Medical Coverage Policy

Effective Date **1/15/2022**
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Coverage Policy Number **0533**

Stem Cell Transplantation: Blood Cancers

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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 of relapse* **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 *High-risk of disease relapse or poor prognosis ALL includes ANY of the following criteria: • infancy (age younger than one year)

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	• age ≥ 10 years • failure to achieve a complete remission (CR) within four weeks of induction therapy • minimal residual disease at end of remission induction • relapse while on chemotherapy • first CR lasting < 24 months • white blood cell count (WBC) > 50,000/mcL • WBC greater than 30 X 109 /L (30,000/μL) in B-cell lineage ALL • extramedullary disease • presence of chromosomal abnormalities [e.g., t(9;22)(q34;q11) (the Philadelphia chromosome), t(4;11), t(8,14), t(1,19), or MLL gene (11q23) or t(1;19)] • complex karyotype (i.e., ≥5 chromosomal abnormalities) • hypodiploidy • deletion of chromosome 7 • trisomy 8 • near-haploid ALL (i.e., 24 to 28 chromosomes) • elevated beta 2 microglobulin • acute lymphoblastic leukemia resulting from prior cancer therapy
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 a high-risk* individual • second or subsequent remission • failed induction • 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 low/intermediate risk individual • second or subsequent remission **Tandem HSCT is considered experimental, investigational or unproven for the treatment of AML** ***High-risk includes ANY of the following:** ➢ multiple cytogenetic abnormalities ➢ requiring more than one cycle to achieve remission

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	➢ disease refractory to chemotherapy ➢ white blood cell (WBC) count > 100,000/ml3 ➢ French-American-British (FAB) subtype M4 and M5 ➢ chromosome translocations t(10;11), t(1;22), t(6;9), t(9;22) ➢ abnormalities of chromosome 7 or 5, the long arm of chromosome 3, or 11q23 ➢ trisomy 8 ➢ antigen CD34 and/or P-glycoprotein (MDR1 gene product) ➢ internal tandem duplication mutations of the FLT3 gene ➢ history of CNS involvement ➢ treatment-induced AML ➢ history of myelodysplastic syndrome
Amyloidosis (systemic light-chain)	**Autologous HSCT is considered medically necessary for the treatment of amyloidosis (systemic light-chain) when ALL of the following criteria are met:** • Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (i.e., at a minimum, ambulatory and able to perform most, if not all, self-care) • asymptomatic or compensated cardiac function (i.e., absence of congestive heart failure, echocardiographic left ventricular ejection fraction > 30%, interventricular septal thickness < 15 mm) • adequate pulmonary status as noted on pulmonary function testing, oxygen saturation results on room air and a DLCO > 50% predicted • adequate liver function (i.e., bilirubin < 3.0 mg/dL) • adequate renal function (i.e., creatinine clearance > 51 ml/min, serum creatinine ≤ 2.0 ml/dL) • 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.**
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.**

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
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 for EITHER of the following indications:** • after response to primary therapy • refractory to primary therapy in an individual with relapse or progressive disease **A second or tandem autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary following autologous HSCT.** **A third autologous HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary in an individual with progressive disease following a previous autologous HSCT.** **Allogeneic HSCT for the treatment of active (i.e., symptomatic) MM is considered medically necessary in an individual with progressive disease following autologous HSCT.**
Myelodysplastic Syndromes	**Allogeneic HSCT is considered medically necessary for the treatment of an individual with intermediate- or high-risk myelodysplastic syndrome (MDS).** **Autologous HSCT is considered medically necessary for the treatment of intermediate- or high-risk MDS when ALL of the following criteria are met:** • individual is in complete remission • individual is not a candidate for allogeneic HSCT • an appropriately-matched HLA donor is not available
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).**

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria All allogeneic transplantations must be from an appropriately-matched human leukocyte antigen (HLA) donor.
	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. **Myeloablative 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 • non-myeloablative allogeneic HSCT in a child • tandem autologous OR allogeneic HSCT in an adult or a child (For primary CNS lymphoma, see CP 0534 Stem Cell Transplantation: Solid Tumors)
POEMS Syndrome	**Autologous HSCT is considered medically necessary for the treatment of POEMS syndrome.**
Primary Central Nervous System (CNS) Lymphoma	Refer to CP 0534 Stem Cell Transplantation: Solid Tumors.
Systemic Mastocytosis	**Allogeneic hematopoietic stem-cell transplantation (HSCT) is considered medically necessary for the treatment of advanced / aggressive systemic mastocytosis.**

General Background

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

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

- Autologous transplant — In autologous transplantation, an individual's own hematopoietic stem cells are removed before the high dose chemotherapy or radiation is given, and they are then frozen for storage and later use. After chemotherapy or radiation is complete, the harvested cells are thawed and returned to the individual, like a transfusion.
- Allogeneic transplant — In allogeneic transplantation, the hematopoietic stem cells come from a donor, ideally a brother or sister with a similar genetic makeup. If an individual does not have a suitably matched sibling, an unrelated person with a similar genetic makeup may be used. Under some circumstances, a parent or child who is only half-matched can also be used; this is termed a haploidentical transplant. In other circumstances, umbilical cord blood may be used in an umbilical cord blood transplant.

- Myeloablative transplant — A myeloablative transplantation uses very high doses of chemotherapy or radiation prior to transplantation with autologous or allogeneic hematopoietic stem cells.
- Non-myeloablative transplant — A non-myeloablative transplantation, sometimes referred to as reduced intensity transplant, allows an individual to have less intensive chemotherapy before transplantation with allogeneic hematopoietic stem cells. The idea is to minimize up front toxicity by using lower doses of intensive therapy, while retaining the immune graft versus tumor effect. This approach may be recommended for a variety of reasons including age, type of disease, other medical issues, or prior therapies.

Racial disparities
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 (Majhail, et al., 2012).

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) - 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.

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>
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CR1, standard risk</td><td>N</td><td>N</td></tr>
<tr><td>Acute lymphoblastic leukemia
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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</td><td>C *</td><td>N</td></tr>
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*Used in clinical practice but associated with high failure rates; hence, recommend clinical trial enrollment and nontransplant strategies when available.		

