outcome of AL amyloidosis after high-dose melphalan and autologous stem-cell transplantation: long-term results in a series of 421 patients. Blood. 2011 Oct 20;118(16):4346-52.

3. Sanchorawala V, Skinner M, Quillen K, Finn KT, Doros G, Seldin DC. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation. Blood. 2007 Nov 15;110(10):3561-3.

Chronic Lymphocytic Leukemia (CLL)

1. Brion A, Mahé B, Kolb B, Audhuy B, Colombat P, et al. Autologous transplantation in CLL patients with B and C Binet stages: final results of the prospective randomized GOELAMS LLC 98 trial. Bone Marrow Transplant. 2012 Apr;47(4):542-8.

2. Brown JR, Kim HT, Li S, Stephans K, Fisher DC, Cutler C, et al. Predictors of improved progression-free survival after nonmyeloablative allogeneic stem cell transplantation for advanced chronic lymphocytic leukemia. Biol Blood Marrow Transplant. 2006 Oct;12(10):1056-64.

3. Dreger P, Dohner H, McClanahan F, Busch R, Ritgen M, Greinix H, et al. Early autologous stem cell transplantation for chronic lymphocytic leukemia: long-term follow-up of the German CLL Study Group CLL3 trial. Blood. 2012 May 24;119(21):4851-9.

4. Khouri IF, Saliba RF, Admirand J, O'Brien S, Lee MS, Korbling M, et al. Graft-versus-leukaemia effect after non-myeloablative haematopoietic transplantation can overcome the unfavourable expression of ZAP-70 in refractory chronic lymphocytic leukaemia. Br J Haematol. 2007 May;137(4):355-63.

5. Magni M, Di Nicola M, Patti C, Scimè R, Mulè A, Rambaldi A, et a. Results of a randomized trial comparing high-dose chemotherapy plus Auto-SCT and R-FC in CLL at diagnosis. Bone Marrow Transplant. 2014 Apr;49(4):485-91.

6. Michallet M, Dreger P, Sutton L, Brand R, Richards S, van Os M, et al. Autologous hematopoietic stem cell transplantation in chronic lymphocytic leukemia: results of European intergroup randomized trial comparing autografting versus observation. Blood. 2011 Feb 3;117(5):1516-21.

7. Moreno C, Villamor N, Colomer D, Esteve J, Martino R, Nomdedeu J, et al. Allogeneic stem-cell transplantation may overcome the adverse prognosis of unmutated VH gene in patients with chronic lymphocytic leukemia. J Clin Oncol. 2005 May 20;23(15):3433-8.

8. Oscier D, Fegan C, Hillmen P, Illidge T, Johnson S, Maguire P, Matutes E, Milligan D; Guidelines Working Group of the UK CLL Forum. British Committee for Standards in Haematology. Guidelines on the diagnosis and management of chronic lymphocytic leukaemia. Br J Haematol. 2004 May;125(3):294-317.

9. Reljic T, Kumar A, Djulbegovic B, Kharfan-Dabaja MA. High-dose therapy and autologous hematopoietic cell transplantation as front-line consolidation in chronic lymphocytic leukemia: a systematic review. Bone Marrow Transplant. 2015 Aug;50(8):1069-74.

Chronic Myeloid Leukemia (CML)

1. Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J, et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood. 2007 Jun 1;109(11):4686-92.

2. Kebriaei P, Detry MA, Giralt S, Carrasco-Yalan A, Anagnostopoulos A, et al. Long-term follow-up of allogeneic hematopoietic stem-cell transplantation with reduced-intensity conditioning for patients with chronic myeloid leukemia. Blood. 2007 Nov 1;110(9):3456-62.

CMML/JMML

1. Park S, Labopin M, Yakoub-Agha I, Delaunay J, Dhedin N, Deconinck E, et al. Allogeneic stem cell transplantation for chronic myelomonocytic leukemia: a report from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Eur J Haematol 2013 May;90(5):355-64.

2. Symeonidis A, van Biezen A, de Wreede L, Piciocchi A, Finke J, Beelen D, et al. Achievement of complete remission predicts outcome of allogeneic haematopoietic stem cell transplantation in patients with chronic myelomonocytic leukaemia. A study of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Br J Haematol. 2015 Jul 26.

3. Yabe M, Ohtsuka Y, Watanabe K, Inagaki J, Yoshida N, Sakashita K, et al. Transplantation for juvenile myelomonocytic leukemia: a retrospective study of 30 children treated with a regimen of busulfan, fludarabine, and melphalan. Int J Hematol. 2015 Feb;101(2):184-90.

