

07.03.11 Hematopoietic Stem Cell Transplantation Autologous and Allogeneic*

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Related Policies:

- [Donor Lymphocyte Infusion \(DLI\) and Hematopoietic Progenitor Cell \(HPC\) Boost](#)
- [Colony-Stimulating Factors and Stem Cell Mobilizers](#)
 - *Colony-Stimulating Factors and Stem Cell Mobilizers given as part of the stem cell transplant regimen, refer to [Drug Authorizations](#) for any applicable Pharmacy Policies for prior approval requirements and applicable criteria.*

Summary

Description

Hematopoietic stem cell transplantation (HSCT) (also referred to as bone marrow transplantation; or peripheral blood stem cell transplantation) are used to restore stem cells destroyed by high-dose chemotherapy and/or radiation therapy. Transplantation is accomplished in the same manner as a blood

transfusion. HSCT has been utilized in the treatment of various non-cancer disorders: (e.g., autoimmune disease, genetic disorders (acquired anemias and other bone marrow failure syndromes [inherited]) and oncologic indications [e.g., solid tumors and blood cancers]).

Summary of Evidence

For those indications in which the type of transplant and the individual's condition meets the criteria outlined in [Policy](#) section below, either (1) the available evidence has shown that the transplant (autologous/allogeneic) improves overall survival (OS) and the evidence is sufficient to determine that the technology results in an improvement in the net health outcome OR (2) despite insufficient evidence from peer-review medical scientific studies, transplant use is supported by relevant professional societies as in accordance with generally accepted standards of medical practice in the United States.

For those indications in which the type of transplant and the individual's condition does not meet the criteria outlined in [Policy](#) section below, the available evidence is insufficient and does not demonstrate improved net health outcomes and would be considered investigational.

Additional Information

2020 Clinical Input

Clinical input was sought to help determine whether the use of either second autologous HCT for relapsed HL or tandem autologous HCT for HL would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 4 respondents, including 3 complete responses including 2 physician-level responses identified through specialty societies and 1 physician-level response identified through an academic medical center.

For individuals with relapsed HL after an autologous HCT who receive second autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals with HL who receive tandem autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

Further details from clinical input are included in the Appendix.

OBJECTIVE

The objective of this evidence review is to evaluate the safety and efficacy of allogeneic and autologous hematopoietic stem cell transplantation (HSCT) on the net health outcome of individuals with non-cancer disorders: autoimmune disease, genetic disorders (acquired anemias and other bone marrow failure syndromes [inherited]); or Oncologic indications: solid tumors and blood cancers.

PRIOR APPROVAL

Prior approval is required.

POLICY

Coverage for hematopoietic stem cell transplantation (HCST) is provided when both the type of transplant and the individual's condition meet the medical necessity criteria outlined below.

For those indications in which the type of transplant and the individual's condition does not meet the criteria outlined below the available evidence is insufficient and does not demonstrate improved net health outcomes and would be considered investigational as outlined below.

Hematopoietic Stem Cell Transplantation (HSCT): Non-Cancer Disorders

Autoimmune Diseases	
Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria
	Note: When considered medically necessary allogeneic transplantation must be from an appropriately HLA matched donor (related, unrelated matched, cord blood or haploidentical)
Multiple Sclerosis	Medically Necessary A <i>single</i> autologous (ablative or non-myeloablative) hematopoietic stem cell transplantation (HSCT) may be considered medically necessary for individuals with multiple sclerosis (MS) when ALL the following criteria are met: • Individual is between 18 and 55 years of age with disease duration less than ≤ 10 years; • Individual has relapsing-remitting* (RR) or secondary progressive* (SP) multiple sclerosis (MS) • Expanded Disability Status Scale (EDSS) score between 2.0 and 6.0; • The individual has highly active and treatment disease meeting criteria 1 and 2 below: 1. Highly active disease as seen by 1.a or 1.b below: a. Two or more clinical relapses* at separate times but within the previous 12 months; or b. One clinical relapse* and one or more magnetic resonance imaging (MRI) with enhancing lesion(s) typical for MS with MRI lesion occurring at a separate time than the clinical relapse but both occurring within the previous 12 months (Note: The use of gadolinium [contrast] in a patient already diagnosed with MS is up to the discretion of the neurologist and/or radiologist); and 2. Treatment resistant disease as seen by the disease activity meeting criteria D1 above occurring despite disease-modifying treatment (DMT) meeting ALL of the following requirements: a. Each relapse or episode of new MRI lesion(s) must occur after at least 3 months of treatment with a U.S. Food and Drug Administration – approved DMT;