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

NCCN GUIDELINES™ Acute Lymphoblastic Leukemia (v.1.2021, April 6, 2021)

Ph+ ALL Consolidation Therapy (AYA/Adult) (algorithms)
Allogeneic hematopoietic cell transplantation (HCT) is noted as an option. Footnotes include:
It is reasonable to approach the initial treatment of blast phase CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT.
Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate minimal/measurable residual disease (MRD) prior to transplantation. Proceeding to allogeneic HCT with MRD is not optimal.
Data suggests that for younger patients age ≤21 years, particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + tyrosine kinase inhibitor (TKI).
Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities and social support.
Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. (ALL-3, ALL-3A)

Ph- ALL Consolidation Therapy (AYA) (algorithms)
Allogeneic hematopoietic cell transplantation (HCT) is noted as an option including MRD+, MRD-, and MRD unavailable. For MRD- and MRD unavailable, consider allogeneic HCT, especially if high-risk features.
Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplant. Proceeding to allogeneic HCT with MRD is not optimal.
Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities, and social support.
Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. (ALL-4, ALL-4A)

Ph- ALL Consolidation Therapy (Adult) (algorithms)
Allogeneic hematopoietic cell transplantation (HCT) is noted as an option including MRD+, MRD-, and MRD unavailable. For MRD- and MRD unavailable, consider allogeneic HCT, especially if high-risk features.

Cancer	
	Footnotes include: Optimal timing of HCT is not clear. For fit patients, additional therapy is recommended to eliminate MRD prior to transplantation. Proceeding to allogeneic HCT with MRD is not optimal. Many variables determine eligibility for allogeneic HCT including donor availability, depth of remission, comorbidities and social support. Although long term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. (ALL-5). <u>Relapsed/refractory Disease (algorithms)</u> Consider HCT. If second remission is achieved prior to transplant and patient has not had a prior HCT, consolidative HCT is recommended. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or donor lymphocyte infusion The role of allogeneic HCT following tisagenlecleucel is unclear. (ALL-7,ALL-7A) <u>Overview of Treatment Phases in ALL Management</u> Allogeneic HCT is more likely to be a primary part of post-consolidative therapy in AYA and adult patients with evidence of high-risk features (including Ph-positivity, Ph-like disease, or persistent MRD). Notably, while younger patients may experience lower transplant-related mortality, older age is by itself not a contraindication. (MS-13) <u>Initial treatment in AYA patients with Ph-Positive ALL</u> Allogeneic HCT has been considered the standard of care for AYA patients with Ph-Positive ALL; however, its role has become less clear with the advent of *BCR-ABL*-targeted TKIs. (MS-15) <u>Initial treatment in Adults with Ph-Positive ALL</u> The incorporation of imatinib in the HCT treatment regime has led to improvements in outcomes over chemotherapy alone. (MS-18) <u>Treatment of relapsed Ph-Positive ALL</u> Evidence from prospective studies is needed to establish the role of donor lymphocyte infusion (DLI), with or without TKIs, in the treatment of relapsed disease. (MS-22) <u>Initial Treatment in AYA Patients with Ph-Negative ALL</u> For AYA patients with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases—particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics (eg, hypodiploidy, *MLL* rearrangement) at diagnosis. (MS-28) Matched sibling HCT has been established as a valuable treatment strategy for patients with high-risk Ph-negative ALL, but more recently studies have examined the role of URD transplants. (MS-29) Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses. (MS-30) <u>Initial Treatment in Adults with Ph-Negative ALL</u> Studies evaluating HCT in first CR for AYA patients with Ph-negative ALL have generally been inclusive of adult patients. More aggressive therapies are being considered for older or less fit patients. (MS-34)

Cancer	
	Treatment of Relapsed Ph-Negative ALL HCT is the only potentially curative modality for R/R ALL (MS-38). AYA Patients with Ph-Negative ALL For patients experiencing a CR following initial induction therapy, monitoring for MRD should be initiated • If the resulting MRD status is negative, continuation of the multiagent chemotherapy protocol for consolidation and maintenance would be appropriate. Consolidation with allogeneic HCT may also be considered, especially if the patient has high-risk features • If the MRD status is positive, blinatumomab (for B-ALL) is recommended or allogeneic HCT may be considered. Although long-term remission after blinatumomab treatment is possible, allogeneic HCT should be considered as consolidative therapy. • If the MRD status is unknown, allogeneic HCT is recommended, especially if the patient has high-risk features. In all cases, the optimal timing of HCT is unclear. (MS-43) Adult Patients with Ph-Negative ALL For relatively fit patients (aged <65 years without substantial comorbidities), the recommended treatment approach is similar to that for AYA patients. (MS-44) Patients with Relapsed/Refractory Ph-Negative ALL If transplant-naïve patients experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucel is unclear. (MS-45) Management of Lymphoblastic Lymphoma Patients with lymphoblastic lymphoma generally benefit from treatment with ALL-like regimens. (MS-43) MRD Assessment Collectively, studies show the high prognostic value of MRD in assessing risk for relapse in patients with ALL, and the role of MRD monitoring in identifying subgroups of patients who may benefit from further intensified therapies or alternative treatment strategies. In general, MRD positivity at the end of induction predicts high relapse rates and should prompt an evaluation for allogeneic HCT. When possible, therapy aimed at eliminating MRD prior to allogeneic HCT is preferred. (MS-54) **NCCN GUIDELINES™ Pediatric Acute Lymphoblastic Leukemia (v.2.2021, October 22, 2020)** NCCN Principles of Hematopoietic stem cell transplant are listed on pages PEDALL-J, and provide detailed indications for: • HSCT (B-cell) in First Remission • HSCT (B-cell) in Non-First Remission Settings • HSCT (T-cell) **NCCN GUIDELINES™ Adolescent and Young Adult (AYA) Oncology (V.1.2021, September 10, 2020)** Hematopoietic Stem Cell Transplant

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>HSCT is a potentially curative treatment option for an increasing number of AYA patients with leukemias and lymphomas. Graft-versus-host disease (GVHD), chronic immunosuppression, and gonadal dysfunction in males and females related to high-dose conditioning chemotherapy and RT are the major post-transplant complications associated with HSCT.
Chronic GVHD has been identified as the leading cause of non-relapse mortality in HSCT survivors. AYA patients are at a higher risk of developing chronic GVHD than younger children.
HSCT survivors are also at increased risk for late complications.
Allogeneic HSCT survivors irradiated at 30 years or younger are at higher risk of developing secondary solid cancers.
Findings highlight the increasingly recognized need for long-term follow-up care that incorporates screening and surveillance of AYA survivors of HSCT. (MS-8, MS-9)</td></tr>
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<tr><td>Acute promyelocytic leukemia
Relapse</td><td>R</td><td>R</td></tr>
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<tr><td>Acute myeloid leukemia
Therapy-related, CR1</td><td>S</td><td>N</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Acute promyelocytic leukemia
CR1</td><td>N</td><td>N</td></tr>
<tr><td>Acute promyelocytic leukemia
CR2, molecular remission</td><td>C</td><td>S</td></tr>
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Cancer	

