Medical Coverage Policy

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Stem Cell Transplantation: Blood Cancers

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INSTRUCTIONS FOR USE

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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

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately matched human leukocyte antigen (HLA) donor.

	• no induction treatment and any of the following:
	  ➢ 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
POEMS Syndrome	**Autologous HSCT is considered medically necessary for the treatment of POEMS syndrome.**
Primary Central Nervous System (CNS) Lymphoma	**Autologous HSCT is considered as medically necessary for the treatment of relapsed or refractory primary CNS lymphoma.**
Systemic Mastocytosis	**Allogeneic hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of advanced / aggressive systemic mastocytosis.**

Health Equity Considerations

Health equity is the highest level of health for all people; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which people are born, grow, live, work, and age.

Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include safe housing, transportation, and neighborhoods; racism, discrimination and violence; education, job opportunities and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

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) 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).

Primary Central Nervous System Lymphomas (PCNSL) accounts for approximately 3% of all neoplasms and 4% to 6% of all extranodal lymphomas. It is an aggressive form of non-Hodgkin lymphoma that develops within the brain, spinal cord, eye, or leptomeninges without evidence of systemic involvement. Pathologically, PCNSL is an angiocentric neoplasm composed of a dense monoclonal proliferation of lymphocytes, usually diffuse large B cells. More than 90% of these primary CNS diffuse large B-cell lymphoma cases are of the activated B-cell–like (ABC) subtype. The tumor is infiltrative and typically extends beyond the primary lesion, as shown by CT or MRI scans, into regions of the brain with an intact blood-brain barrier. The brain parenchyma is involved in more than 90% of all PCNSL patients, and the condition can be multifocal in more than 50% of cases (NCCN, 2023).

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
CR1, standard risk</td><td>N</td><td>N</td></tr>
<tr><td>Acute lymphoblastic leukemia
CR1, high risk</td><td>S</td><td>N</td></tr>
<tr><td>Acute lymphoblastic leukemia
CR2</td><td>S</td><td>N</td></tr>
<tr><td>Acute lymphoblastic leukemia
CR3+</td><td>C</td><td>N</td></tr>
<tr><td>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.</td><td>C *</td><td>N</td></tr>
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Cancer	
	NCCN GUIDELINES™ Acute Lymphoblastic Leukemia (Version 4.2023 — February 05, 2024) As part of post-remission 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 disease with evidence of high-risk features (including 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 patients with newly diagnosed disease and patients with relapsed disease who have not yet undergone transplant to facilitate timely donor identification, and ultimately allogeneic transplant if warranted. (MS-14) **NCCN GUIDELINES™ Pediatric Acute Lymphoblastic Leukemia (Version 5.2024 — April 03, 2024)** 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) Allogeneic HCT has demonstrated improved clinical outcomes in pediatric patients with ALL with evidence of certain high-risk features and/or persistent disease. In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor). Both total body irradiation (TBI) and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL. Non-TBI–containing regimens are currently under investigation. The benefit of allogeneic HCT in infants with ALL is controversial, although some studies have demonstrated a role in patients with high-risk disease with *KMT2A* rearrangements and other poor-risk factors. Based on the data, it is reasonable to consider HCT in first remission (CR1) for certain patients as described in the HCT sections throughout the discussion. (MS-13) **NCCN GUIDELINES™ Adolescent and Young Adult (AYA) Oncology (Version 2.2024 — July 7, 2023)** HCT 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 related to high-dose conditioning chemotherapy and RT are the major post-transplant complications associated with HCT. Chronic GVHD has been identified as the leading cause of non-relapse mortality in HCT survivors. AYA patients are at a higher risk of

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>developing chronic GVHD than younger children.
HCT 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.
Findings highlight the increasingly recognized need for long-term follow-up care that incorporates screening and surveillance of AYA survivors of HCT. (MS-9, 10)

<u>NCCN GUIDELINES™ Older Adult Oncology (Version 1.2024 — December 08, 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>
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<tr><td>Acute myeloid leukemia
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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>
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<tr><td>Acute myeloid leukemia
Not in remission</td><td>S</td><td>N</td></tr>
<tr><td>Acute myeloid leukemia
Therapy-related, CR1</td><td>S</td><td>N</td></tr>
</table>
</td></tr>
</table>

Cancer	

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
- 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

<table>
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<tr><td></td><td>
<u>American Society of Transplantation and Cellular Therapy</u>
<u>(Dholaria 2021)</u>
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.