	b. At least 1 episode must be a clinical response, and MRI evidence of activity must include at least 2 unique or active lesion(s) in the brain or spinal cord; c. At least 1 of those episodes must occur after treatment with a DMT considered to be highly efficacious (natalizumab, ocrelizumab, rituximab, or alemtuzumab). *Definitions: • Relapsing-remitting Multiple Sclerosis (RRMS): A multiple sclerosis course characterized by relapses with stable disability between episodes. • Secondary Progressive Multiple Sclerosis (SPMS): A progressive course (steadily increasing objectively documented neurological disability independent of relapses) following an initial relapsing-remitting course. • Relapse: a monophasic clinical episode with patient-reported symptoms and objective findings typical of multiple sclerosis, reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system (CNS), developing acutely or sub-acutely, with a duration of at least 24 hours, with or without recovery, and in the absence of fever or infection. Expanded Disability Status Scale (EDSS) The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10 in 0.5-unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. EDSS is a two-part assessment based on measures of impairment in eight functional systems (FS): • Pyramidal - muscle weakness or difficulty moving limbs • Cerebellar -ataxia, loss of balance, coordination or tremor • Brainstem– problems with speech, swallowing and nystagmus • Sensory – numbness or loss of sensations • B and bladder function • V - problems with sight • Cerebral or mental (cognitive function) • Other (miscellaneous functions) From levels to 1.0 to 4.0 the score is determined by the specific FS scores. From level 4.0 upwards, the score is heavily weighted based on ambulation (walking ability) and the need for assistive devices. Interpreting Scores • 0.0 to 3.5: Fully ambulatory with <i>mild to moderate</i> neurological impairment • 4.0 to 5.5: Ambulatory without aids, but with limitations that restrict fully daily activities (e.g., restricted walking distances ranging from 500 meters to 100 meters) • 6.0 to 6.5: Requires intermittent, unilateral, or constant bilateral walking assistance (such as cane or crutches)
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	• 7.0 to 9.5: Restricted to wheelchair or bedbound; varying levels of dependency for transfers of selfcare • 10.0 Death directly attributed to MS Investigational • Autologous HSCT is considered investigational for the treatment of multiple sclerosis not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. • Allogeneic hematopoietic stem cell transplantation (HSCT) is considered investigational for the treatment of multiple sclerosis (MS) for all indications because the evidence is insufficient in demonstrating improved net health outcomes.
Other Autoimmune Diseases	Investigational Autologous or allogeneic HSCT is considered investigational as a treatment of autoimmune diseases, including, but not limited to the following: • Systemic lupus erythematosus • Juvenile idiopathic arthritis • Rheumatoid arthritis • Chronic inflammatory demyelinating polyneuropathy • Type 1 diabetes Most individuals with autoimmune disorders respond to conventional drug therapies, however, conventional drug therapies are not curative, and a proportion of individuals suffer from autoimmune diseases that range from severe to the recalcitrant to the rapidly progressive. It is in this group of individuals with severe autoimmune disease that alternative therapies have been sought, including HSCT. The guideline from the American Society for Blood and Marrow Transplantation regarding indications for autologous and allogeneic hematopoietic stem cell transplantation (HSCT) states the following regarding rheumatoid arthritis and systemic lupus erythematosus: allogeneic HSCT is not currently recommended for these indications and clinical practice does not support the routine use of HSCT, transplantation for these indications may be pursued within the context of a clinical trial; autologous HSCT developmental indications where pre-clinical and/or early phase clinical studies show HSCT to be a promising treatment option, but HSCT is best pursued for these indications as part of a clinical trial. Additional controlled trials (with appropriate comparator therapies) that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the safety and/or efficacy of autologous or allogeneic HSCT for the treatment of these autoimmune diseases.
Systemic Sclerosis/Scleroderma	Medically Necessary Autologous HSCT may be considered medically necessary as a treatment for systemic sclerosis/scleroderma if ALL of the following criteria are met: • Adult individuals < 60 years of age; • Maximum duration of condition of 5 years; • Modified Rodnan Scale Score > 15; • Internal organ involvement indicated by any of the following measurements: ▪ Cardiac: abnormal electrocardiogram; or ▪ Pulmonary: diffusing capacity of carbon monoxide (DLCo) < 80% of predicted value; decline of forced vital capacity