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

NCCN GUIDELINES™ Acute Myeloid Leukemia (v.3.2021, March 2, 2021)

Acute Promyelocytic Leukemia (Age ≥18 years) Therapy for Relapse/Additional Therapy (algorithm)

- PCR negative: autologous HCT
- PCR positive: matched sibling or alternate donor HCT. (APL-6)

AML (Age ≥18 years) (algorithm)
After specific chemotherapy regimens, inductions failure, option is matched sibling or alternate donor HCT. (AML-2, AML-3)
Post-remission therapy, HCT (AML – 4)

AML (Age ≥18 years) (algorithm)
Physiologic Age ≥60
After induction, with residual disease, consider allogeneic HCT
(AML-7)
Allogeneic transplant is a reasonable option in patients who experience failure after re-induction with certain regimens (eg, intermediate- or high-dose cytarabine), and have identified donors available to start conditioning within 4–6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. HCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with <10% blasts). It is preferred that this approach be given in the context of a clinical trial.
Post-remission therapy, allogeneic HCT (AML-8)
Post-induction therapy, allogeneic HCT (AML-9)

AML (Age ≥18 years) Surveillance and relapse/refractory disease (algorithm)
matched sibling or alternate donor HCT
If a second complete response is achieved, then consolidation with allogeneic HCT should be considered. (AML-10)

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN) (Age ≥18 years) (algorithm)
Following complete remission, consider Allogeneic HSCT, Autologous HSCT
(BPDCN-2)

General Principles of BPDCN
Studies suggest that being in first remission (CR1) during receipt of allogeneic HCT significantly enhances the median OS. Reduced intensity conditioning may be considered in patients who achieve CR but cannot tolerate myeloablative transplantation. (BPDCN-A)

Cancer	
	Management of AML in Patients Younger Than 60 Years NCCN Recommendations Patients with antecedent hematologic disease or treatment-related AML are considered poor-risk, unless they have favorable cytogenetics. HLA testing should be performed promptly in those who may be candidates for either fully ablative or reduced-intensity conditioning (RIC) allogeneic HCT from a matched sibling or an alternative donor, which constitutes the best option for long-term disease control (MS-34) Intermediate-Risk Cytogenetics and/or Molecular Abnormalities Including MRD Positive NCCN Recommendations The panel members agree that transplant-based options (either matched sibling or alternate donor allogeneic HCT) or 3 to 4 cycles of HiDAC affords a lower risk of relapse and a somewhat higher DFS when given as consolidation for patients with intermediate-risk cytogenetics. The role of autologous HCT in the intermediate-risk group outside of clinical trials is diminishing due to improvements in allogeneic transplants, which are expanding the pool of potential donors outside the family setting. While autologous HCT is still incorporated into the clinical trial design in Europe, the consensus of the NCCN AML Panel was that autologous HCT should not be a recommended consolidation therapy outside the setting of a clinical trial. (MS-40) Treatment-Related Disease Other than CBF and/or Unfavorable Cytogenetics and/or Molecular Abnormalities NCCN Recommendations If remission is observed, consolidation therapy is recommended, and strong consideration should be given to allogeneic HCT with matched sibling or alternative donor (including umbilical cord blood products) as part of consolidation strategy.(MS-41) Management of AML in Patients Older than 60 years The role of myeloablative allogeneic HCT is limited in older patients because of significant comorbidities; however, ongoing interest has been shown in reduced-intensity conditioning (RIC) allogeneic HCT as consolidation therapy (MS-51) Studies suggest that (RIC) allogeneic HCT is a feasible treatment option for patients aged 60 years and older, particularly those in first CR with minimal comorbidities and who have an available donor. RIC allogeneic HCT is considered an additional option for patients age 60 years and older as post remission therapy in those experiencing a complete response (CR) to induction therapy. (MS-52) Relapsed/Refractory AML NCCN Recommendations The NCCN AML Panel recommends enrollment in a clinical trial for the management of R/R AML as a strongly preferred option. Other options include targeted therapy or chemotherapy followed by allogeneic HCT. (MS-59) If a second CR is achieved, consolidation with allogeneic HCT should be considered. (MS-60). Management of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPCDN)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>Due to the rarity of BPDCN, there have been limited established standardized therapeutic approaches.422 Hematopoietic cell transplantation (HCT) seems to generate durable remissions, especially if given in first CR. (MS-64)

<u>BPCDN NCCN Recommendations</u>
If CNS disease is documented at diagnosis or if clinically indicated, IT chemotherapy should also be given. With all treatment options, if CR is observed, allogeneic HCT or autologous HCT should be considered.(MS-65)</td></tr>
<tr><td>Amyloidosis</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

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

<u>NCCN GUIDELINES™ Systemic Light chain Amyloidosis (v.2.2021, February 8, 2021)</u>
The NCCN panel members recommend that treatment of systemic light chain amyloidosis 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. Based on the evidence discussed above, the current NCCN Guidelines list the following as therapeutic considerations for management of patients with systemic light chain amyloidosis (all category 2A recommendation) along with best supportive care: high-dose melphalan followed by autologous SCT; and other medications. (MS -7)</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></td><td></td><td></td></tr>
<tr><td>Hairy cell leukemia
First remission</td><td>N</td><td>N</td></tr>
<tr><td>Hairy cell leukemia
Second remission</td><td>N</td><td>N</td></tr>
<tr><td>Hairy cell leukemia
≥ third remission or refractory disease</td><td>R</td><td>N</td></tr>
</table>

<u>NCCN GUIDELINES™ Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (V.4.2021, April 29, 2021)</u>

<u>CLL/SLL Relapsed/Refractory therapy (algorithms)</u></td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>CLL/SLL without and with deletion of 17P/TP53 mutation, consider allogeneic HCT if without significant comorbidities in patients with CLL refractory to small molecule inhibitor therapy. (CSLL-4, CSLL-5)
Richter’s transformation, Initial therapy, consider HCT. (HT-3)

<u>Allogeneic Hematopoietic Cell Transplant</u>
Allogeneic HCT can be considered for CLL/SLL refractory to small-molecule inhibitor therapy in patients without significant comorbidities. HCT-specific comorbidity index (HCT-CI) could be used for the assessment of comorbidities prior to HCT and to predict the risks of non-relapse mortality and the probabilities of survival after HCT. For patients with CLL/SLL with del(17p) or TP53 mutation, a discussion of allogeneic HCT could be considered for patients in remission with or after ibrutinib therapy, if CK (≥3 abnormalities) is present. (MS-22)

<u>Richter’s transformation to DLBCL</u>
Allogeneic HCT can be considered for patients with disease responding to initial chemoimmunotherapy. (MS-24)
Autologous HCT may also be appropriate for patients with disease responding to initial therapy but who are not candidates for allogeneic HCT due to age, comorbidities, or lack of a suitable donor. (MS-24)