<u>NCCN GUIDELINES™ Acute Myeloid Leukemia (Version 3.2024 — May 17, 2024)</u>

This NCCN guideline frequently refers readers to the NCCN Guidelines for Hematopoietic Cell Transplantation. HCT is noted as a treatment option in several algorithms, including
• Acute Promyelocytic Leukemia (Age ≥18 years)
• Acute Myeloid Leukemia (Age ≥18 years)
• Blastic Plasmacytoid Dendritic Cell Neoplasm (Age ≥18 years)
</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>
</table>
</td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>
<table>
<tr><td>Amyloid light chain amyloidosis</td><td>N</td><td>S</td></tr>
</table>

<u>NCCN GUIDELINES™ Systemic Light chain Amyloidosis (Version 2.2024 — December 12, 2023)</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 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 (Version 3.2024 — March 26, 2024)</u>

Long-term results from several prospective studies showed that allogeneic hematopoietic cell transplant (HCT) can provide long-term disease control and also overcome the poor prognosis associated with del(17p) and TP53 mutations.
Given the favorable outcome of patients with del(17p) or TP53 mutation treated with covalent BTKi as first-line therapy and the availability of
</td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>venetoclax as an effective treatment option for relapsed or refractory CLL, allogeneic HCT is not considered as a reasonable treatment option for relapsed/refractory CLL after initial purine analogue-based therapy. Allogeneic HCT can be considered for relapsed/refractory disease after prior therapy with BTKi- and venetoclax-based regimens 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. (MS-25)

<u>NCCN GUIDELINES™ Hairy Cell Leukemia (Version 2.2024 — April 22, 2024)</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)

<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 (Version 2.2024 — December 5, 2023)</u>

Management of Advanced Phase CML
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</td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>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. Several studies have confirmed that prior TKI therapy does not compromise the outcome following allogeneic HCT or increase transplant-related toxicity. (MS-23)</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)

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

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

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td><u>NCCN GUIDELINES™ Hodgkin Lymphoma (Version 3.2024 — March 18, 2024 <s>V.2.2023 — November 8, 2022</s>)</u>
Second-line systemic therapy followed by high-dose therapy/autologous stem cell rescue HDT/ASCR with or without RT is recommended for patients with relapsed or refractory classic Hodgkin lymphoma (CHL). (MS-30)

<u>NCCN GUIDELINES™ Pediatric Hodgkin Lymphoma (Version 1.2024 — May 14, 2024)</u>

<u>NCCN Recommendations for Relapsed or Refractory CHL</u>
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. (MS-15)

<u>NCCN GUIDELINES™ Cancer in People with HIV (Version 2.2024 — April 4, 2024)</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. Allogeneic HCT also appears to be safe in this population. (MS-16,17)</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>
<tr><td>Plasma cell disorders,
Relapse after autologous transplant</td><td>C</td><td>C</td></tr>
<tr><td>Plasma cell leukemia</td><td>S</td><td>C</td></tr>
</table>

<u>NCCN GUIDELINES™ Multiple Myeloma (Version 4.2024 — April 26, 2024)</u>

Transplant Eligibility</td></tr>
</table>

Cancer	
	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-22) Autologous Hematopoietic Cell Transplantation Autologous HCT results in high response rates and remains the standard of care after primary therapy for eligible patients. (MS-22) 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-24) 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. (MS-24) 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-25) A second autologous HCT can be considered at the time of disease relapse. (MS-25) 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-25) 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

Cancer	
	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-26) **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 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)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>
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 RR MM:

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)
</td></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</td><td>S</td><td>N</td></tr>
</table>
</td></tr>
</table>

Therapy related		

Adults	Allogeneic HCT	Autologous HCT
Myelodysplastic syndromes Low/intermediate – 1 risk	C	N
Myelodysplastic syndromes Intermediate-2/high risk	S	N
Myelodysplastic syndromes Therapy-related, CR1	S	N

American Society for Transplantation and Cellular Therapy
(DeFilipp, 2023)
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

- 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

NCCN GUIDELINES™ Myelodysplastic Syndromes (Version 2.2024 — May 22, 2024)

Myelodysplastic/Myeloproliferative Neoplasms
The category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) was added to the 2008 update of the WHO classification of myeloid neoplasms.
In the 2022 update, this category includes chronic myelomonocytic leukemia (CMML)-1 and CMML-2, MDS/MPN and neutrophilia (previously aCML), MDS/MPN with SF3B1 mutation and thrombocytosis (previously MDS/MPN with ring sideroblasts and thrombocytosis), and MDS/MPN

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>NOS (previously MDS/MPN unclassifiable). Juvenile myelomonocytic leukemia (JMML) is classified as a myeloproliferative neoplasm. (MS-5)

Therapy for Higher-Risk Disease (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High):
Allogeneic HCT is recommended for eligible patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is generally the strategy in older individuals. (MS-40)

Supportive care:
This NCCN guideline refers readers to the NCCN Guidelines for Hematopoietic Cell Transplantation.