Hodgkin Disease:

1. Rancea M, Monsef I, von Tresckow B, Engert A, Skoetz N. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed/refractory Hodgkin lymphoma. Cochrane Database Syst Rev. 2013 Jun 20;6:CD009411

2. Rashidi A, Ebadi M, Cashen AF. Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis. Bone Marrow Transplant. 2016 Apr;51(4):521-8.

Multiple Myeloma

1. Barlogie B, Kyle R, Anderson K, Greipp P, Lazarus H, Hurd D, et al. [a] Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US intergroup trial S9321. J Clin Oncol. 2006 Feb 20;24(6):929-36.

2. Barlogie B, Zangari M, Bolejack V, Hollmig K, Anaissie E, van Rhee F, et al. [b] Superior 12-year survival after at least 4-year continuous remission with tandem transplantations for multiple myeloma. Clin Lymphoma Myeloma. 2006 May;6(6):469-74.
3. Barlogie B, Tricot GJ, van Rhee F, Anqtuaco E, Walker R, Epstein J, et al. [c] Long-term outcome results of the first tandem autotransplant trial for multiple myeloma. Br J Haematol. 2006 Oct;135(2):158-64.

4. Bruno B, Rotta M, Patriarca F, Mordini N, Allione B, Carnevale-Schianca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med. 2007 Mar 15;356(11):1110-20.

5. Dhakal B, Shah N, Kansagra A, Kumar A, Lonial S, et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Multiple Myeloma. Transplant Cell Ther. 2022 Jun;28(6):284-293.

6. Giralt S, Garderet L, Durie B, Cook G, Gahrton G, Bruno B, et al. Biol Blood Marrow Transplant. 2015 Dec;21(12):2039-51.

7. Kennedy GA, Butler J, Morton J, Hill G, Western R, Cummings J, et al. Myeloablative allogeneic stem cell transplantation for advanced stage multiple myeloma: very long-term follow up of a single center experience. Clin Lab Haematol. 2006 Jun;28(3):189-97.

8. Kumar A, Kharfan-Dabaja MA, Glasmacher A, Djulbegovic B. Tandem versus single autologous hematopoietic cell transplantation for the treatment of multiple myeloma: a systematic review and meta-analysis. J Natl Cancer Inst. 2009 Jan 21;101(2): 100-6.

9. Kuruvilla J, Shepard JD, Sutherland HJ, Nevill TJ, Nitta J, Le A, et al. Long-term outcome of myeloablative allogeneic stem cell transplantation for multiple myeloma. Biol Blood Marrow Transplant. 2007 Aug;13(8):925-31.

10. Rotta M, Storer BE, Sahebi F, Shizuru JA, Bruno B, Lange T, et al. Long-term outcomes of patients with multiple myeloma after autologous hematopoietic cell transplantation and nonmyeloablative allografting. Blood. 2009 Apr 2;113(14):3383-91.

11. Shah N, Callander N, Ganguly S, Gul Z, Hamadani M, American Society for Blood and Marrow Transplantation, et al. Hematopoietic Stem Cell Transplantation for Multiple Myeloma: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2015 Jul;21(7):1155-66.

Myelodysplastic Syndromes

1. Alessandrino EP, Amadori S, Barosi G, Cazzola M, Grossi A, Liberato LM, et al. Evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes. A statement from the Italian Society of Hematology. Haematologica 2002 Dec;87(12):1286-306.

2. DeFilipp Z, Ciurea SO, Cutler C, Robin M, Warlick ED, et al. Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. Transplant Cell Ther. 2023 Feb;29(2):71-81.

3. de Witte T, Oosterveld M, Muus P. Autologous and allogeneic stem cell transplantation for myelodysplastic syndrome. Blood Rev. 2007 Jan;21(1):49-59.

4. Kebriaei P, Kline J, Stock W, Kasza K, Le Beau MM, Larson RA, van Besien K. Impact of disease burden at time of allogeneic stem cell transplantation in adults with acute myeloid leukemia and myelodysplastic syndromes. Bone Marrow Transplant. 2005;35:965-70.

5. Kroger N, Brand R, van Biezen A, Cahn JY, Slavin S, Blaise D, Sierra J, Zander A, Niederwieser D, de Witte T; Myelodysplastic Syndromes Subcommitee of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Autologous stem cell transplantation for therapy-related acute myeloid leukemia and myelodysplastic syndrome. Bone Marrow Transplant. 2006 Jan;37(2):183-9.

Myelofibrosis

1. Jain T, Mesa RA, Palmer JM. Allogeneic Stem Cell Transplantation in Myelofibrosis. Biol Blood Marrow Transplant. 2017 Sep;23(9):1429-1436.