Pure red cell aplasia (PRCA): In very refractory cases, allogeneic may be necessary.(MS-27)

<u>NCCN GUIDELINES™ Hairy Cell Leukemia (V2.2021, March 11, 2021)</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>
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<table>
<tr><th>Children (<18 years)</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Accelerated phase</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Blast phase</td><td>C</td><td>N</td></tr>
</table>

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 1, TKI intolerant</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 1, TKI refractory</td><td>C</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Chronic phase 2+</td><td>S</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Accelerated phase</td><td>S</td><td>N</td></tr>
<tr><td>Chronic myeloid leukemia
Blast phase</td><td>S</td><td>N</td></tr>
</table>

<u>NCCN GUIDELINES™ Chronic Myeloid Leukemia (V.3.2021, January 13, 2021)</u></td></tr>
</table>

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>Chronic Myeloid Leukemia (algorithm)
Accelerated phase and blast phase CML, allogeneic HCT. (CML-4)
Indications for allogeneic HCT: Advanced phase CML at presentation or disease progression to blast phase.(CML-6)

Advanced Phase CML
Flow cytometry to determine cell lineage, mutational analysis, and human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT), are recommended for patients with advanced phase CML.
(MS-6)

Chronic Phase (CP) CML
Management of CP-CML, allogeneic HCT is no longer recommended as a first-line treatment option for patients with CP-CML.(MS-6)

Response Milestones After First-Line TKI Therapy (CML-3)
Patients with >10% BCR-ABL1 at 3 months or >1% BCR-ABL1 at 12 months can continue the same dose of dasatinib or nilotinib or bosutinib for another 3 months.
BCR-ABL1 mutational analysis and evaluation for allogeneic HCT should be considered.
Patients with >10% BCR-ABL1 IS at 6 and 12 months are considered to have TKI-resistant disease.
Evaluation for allogeneic HCT (that is, a discussion with a transplant specialist, which might include HLA testing) is recommended. (MS-12)

Second-line Therapy
Patients who do not achieve cytogenetic or molecular responses at 3, 6, or 12 months after second-line and subsequent TKI therapy should be considered for alternative therapies or allogeneic HCT if deemed eligible. (MS- 12)

Management of Advanced Phase CML
Treatment considerations - participation in clinical trials and evaluation for allogeneic HCT is recommended for all patients with AP-CML and BP-CML. (MS-19)

Allogeneic Hematopoietic Cell Transplant
Allogeneic HCT is an appropriate treatment option for the very rare patient 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. (MS-19)</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>
</table>
</td></tr>
</table>

Cancer	

Hodgkin lymphoma First relapse, sensitive	N	S
Hodgkin lymphoma First relapse, resistant	C	N
Hodgkin lymphoma Second or greater relapse	C	C

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

NCCN GUIDELINES™ Hodgkin Lymphoma (V.4.2021, April 20, 2021)

Classic Hodgkin lymphoma (CHL), refractory disease (algorithm)
Deauville 1-3, high dose therapy and autologous stem cell rescue HDT/ASCR (Category 1)
Deauville 4, HDT/ASCR,
Deauville 5, Autologous or allogeneic SCT if response to secondary therapy (HODG-11)

Classic Hodgkin lymphoma (CHL), suspected relapse (algorithm)
Second-line Systemic therapy followed by HDT/ASCR ± ISRTr
Footnote: Allotransplant is an option in select patients as a category 3 recommendation. (HODG-12)

Refractory CHL
Although further cytoreduction and HDT/ASCR (with RT if not previously given) are often appropriate, occasional clinical circumstances may warrant the use of RT or systemic therapy with or without RT. Conventional-dose second-line systemic therapy may precede HDT/ASCR. RT should be strongly considered for selected sites of relapse that have not been previously irradiated. In radiation-naïve patients, TLI may be an appropriate component of HDT/ASCR. (MS-24)

Second-line systemic therapy followed by response assessment with PET is recommended for all patients. Patients with a Deauville score of 1 to 3 should proceed to HDT/ASCR with or without RT (category 1 recommendation).
An option for patients with a Deauville score of 4 is to proceed with HDT/ASCR with or without RT.(MS-24)

Refractory or relapsed CHL
Compared with conventional chemotherapy alone, HDT/ASCR is the best

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>treatment option for patients with refractory or relapsed CHL that is not cured with primary treatment. Second-line therapy (second-line systemic therapy with or without RT) may be given prior to HDT/ASCR.
Maintenance therapy with brentuximab vedotin (for one year) following HDT/ASCR is included as an option for patients with primary refractory disease. (MS-26)

<u>NCCN GUIDELINES™ Pediatric Hodgkin Lymphoma (V.3.2021, March 18, 2021)</u>
<u>Suspected Relapsed/Refractory disease</u>
If metabolic CR (Deauville ≤3) proceed to high-dose therapy and autologous stem cell rescue (HDT/ ASCR) ± ISRT ± maintenance chemotherapy.
Recommendations for those who may avoid ASCR: initial stage other than IIIB or IVB, no prior exposure to RT, duration of CR1 >1 year, absence of extranodal disease or B symptoms at relapse.
Allotransplant is an option in select patients who relapse post-ASCT as a category 3 recommendation. (PHL-7)

<u>NCCN GUIDELINES™ Cancer in People with HIV (V.2.2021, April 26, 2021)</u>

<u>Management of Hodgkin Lymphoma in People with HIV (PWH)</u>
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 (PWH with acute leukemia, myelodysplasia, or lymphoma) (MS-15, MS-16)</td></tr>
<tr><td>Juvenile Myelomonocytic Leukemia (JMML)</td><td>See Myelodysplastic Syndromes</td></tr>
<tr><td>Multiple Myeloma (MM)</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myeloma, initial response</td><td>D</td><td>S</td></tr>
<tr><td>Myeloma, sensitive relapse</td><td>S</td><td>S</td></tr>
<tr><td>Myeloma, refractory</td><td>C</td><td>C</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Plasma cell disorders,
Relapse after autologous transplant</td><td>C</td><td>C</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>Plasma cell leukemia</td><td>S</td><td>C</td></tr>
</table>
<u>NCCN GUIDELINES™ Multiple Myeloma (V.7.2021, April 26, 2021)</u>

<u>Symptomatic, after primary therapy (algorithm)</u>
Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high dose therapy and hematopoietic cell transplant. (MYEL-4)

<u>Symptomatic, Response After primary therapy (algorithm)</u>
Autologous hematopoietic cell transplant (category 1). Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and hematopoietic cell transplant.