<u>NCCN GUIDELINES™ Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (Version 1.2024 — December 21, 2023)</u>

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)

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 (Version 1.2024 — December 21, 2023)</u></td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>Under TREATMENT FOR HIGHER-RISK MYELOFIBROSIS, this NCCN guideline refers readers to the NCCN Guidelines for Hematopoietic Cell Transplantation. (MF-2A)

Allogeneic HCT is the only potentially curative treatment option resulting in long-term remissions for patients with MF. (MS-20)</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)

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

Cancer	

CR1, high risk		
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
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

Cancer					
		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* rearrangements Primary refractory, sensitive	R	C	
		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	C	N	

Cancer	

Relapse after autologous transplant		
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 Second or greater relapse	S	S
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

American Society for Transplantation and Cellular Therapy Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma (Epperla, et al., 2023)

Table 3
Final Clinical Practice Guidelines Consensus Statements for Transplantation and CAR-T Therapy following First-Line Chemoimmunotherapy in DLBCL Consensus Statement:

Consensus Statement	Grading of Recommendations*
The panel does not recommend autologous HCT in DLBCL (regardless of IPI score) as consolidation in complete remission after first-line (R-CHOP or similar) therapy.	A
The panel does not recommend autologous transplantation in HGBCL with *MYC/BCL2* and or *BCL6* rearrangement as consolidation	B

Cancer	
	therapy in PET negative complete remission after DA-R-EPOCH or similar high-intensity regimens.	
	Autologous HCT may be considered for ineligible patients with HGBCL with *MYC/BCL2* and or *BCL6* rearrangement As consolidation therapy in PET-negative complete remission after first-line R-CHOP or similar therapy.	B
	Autologous HCT may be considered for eligible patients with DLBCL with secondary CNS involvement at diagnosis achieving complete remission and with undetectable CNS disease after first-line therapy.	C
	The panel recommends consolidation with autologous HCT for eligible primary CNS lymphoma patients in CR1.	A
	The panel recommends a thiotepa-containing conditioning regimen when using autologous HCT consolidation for eligible primary CNS lymphoma patients in CR1.	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.

NCCN GUIDELINES™ B-cell Lymphoma (Version 2.2024 — April 30, 2024)

HCT is addressed in the treatment algorithms of:

- Classic Follicular Lymphoma
- Marginal Zone Lymphomas
- Mantle Cell Lymphoma
- Diffuse Large B-Cell Lymphoma
- ALK-Positive Large B-cell Lymphomas (ALK+ LBCL)
- Histologic Transformation of Indolent Lymphomas to DLBCL
- Burkitt Lymphoma

NCCN GUIDELINES™ Pediatric Aggressive Mature B-Cell Lymphomas (Version 1.2024 — April 8, 2024)

HCT is addressed in the treatment algorithms of:

- Burkitt Lymphoma and Diffuse Large B-Cell Lymphoma
- Primary Mediastinal Large B-Cell Lymphoma

Cancer	
	NCCN GUIDELINES™ Primary Cutaneous Lymphomas (Version 2.2024 — May 6, 2024) 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-30) Autologous HCT is not recommended for patients with CTCL, due to short duration of response despite its toxicity, thus limiting its utility. (MS-31) 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-32) **NCCN GUIDELINES™ T-cell Lymphomas (Version 3.2024 — April 11, 2024)** HCT is addressed in the treatment algorithms of: • Peripheral T-Cell Lymphomas • T-Cell Prolymphocytic Leukemia • Adult T-Cell Leukemia/Lymphoma • Hepatosplenic T-Cell Lymphoma • Extranodal NK/T-Cell Lymphomas **NCCN GUIDELINES™ Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma (Version 2.2024 — December 5, 2023)** Therapy for Previously Treated WM/LPL In selected patients HCT may be appropriate with either: • Allogeneic HCT (ablative or nonablative) • Autologous HCT (WM/LPL-B, 3 OF 4) **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