2. Tefferi A. Primary myelofibrosis: 2017 update on diagnosis, risk-stratification, and management. Am J Hematol. 2016 Dec;91(12):1262-1271.

3. Wolfe HR, Horwitz ME, Rein LAM. The Use of Allogeneic Hematopoietic Stem Cell Transplantation in Primary Myelofibrosis. J Pers Med. 2022 Apr 2;12(4):571.

Non-Hodgkin Lymphoma

1. Kasamon YL, Jones RJ, Piantadosi S, Ambinder RF, Abrams RA, Borowitz MJ, et al. High-dose therapy and blood or marrow transplantation for non-Hodgkin lymphoma with central nervous system involvement. Biol Blood Marrow Transplant. 2005;11:93-100.

2. Kim SW, Tanimoto TE, Hirobayashi N, Goto S, Kami M, Yoshioka S, et al. Myeloablative allogeneic hematopoietic stem cell transplantation for non-Hodgkin lymphoma: a nationwide survey in Japan. Blood. 2006 Jul 1;108(1):382-9.

3. Laudi N, Arora M, Burns LJ, McGlave PB, Miller JS, Bohac G, et al. Efficacy of high-dose therapy and hematopoietic stem cell transplantation for mantle cell lymphoma. Am J Hematol. 2006 Jul;81(7):519-24.

4. Munshi PN, Hamadani M, Kumar A, Dreger P, Friedberg JW, et al. American Society of Transplantation and Cellular Therapy, Center of International Blood and Marrow Transplant Research, and European Society for Blood and Marrow Transplantation Clinical Practice Recommendations for Transplantation and Cellular Therapies in Mantle Cell Lymphoma. Transplant Cell Ther. 2021 Sep;27(9):720-728.

5. Oyan B, Koc Y, Ozdemir E, Kars A, Turker A, Tekuzman G, et al. High dose sequential chemotherapy and autologous stem cell transplantation in patients with relapsed/refractory lymphoma. Leuk Lymphoma. 2006 Aug;47(8):1545-52.

6. Rezvani AR, Storer B, Maris M, Sorror ML, Agura E, Maziarz RT, et al. Nonmyeloablative allogeneic hematopoietic cell transplantation in relapsed, refractory, and transformed indolent non-Hodgkin's lymphoma. J Clin Oncol. 2008 Jan 10;26(2):211-7.

7. Sandlund JT, Bowman L, Heslop HE, Krance R, Mahmoud H, Pui CH, et al. Intensive chemotherapy with hematopoietic stem-cell support for children with recurrent or refractory NHL. Cytotherapy. 2002;4(3):253-8.

8. Song KW, Barnett MJ, Gascoyne RD, Chhanabhai M, Forrest DL, Hogge DE, et al. Primary therapy for adults with T-cell lymphoblastic lymphoma with hematopoietic stem-cell transplantation results in favorable outcomes. Ann Oncol. 2007 Mar;18(3):535-40.

9. Tomblyn MR, Ewell M, Bredeson C, Kahl BS, Goodman SA, Horowitz MM, et al. Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response. Biol Blood Marrow Transplant. 2011 Jul;17(7):1051-7.

10. Vigouroux S, Michallet M, Porcher R, Attal M, Ades L, Bernard M, et al. Long-term outcomes after reduced-intensity conditioning allogeneic stem cell transplantation for low-grade lymphoma: a survey by the French Society of Bone Marrow Graft Transplantation and Cellular Therapy (SFGM-TC). Haematologica. 2007 May;92(5):627-34.

11. Won SC, Han JW, Kwon SY, Shin HY, Ahn HS, Hwang TJ, et al. Autologous peripheral stem cell transplantation in children with non-Hodgkin's lymphoma: a report from the Korean society of pediatric hematology-oncology. Ann Hematol. 2006 Nov;85(11):787-94.

POEMS Syndrome

1. Jurczyszyn A, Castillo JJ, Olszewska-Szopa M, Kumar L, Thibaud S, et al. POEMS Syndrome: Real World Experience in Diagnosis and Systemic Therapy - 108 Patients Multicenter Analysis. Clin Lymphoma Myeloma Leuk. 2022 May;22(5):297-304.

2. Khouri J, Nakashima M, Wong S. Update on the Diagnosis and Treatment of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes) Syndrome: A Review. JAMA Oncol. 2021 Sep 1;7(9):1383-1391.

3. National Organization for Rare Disorders (NORD). POEMS Syndrome. Accessed June 2023. Available at URL address: https://rarediseases.org/rare-diseases/poems-syndrome/

Systemic Mastocytosis

1. Pardanani A. Systemic mastocytosis in adults: 2023 update on diagnosis, risk stratification and management. Am J Hematol. 2023 Jul;98(7):1097-1116.