Allogeneic hematopoietic cell transplant, under certain circumstances.</td></tr>
</table>

Cancer	
	Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible. (MYEL-5) <u>Post-autologous stem cell transplant (single or tandem), progressive disease</u> Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible. Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression. Retrospective studies suggest a 2- to 3-year minimum length of remission for consideration of a second autologous hematopoietic cell transplant. (MYEL-6, MYEL-7) 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. (MS-20) Autologous HCT Autologous HCT results in high response rates and remains the standard of care after primary therapy for eligible patients. According to the NCCN Guidelines, for transplant-eligible patients autologous HCT is the preferred option after primary induction therapy while a delayed HCT after early stem cell collection and storage is appropriate as well. (category 1) A repeat HCT can be considered for treatment of progressive/refractory disease after primary treatment in patients with prolonged response to initial HCT. (MS-20,MS-22) 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. 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. A second autologous HCT can be considered at the time of disease relapse. (MS-22,23) 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. The prognosis of patients who relapse after autologous HCT appears to differ depending on the timing of the relapse (MS-24) <u>Autologous Stem Cell Transplants</u> According to the NCCN Guidelines, for transplant-eligible patients autologous SCT is an option after primary induction therapy (category 1) and for treatment of progressive/refractory disease after primary treatment. (MS-23) <u>Tandem Stem Cell Transplants</u> Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first course. The NCCN Multiple Myeloma Panel recommends collecting enough stem cells for 2 transplants in all eligible patients. According to the NCCN Multiple Myeloma Panel, a tandem transplant with or without maintenance therapy can be considered for all

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT.
A second autologous SCT can be considered at the time of disease relapse. According to the NCCN Multiple Myeloma Panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding SCT and documented progression. (MS-23, MS-24)

<u>Allogeneic Hematopoietic Cell Transplantation</u>
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. (MS-24)

<u>Therapy for previously treated Multiple Myeloma</u>
Therapy for previously treated relapsed/refractory MM is considered in the following clinical situations: patients with relapsed disease after allogeneic or autologous HCT; patients with primary PD after initial autologous or allogeneic HCT; and patients ineligible for HCT with progressive or relapsing disease after initial primary therapy. (MS-27, MS-28)</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 Therapy related</td><td>S</td><td>N</td></tr>
</table>
<table>
<tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr>
<tr><td>Myelodysplastic syndromes Low/intermediate – 1 risk</td><td>C</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes Intermediate-2/high risk</td><td>S</td><td>N</td></tr>
<tr><td>Myelodysplastic syndromes Therapy-related, CR1</td><td>S</td><td>N</td></tr>
</table>
<u>NCCN GUIDELINES™ Myelodysplastic Syndromes (V.3.2021, January 15, 2021)</u>

<u>Prognostic category (algorithm)</u>
IPSS-R: very low, low, Intermediate
IPSS: Low/Intermediate-1
WPSS: Very low, Low, Intermediate
Clinical trial or consider allogeneic HCT for selected patients (MDS-3, MDS-4)</td></tr>
</table>

Cancer	
	IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. (Matched sibling, unrelated donor, or alternative [haploidentical or cord blood when appropriate] donor, including standard and reduced-intensity preparative approaches, may be considered).(MDS-5A) Prognostic category (algorithm) IPSS-R: Intermediate, High, Very high IPSS: Intermediate-2, High WPSS: High, Very high If transplant candidate. Allogeneic HCT from most suitable donor following standard or reduced-intensity conditioning regimens. Consider allogeneic HCT or donor lymphocyte infusion if relapse after allogeneic HCT or no response. Consider second transplant or donor lymphocyte infusion immune-based therapy for appropriate patients who had a prolonged remission after first transplant. (MDS-6) Myelodysplastic syndromes (MDS) The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). (MS-2) Myelodysplastic/Myeloproliferative Neoplasms The category of myelodysplastic/myeloproliferative neoplasms (MDS/MPN) includes chronic myelomonocytic leukemia (CMML); atypical chronic myeloid leukemia (aCML), BCR-ABL1 negative; and juvenile myelomonocytic leukemia (JMML) as disorders having overlapping dysplastic and proliferative features. CMML has been subdivided into two groups based on molecular and clinical differences: proliferative-type CMML (WBC count ≥13 x 109/L) and dysplastic type CMML (WBC < 13 x 109/L). (MS-5) Patients with CMML may also have systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) and KIT816V mutation responsive to midostaurin. In patients with blastic plasmacytoid dendritic cell neoplasm skin lesions, about 10-20% of cases are associated or develop into other myeloid neoplasms, including CMML, MDS, or AML. Although the data on HCT procedures are limited, allogeneic HCT is the only treatment modality that can induce long-term remissions in aCML. (MS-6) JMML is a rare childhood cancer that presents in infants and young children. Allogeneic HCT is the main treatment option for JMML. (MS-6) Pediatric MDS HCT is the only curative option in childhood MDS with 3- year disease-free survival rates of approximately 50%. Myeloablative therapy followed by either matched family or matched unrelated donor allogeneic HCT is the treatment of choice for children with MDS. (MS-9) High-Intensity Therapy High-intensity therapy includes intensive induction chemotherapy or HCT. Although these approaches have the potential to change the natural history of the disease, there is an attendant greater risk of regimen-related morbidity and mortality. The panel recommends that such treatments be given in the context of clinical trials. Allogeneic HCT from an HLA-matched sibling, matched unrelated, or alternative (including haploidentical or cord blood when appropriate) donor is a preferred

Cancer	
	approach for treating select patients with MDS, particularly those with high-risk disease. Allogeneic HCT may also be considered in select lower-risk MDS patients (IPSS int-1, IPSS-R, and WPSS intermediate) with severe cytopenias. Whether transplants should be performed before or after patients achieve remission following induction chemotherapy has not been prospectively established. Comparative clinical trials are needed to address these issues. (MS-32) Therapy for Lower-Risk Patients (IPSS Low, Intermediate-1; IPSS-R Very Low, Low, Intermediate; or WPSS Very Low, Low, Intermediate) Non-responders to certain treatments could be considered for a clinical trial or for allogeneic HCT. (MS-35) Therapy for high-risk patients (IPSS Intermediate-2, High; IPSS-R Intermediate, High, Very High; or WPSS High, Very High) For patients who are transplant candidates, an HLA-matched sibling or HLA-matched unrelated donor can be considered. Results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is generally the strategy in older individuals. (MS-35) There are limited data regarding the use of allogeneic HCT in older adults with MDS; however, studies suggest that age alone should not be an exclusionary factor for eligibility. (MS-36) **NCCN GUIDELINES™ Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes (Version 3.2021, August 21, 2020) (not updated)** Clonal eosinophilia associated with tyrosine kinase (TK) fusion gene rearrangements (PDGFRA, PDGFRB, FGFR1, JAK2, ABL1, or FLT3) can have diverse clinical presentations including Ph-negative myeloproliferative neoplasms (MPN) with eosinophilia, myelodysplastic syndromes (MDS)/MPN with eosinophilia, acute myeloid leukemia (AML), B cell or T cell lymphomas, acute lymphoblastic leukemia (ALL), or mixed lineage leukemias/lymphomas. (MLNE/INTRO-1) 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-11) Myeloid/Lymphoid Neoplasms with Eosinophilia and *FGFR1 or JAK2 or FLT3* or *ABL1* 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-12)
Myelofibrosis	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. Myelofibrosis may occur as a secondary characteristic of polycythemia vera or essential thrombocytyemia. Most therapeutic interventions are directed toward