Cancer	
	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 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 <u>for R/R MCL</u>: 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)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>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.
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>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td>Primary Central Nervous System (CNS) Lymphoma (PCNSL)</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></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Primary central nervous system Lymphoma, CR1/first partial remission (consolidation)</td><td>N</td><td>C</td></tr>
<tr><td>Primary central nervous system Lymphoma, Relapse, sensitive</td><td>N</td><td>C</td></tr>
</table>

<u>NCCN GUIDELINES™ Central Nervous System (CNS) Cancers (V. 1.2023 — March 24, 2023)</u>

Primary CNS Lymphomas (PCNSLs)
NCCN Recommendations
Newly diagnoses disease - Treatment following induction high-dose methotrexate-based therapy depends on disease response. Given the rarity of this disease, there are few high-quality studies to inform treatment decision-making. For patients who have a complete or unconfirmed complete response, consolidation therapy options that may be considered include high-dose chemotherapy (cytarabine/thiotepa followed by carmustine/thiotepa; or thiotepa/busulfan/cyclophosphamide [TBC]) with stem cell rescue or low-dose WBRT. (MS-31)

Relapsed or Refractory Disease – High-dose chemotherapy with stem cell rescue may also be considered as treatment for relapsed/refractory disease in patients who did not previously receive this treatment (ie, patients who were treated with high-dose methotrexate-based therapy or with WBRT) (category 2B). Regardless of primary treatment received, stem cell rescue should only be used for relapsed/refractory disease if there is a complete or partial response to reinduction high-dose chemotherapy.

For patients previously treated with high-dose chemotherapy with stem cell rescue, retreatment may be considered if there was a previous disease response and if time to relapse was at least one year. For patients who did not have a response to high-dose chemotherapy with stem cell rescue, and the time to relapse was less than one year, treatment options include RT to the whole brain or to the involved field. Regardless of time to relapse, using a different systemic therapy regimen (without stem cell rescue) and best supportive care are also options. (MS-32)

</td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>The NCCN Pediatric Central Nervous System Cancers (Version 1.2024 — February 26, 2024) does not address Primary CNS Lymphomas.</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 (Version 3.2024 — April 24, 2024)</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.

MCL subtype was the strongest risk factor for poor OS. The role of allogeneic HCT needs to be determined in a prospective trial. In 2024, best practice recommendations were published for allogeneic HCT in patients with advanced SM (McLornan/European Society for Blood and Marrow Transplantation, 2024).

Evaluation for allogeneic HCT is a consideration for patients with advanced SM after adequate response to prior treatment. For patients with advanced SM with inadequate response or loss response to prior treatment, second-line therapy and allogeneic HCT should be considered after re-staging. Among patients with SM-AHN, allogeneic HCT should also be considered as part of initial treatment when the AHN component requires HCT or if the AHN component progresses. (MS-19)</td></tr>
</table>

<u>American Society for Transplantation and Cellular Therapy (ASTCT 2023)</u>
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.

The NCCN Supportive Care Guideline on Hematopoietic Cell Transplantation (HCT) (Version 1.2024 — April 26, 2024) addresses Graft-Versus-Host Disease.

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.

Primary Central Nervous System (CNS) Lymphoma: Peer-reviewed published data are limited to small prospective case series and retrospective reviews and support the use of autologous HSCT in the treatment of relapsed or refractory primary CNS lymphoma (Alnahhas, et al., 2019; DeFilipp, 2017; Stephanoni, et al., 2023).

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).

Medicare Coverage Determinations

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

	Contractor	Determination Name/Number	Revision Effective Date
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 4.2023 — February 05, 2024)

	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
CYTOGENETIC AND MOLECULAR PROGNOSTIC RISK STRATIFICATION FOR B-ALL Poor 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*) ➢ 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*	*RAS/PTEN* mutation and/or *NOTCH1/FBXW7* wild type

	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 (NCCN, AML-A)

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 since the American Medical Association (AMA) and Centers for Medicare & Medicaid Services (CMS) code updates may occur more frequently than policy updates.
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
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

CPT®* Codes	Description
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

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Revision Details

Type of Revision	Summary of Changes	Date
Annual review	• No clinical policy statement changes.	8/15/2024
Focused review	• Content addressing primary central nervous system lymphoma (PCNSL) was removed from CP 0534 and added to this Coverage Policy.	01/15/2024