Cancer	
	symptom palliation and supportive measures. Current medical therapeutic options for patients with primary myelofibrosis, myelofibrosis after polycythemia, or essential thrombocytopenia have not demonstrated an impact on disease course. Some individuals with primary myelofibrosis have been treated with allogeneic or autologous stem cell transplantation. The National Comprehensive Cancer Network (NCCN®) Clinical Practice Guideline on Myeloproliferative Neoplasms, NCCN (v.2.2021, Aug 18, 2021) addresses myelofibrosis: <u>Treatment for Lower-Risk Myelofibrosis</u> Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics. Identification of “higher-risk” mutations may be helpful in the decision-making regarding allogeneic HCT for patients with Primary Myelofibrosis (PMF). (MF-1) <u>Treatment for Higher-Risk Myelofibrosis</u> Evaluation for allogeneic HCT is recommended for all patients. Identification of “higher-risk” mutations may be helpful in the decision-making regarding allogeneic HCT for patients with PMF. The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Early referral to transplant is recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. (MF-2) <u>Disease Progression to Advanced-Phase AML</u> The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Early referral to transplant is recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. (MF-4) <u>Treatment Options - Allogeneic Hematopoietic Cell Transplant</u> Allogeneic HCT is the only potentially curative treatment option resulting in long-term remissions for patients with MF. However, the use of myeloablative conditioning is associated with higher rates of non-relapse mortality (NRM). (MS-16) <u>Treatment Recommendations Based on Symptom Assessment and Risk Stratification</u> Although the outcomes following allogeneic HCT are better for patient with lower-risk MF, due to the high transplantation-related morbidity and mortality, treatment decisions regarding allogeneic HCT should be individualized. Allogeneic HCT should be considered for lower-risk MF in patient with either refractory, transfusion-dependent anemia; circulating blast cells greater than 2% in peripheral blood; or adverse cytogenetics. Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics.(MS-18) Evaluation for allogeneic HCT is recommended for all patients with higher-risk MF. The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. (MS-19) Allogeneic HCT is recommended for patients with higher-risk MF if they are candidates for transplant. Early referral to transplant is recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts to an acceptable

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>level prior to allogeneic HCT. The results of recent studies suggest that prior exposure to ruxolitinib may improve outcomes after allogeneic HCT. (MS-19)

<u>Disease Progression to Advanced Phase or Transformation to Acute Myeloid Leukemia</u>
Allogeneic HCT remains the only curative option resulting in long-term disease control in selected transplant-eligible patients who achieve a CR to induction chemotherapy. (MS-25)

<u>Treatment Recommendations Based on Eligibility for Transplant</u>
The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. Patients may be taken to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant. (MS-25)</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></td><td></td><td></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></td><td></td><td></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>
</table>
</td></tr>
</table>

Cancer			
	Lymphoblastic B-cell non-Hodgkin lymphoma (non-Burkitt), Not in remission	C	N
	T cell non-Hodgkin lymphoma CR1, standard risk	N	R
	T cell non-Hodgkin lymphoma CR1, high risk	R	R
	T cell non-Hodgkin lymphoma CR2	S	C
	T cell non-Hodgkin lymphoma CR3+	C	C
	T cell non-Hodgkin lymphoma Not in remission	C	N

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

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

Cancer			
	Lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia Relapse after autologous transplant	C	N
	Mantle cell lymphoma CR 1/first partial remission	C	S
	Mantle cell lymphoma Primary refractory, sensitive	S	S
	Mantle cell lymphoma Primary refractory, resistant	C	N
	Mantle cell lymphoma First relapse, sensitive	S	S
	Mantle cell lymphoma First relapse, resistant	C	N
	Mantle cell lymphoma 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

NCCN GUIDELINES™ B-cell Lymphoma (V.4.2021, May 5, 2021)

Follicular lymphoma (grade 1-2)
Histologic transformation to diffuse large B-cell lymphoma: (DLBCL) high-dose therapy with autologous stem cell rescue (HDT/ASCR) or allogeneic HCT in selected cases is a treatment option (FOLL-7, FOLL-8)
Data on transplant after treatment with anti-CD19 CAR T-cell therapy are not available. HDT/ASCR is not recommended after anti-CD19 CAR T-cell therapy. Allogeneic HCT could be considered but remains investigational. (FOLL-8)

Nodal Marginal Zone lymphoma
Histologic transformation to diffuse large B-cell lymphoma:
HDT/ASCR or allogeneic HCT is a treatment option (NODE-5, NODE-6)
Data on transplant after treatment with anti CD-19 CAR T-cell therapy are not available. HDT/ ASCR is not recommended after anti CD-19 CAR T-cell therapy. Allogeneic HCT could be considered but remains investigational. (NODE-6)

Mantle cell lymphoma
HDT/ASCR may be appropriate (MANT-3, MANT-4)

Cancer	
	Patients who have achieved near CR can proceed to HDT/ASCR. Patients who have achieved minimal PR with substantial disease should be treated as having stable, refractory disease. Patients who have achieved a very good PR may be treated with additional therapy to achieve CR with the goal of proceeding to HDT/ASCR. (MANT-3) Diffuse Large B-Cell Lymphoma Patients achieving high-quality CR/PR following alternative second-line therapy may benefit from an allogeneic HCT. (BCEL-8) Burkitt lymphoma, Consolidation/Additional therapy HDT/ASCR or allogeneic HCT is a treatment option (BURK-3) Follicular lymphoma High-dose therapy with autologous stem cell rescue (HDT/ASCR) is an appropriate consolidative therapy for patients with second or third remission. HDT/ASCR as consolidation therapy has been shown to shown to prolong overall survival and progression-free survival in patients with relapsed or refractory disease. Allogeneic hematopoietic cell transplant (HCT) results in lower relapse rates than HDT/ASCR, but it is associated with high transplant-related mortality (TRM) rate. Allogeneic HCT may also be considered for highly selected patients. (MS-38). Histologically Transformed Follicular Lymphoma HDT/ASCR as consolidation therapy has been evaluated only in retrospective studies with some series reporting survival benefit for patients who did proceed to transplant.Allogeneic HCT has been shown to benefit selected patients with disease relapse following HDT/ASCR, but is also associated with significant TRM. However, it should be noted that the efficacy of HDT/ASCR or allogeneic HCT in patients with TFL has not been confirmed in prospective controlled studies. (MS-39) HDT/ASCR is not recommended after CAR T-cell therapy. Allogeneic HCT could be considered but remains investigational.(MS-40) Nodal Marginal Zone lymphoma High-dose therapy followed by autologous stem cell rescue (HDT/ASCR) has been associated with survival benefit in patients with relapsed or refractory disease.HDT/ASCR is included as an option for consolidative therapy for patients with disease responding to second-line therapy. Allogeneic hematopoietic cell transplant (HCT) may also be considered for highly selected patients.(MS-62) Histologically Transformed Marginal Zone Lymphoma HDT/ASCR and allogeneic HCT may be reasonable treatment options for selected patients with histologically transformed MZL. (MS-67) Mantle cell lymphoma The majority of patients have advanced stage aggressive MCL, requiring systemic therapy. Induction therapy with aggressive regimens is recommended for patients who are candidates for HDT/ASCR, whereas induction therapy with less aggressive regimens is recommended for those who are not candidates for HDT/ASCR. (MS-79). HDT/ASCR as first-line consolidation after aggressive induction therapy has demonstrated promising outcomes in a number of studies (MS-81).

Cancer	
	The panel recommends consolidation with HDT/ASCR for eligible patients in complete remission following induction therapy with aggressive regimens, although nostudies have compared maintenance rituximab with HDT/ASCR for patients in first CR. Rituximab maintenance following HDT/ASCR is included with a category 1 recommendation. (MS-82) Diffuse large B-cell lymphoma (DLBCL) Overall, studies found no benefit to upfront HDT/ASCR as compared with first-line rituximab-based chemoimmunotherapy, except in high-risk IPI patients, but this remains controversial since this finding emerged only on a retrospective subset analysis involving a small number of patients. HDT/ASCR is therefore not routinely recommended. (MS-102). Relapsed or Refractory Disease Second-line combination chemotherapy is recommended for patients with an intention to proceed to transplant. Consolidation therapy with HDT/ASCR (category 1 for patients with CR) with or without RT is recommended for patients with CR or PR to second-line therapy, if they are candidates for transplant. ISRT before HDT/ASCR has been shown to result in good local disease control and improved outcome. Additional RT can be given to limited sites with prior positive disease before or after HDT/ASCR. Allogeneic HCT should be considered in selected patients with mobilization failures and persistent bone marrow involvement or lack of adequate response to second line therapy, though patients should be in CR or near CR at the time of transplant.(MS-107) Burkitt Lymphoma, relapsed or refractory disease: Consolidation with high-dose therapy and autologous stem cell rescue (HDT/ASCR) or allogeneic HCT (if donor available) may be considered for selected patients achieving a CR or PR to second-line therapy. Clinical trial or best supportive care including palliative ISRT are recommended for patients with disease not responding to second-line therapy or those with progressive disease. (MS-133) AIDS-Related B-Cell Lymphomas Consolidation with high-dose therapy followed by autologous stem cell rescue (HDT/ASCR) can be considered following CR after initial therapy for patients with high-risk features. (MS-142) HDT/ASCR is associated with favorable survival outcome in patients with chemosensitive relapsed/refractory disease, similar to the HIV-seronegative population. (MS-142) **NCCN GUIDELINES™ Pediatric Aggressive Mature B-Cell Lymphomas (V. 2.2021, June 7, 2021)** Consolidation/additional therapy Autologous hematopoetic stem cell transplant (HSCT) or allogeneic HSCT from best available donor are options after complete or partial remission. There are no data to support autologous versus allogeneic HSCT; therefore, the decision regarding transplant should be based on physician preference. (PBCL-10) **NCCN GUIDELINES™ Primary Cutaneous Lymphomas (V. 2.2021, March 4, 2021)** Mycosis Fungoides/Sézary Syndrome, inadequate response (algorithm)

Cancer	
	Consider allogeneic HCT. Allogeneic HCT is associated with better outcomes in patients with disease responding to primary treatment prior to transplant. (MFSS-9-MFSS-12) Role of Allogeneic Hematopoietic Cell Transplant in MFSS Allogeneic HCT has a role in a subset of patients with advanced-stage MF and SS who have received multiple lines of therapy as shown in retrospective studies and small prospective series of patients with advanced MF and SS. (MS-27) Allogeneic HCT may be considered for appropriate patients with stage IIB–IV disease that is refractory to multiple primary treatment options. Based on the limited evidence, patients with erythrodermic MF and SS appear to receive the most benefit from allogeneic HCT, despite high post-transplant relapse rate. 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-28) **NCCN GUIDELINES™ T-cell Lymphomas (V.1.2021, October 5, 2020)** Peripheral T-Cell Lymphomas (algorithm footnote) Consider consolidative HDT/ASCR for high-risk IPI patients in CR1.(TCEL-3) Peripheral T-Cell Lymphomas, Relapsed/refractory disease (algorithm) Consider allogeneic hematopoietic cell transplant (HCT) or Consider high-dose therapy with autologous stem cell rescue. Localized areas can be irradiated before or after high-dose therapy. Footnote: Many NCCN Member Institutions would recommend allogeneic HCT in this setting. (TCEL-5) Adult T-Cell Leukemia/Lymphoma (algorithm) Consider allogeneic HCT (ATLL-3) T-cell prolymphocytic leukemia, symptomatic disease (algorithm footnote) Consider allogeneic HCT. Consider HDT/ASCR if a suitable donor is not available. (TPLL-2) Extranodal NK/T-cell lymphoma, nasal type (algorithm) Complete response, Consider HCT. There are no clear data to suggest whether allogeneic or autologous HSCT is preferred and treatment should be individualized. Extranodal NK/T-cell lymphoma, nasal type, No response. HCT if eligible. Allogeneic preferred if donor available. Footnote: There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized. (NKTL-4) Aggressive NK-cell leukemia (ANKL) General Principles of Management and Treatment The Panel favors consolidation with allogeneic HCT over autologous HCT for patients in first remission.(NKTL-C) Hepatosplenic Gamma-Delta T-Cell Lymphoma (algorithm) If Complete or partial response, Allogeneic HCT (preferred). Patients should have very low tumor burden at the time of HCT. The goal of therapy is to induce complete or near complete response before proceeding to HCT. Full-course chemotherapy may not be needed to achieve adequate response to allow HCT.

Cancer	
	Footnote: Consider HDT/ASCR if unfit or lacking a suitable donor. (HSTCL-3) Peripheral T-Cell Lymphoma (PTCL) Treatment for Relapsed or Refractory Disease Role of Transplant Findings suggest that HDT/ASCR less frequently results in durable benefit in patients with relapsed or refractory disease as compared to allogeneic HCT. However, this conclusion is not universal in the literature and those with relapsed ALCL and more chemosensitive relapsed disease appear to benefit from HDT/ASCR more often than those with non-ALCL subtypes and less chemosensitive disease. Allogeneic HCT using RIC may provide a more reliably curative option for the majority of patients with relapsed or refractory PTCL, based on the patient's eligibility for transplant (MS-20) Adult T-Cell Leukemia/Lymphoma HCT has been shown to improve survival for some patients with ATLL, suggesting a contribution of graft-versus-leukemia/lymphoma (GVL) effect. (MS-50) Prospective studies in larger groups of patients are warranted to further evaluate the role of allogeneic HCT and validate the use of ATL-HCT-PI in the management of patients with ATLL. (MS-51) Response Assessment and Additional Therapy Continuation of the prior therapy is recommended for all patients who achieve an initial response to first-line systemic therapy (CR, uncertified PR, or PR at 2 months following start of treatment). Allogeneic HCT should be considered for patients with acute or lymphoma subtype, if donor is available. (MS-52) T-Cell Prolymphocytic Leukemia Data from retrospective studies suggest that allogeneic HCT may offer the best chance for long-term disease control in a subgroup of patients with T-PLL. (MS-61) In patients who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT. (MS-62) Extranodal NK/T-Cell Lymphoma, nasal type Patients with stage IV nasal disease or extranasal disease (stage I-IV) achieving a CR to induction therapy should be considered for HCT. There are no clear data to suggest whether allogeneic or autologous HCT is preferred and treatment should be individualized. Biopsy is recommended for patients with a PR after induction therapy and those with a negative biopsy should be considered for HCT. (MS-73) Clinical trial is the preferred treatment option for relapsed/refractory disease following treatment with pegaspargase-based regimens. Only limited data exist regarding the role of HCT in this patient population. Allogeneic HCT is preferred, if a donor available. (MS-73) **NCCN GUIDELINES™ Waldenstrom Macroglobulinemia/ Lymphoplasmacytic Lymphoma (V.1.2021, September 1, 2020)** Therapy for previously treated WM (algorithm)

<table>
<tr><th>Cancer</th><th></th></tr>
<tr><td></td><td>In selected patients, stem cell transplantation may be appropriate with either
• autologous stem cell transplant or
• allogeneic stem cell transplant (ablative or nonablative) (Should ideally be undertaken in the context of a clinical trial).(WM/LPL-B, 2 of 3)

Primary Treatment Regimens
Agents that limit future treatment options should be avoided in initial therapy. Exposure to continuous oral alkylator therapy ornucleoside analogs should be avoided prior to stem cell harvest if an autologous stem cell transplant (SCT) is being considered.
(MS-6)

<u>Therapy for previously treated WM</u>
For patients with remissions lasting less than 24 months or who show progressive disease/resistance to a first-line regimen, second-line treatment may include agents of a different class of drugs, either alone or in combination. In addition, it is important to avoid exposure to stem cell-damaging agents, such as an alkylator or nucleoside analogs, in patients who are candidates for autologous SCT. (MS-12)

<u>Management of Patients Who Are Intolerant to Rituximab</u>
SCT is an option for relapsed WM in selected patients. SCT options listed in the NCCN guideline are for high-dose therapy with autologous stem cell rescue. According to the NCCN panel, myeloablative or nonmyeloablative allogeneic SCT may be considered but in the context of a clinical trial. (M-14)</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 many patients may be offered high-dose chemotherapy with peripheral blood stem cell transplant.</td></tr>
<tr><td>Systemic Mastocytosis</td><td><u>American Society for Transplantation and Cellular Therapy (2020)</u>
(CR: complete response; N: Not generally recommended; C: standard of care, clinical evidence available; S: standard of care; R: standard of care, rare indication; D: developmental)

<table><tr><th>Adults</th><th>Allogeneic HCT</th><th>Autologous HCT</th></tr><tr><td>Systemic mastocytosis</td><td>R</td><td>N</td></tr></table>
<u>NCCN GUIDELINES™ Systemic Mastocytosis (V.2.2021, June 15, 2021)</u>

<u>Treatment for Systemic Mastocytosis with an associated hematologic neoplasm (SM-AHN) (algorithm)</u>
AHN-directed therapy (including consideration of allogeneic HCT with concurrent management of SM) (SM-6, SM-7)

<u>Treatment for Mast Cell Leukemia (MCL) (algorithm)</u></td></tr>
</table>

Cancer	
	AHN-directed therapy (including multiagent chemotherapy and/or consideration of allogeneic HCT with concurrent management of MCL) (SM-8) Allogeneic HCT Allogeneic HCT has been evaluated in patients with advanced SM and the outcomes are significantly affected by the subtype of SM and the type of conditioning regimen used. Reduced-intensity conditioning regimens were associated with lower survival than myeloablative conditioning regimens.(MS-16) Evaluation for allogeneic HCT should be considered for patients with ASM and MCL if there is adequate response to initial treatment with cytoreductive therapy. Among patients with SM-AHN, allogeneic HCT should be considered as part of initial treatment when the AHN component requires HCT. It should also be considered if the SM component presents as advanced SM (and there is adequate response to initial treatment with cytoreductive therapy) or progresses to advanced SM during treatment. Prophylactic anti-mediator drug therapy (corticosteroids, antihistamines, and epinephrine) should be used with the conditioning regimen in all patients. (MS-17)

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).

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: In several small case series, slow, but progressive improvement of neurological involvement and performance status was noted after autologous HSCT (Laurenti, 2008; Dispenzieri, 2008).

American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative
No relevant statements.

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

Medicare Coverage Determinations

	Contractor	Determination Name/Number	Revision Effective Date
NCD	National	STEM CELL Transplantation (Formerly 110.8.1)	1/27/16
LCD		No Local Coverage Determination found	

Note: Please review the current Medicare Policy for the most up-to-date information.

Coding/Billing Information

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

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

CPT®* Codes	**Description**
38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
38230	Bone marrow harvesting for transplantation; allogeneic

CPT®* Codes	Description
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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