	(FVC) of > 10% in last 12 months; pulmonary fibrosis; ground glass appearance on high resolution chest CT; or - Renal: scleroderma related renal disease; - The individual does not have the following internal organ involvement indicated by the following measurements: - Cardiac: left ventricular ejection fraction < 50%; tricuspid annular plane systolic excursion < 1.8 cm; pulmonary artery systolic pressure >40 mm Hg; mean pulmonary artery pressure > 25 mm Hg - Pulmonary: DLCo < 40% of predicted value; FVC < 45% of predicted value - Renal: creatinine clearance < 40 ml/minute; - History of < 6 months treatment with cyclophosphamide. Notes <i>Autologous HSCT should be considered for individuals with systemic sclerosis (SSc) only if the condition is rapidly progressing and the prognosis for survival is poor. An important factor influencing the occurrence of treatment-related adverse effects and response to treatment is the level of internal organ involvement. If organ involvement is severe and irreversible, HSCT is not recommended.</i> <i>Modified Rodnan Scale Score: This score consists of an evaluation of patient's skin thickness rated by clinical palpation using a 0–3 scale (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness with inability to pinch the skin into a fold) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, (right and left separately) fingers, forearms, upper arms, thighs, lower legs, dorsum of hands and feet. These individual values are added, and the sum is defined as the total skin score.</i> Investigational - Autologous HSCT as a treatment of systemic sclerosis/scleroderma is considered investigational when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes. - Allogeneic HSCT as a treatment of systemic sclerosis/scleroderma is considered investigational because the evidence is insufficient in demonstrating improved net health outcomes.
Genetic Disorders, Acquired Anemias and Other Bone Marrow Failure Syndromes	
Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria <i>Note: When considered medically necessary allogeneic transplantation must be from an appropriately HLA matched donor (related, unrelated matched, cord blood or haploidentical)</i>
Acquired Anemias and Other Bone Marrow Failure Syndromes; and Genetic Disorders	Investigational Autologous HSCT is considered investigational for the treatment of genetic diseases and acquired anemias and other bone marrow failure syndromes, including but not limited to the following indications because the evidence is insufficient in demonstrating improved net health outcomes: Sickle cell anemia

	• Homozygous beta-thalassemia • Aplastic anemia • Fanconi anemia • Dyskeratosis congenita • Shwachman-Diamond Syndrome • Diamond-Blackfan anemia • Acquired forms of aplastic anemia secondary to drug or toxin exposure • Congenital Amegakaryocytic Thrombocytopenia (CAMT) • Paroxysmal Nocturnal Hemoglobinuria (PNH) • Primary immunodeficiencies • Lymphocytic immunodeficiencies • Phagocytic deficiencies • Inherited metabolic disorders Note: See below criteria related to allogeneic HCST acquired anemias and other bone marrow failure syndromes and genetic disorders.
Acquired Anemias and Other Bone Marrow Failure Syndromes	Medically Necessary Allogeneic HCST may be considered medically necessary for the following indications: Hemoglobinopathies ▪ Sickle cell anemia for children or young adults* with at least one of the following complications: ○ Stroke or central nervous system (CNS) hemorrhage; ○ Clinical evidence of progressive neurologic deterioration, for example, abnormal cerebral MRI and arteriogram and impaired neuropsychiatric testing; ○ Sickle cell lung disease, recurrent acute chest syndrome or a combination of both requiring hospitalization and exchange transfusions; ○ Sickle cell nephropathy. ▪ Thalassemia major (Homozygous beta-thalassemia) <i>*NCCN Guidelines for Adolescent and Young Patient (AYA) Oncology includes the following definition of the adolescent and young adult oncology population: The adolescent and young adult (AYA) oncology patient is defined as an individual aged 15-39 years of age at the time of initial cancer diagnosis. This definition is based on the National Cancer Institute (NCI) Progress Review Group recommendations for a national agenda to advance AYA oncology.</i> Bone Marrow Failure Syndromes ▪ Aplastic anemia or acquired aplastic anemia secondary to drug, idiopathic, immune disorder, toxin or viral infection) ▪ Heritable bone marrow syndromes:

	○ Congenital amegakaryocytic thrombocytopenia (CAMT) ○ Diamond-Blackfan anemia (DBA) ○ Dyskeratosis congenita ○ Fanconi's anemia (FA) ○ Schwachman-Diamond syndrome ▪ Paroxysmal nocturnal hemoglobinuria (PNH) Investigational ▪ Allogeneic HSCT is considered investigational for the treatment of hemoglobinopathies and bone marrow failure syndromes not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes.
Genetic Disorders	Medically Necessary Allogeneic HSCT may be considered medically necessary for any of the following indications to include the indications under Guideline 1 and 2 (<i>except for Hunter, Sanfilippo or Morquio syndromes as indicated below</i>): • Primary Immunodeficiencies ▪ Absent or defective T-cell function (e.g., severe combined immunodeficiency (SCID), Wiscott-Aldrich syndrome, X-linked lymphoproliferative syndrome) ▪ Absent or defective natural killer function (e.g., Chediak-Higashi syndrome) ▪ Absent or defective neutrophil function (e.g., Kostmann syndrome, chronic granulomatous disease, leukocyte adhesion defect) ▪ Note: <i>Also see Guideline 1 below</i> • Inherited Metabolic Disorders ▪ Lysosomal and peroxisomal storage disorders; except Hunter, Sanfilippo and Morquio syndromes (see below statement) ▪ Note: <i>Also see Guideline 2 below</i> Guideline 1 The following guideline lists immunodeficiencies that have been successfully treated by allogeneic hematopoietic stem cell transplantation (HSCT): Lymphocyte Immunodeficiencies • Adenosine deaminase deficiency • Artemis deficiency • Calcium channel deficiency • CD40 ligand deficiency • Cernunnos/X-linked lymphoproliferative disease deficiency • CHARGE syndrome with immune deficiency • Common gamma chain deficiency • Deficiencies in CD45, CD3, CD8 • DiGeorge syndrome • DNA ligase IV deficiency syndrome • Interleukin-7 receptor alpha deficiency

	• Janus-associated kinase 3 deficiency • Major histocompatibility class II deficiency • Omenn syndrome • Purine nucleoside phosphorylase deficiency • Recombinase-activating gene 1/2 deficiency • Reticular dysgenesis • Winged helix deficiency • Wiskott-Aldrich syndrome • X-linked lymphoproliferative disease • Zeta-chain associated protein-70 deficiency Phagocytic Deficiencies • Chédiak-Higashi syndrome • Chronic granulomatous disease • Griscelli syndrome type 2 • Hemophagocytic lymphohistiocytosis • Interferon-gamma receptor deficiencies • Leukocyte adhesion deficiency • Severe congenital neutropenias • Shwachman-Diamond syndrome Other Immunodeficiencies • Autoimmune lymphoproliferative syndrome • Cartilage hair hypoplasia • CD25 deficiency • Hyper IgD and IgE syndromes • Immunodeficiency, centromeric instability, and facial dysmorphism syndrome • Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome • Nuclear factor-κ B (NF-κB) essential modulator deficiency • NF-κB inhibitor, NF-κB-α deficiency • Nijmegen breakage syndrome Guideline 2 For inherited metabolic disorders, allogeneic HSCT has been proven effective in some cases of the following: • Hurler, Maroteaux-Lamy and Sly syndromes • Childhood onset ▪ Cerebral X-linked adrenoleukodystrophy ▪ Globoid cell leukodystrophy ▪ Metachromatic leukodystrophy ▪ Alpha-mannosidosis and ▪ Aspartylglucosaminuria. Allogeneic HSCT is possibly effective for the following: • Fucosidosis • Gaucher types 1 and 3 • Farber lipogranulomatosis
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	• Galactosialidosis • GM₁ gangliosidosis • Mucopolidosis II (I-cell disease) • Multiple sulfatase deficiency • Niemann-Pick disease • Neuronal ceroid lipofuscinosis • Sialidosis • Wolman disease Allogeneic HSCT has not been effective in the following: • Hunter • Sanfilippo • Morquio syndromes. Investigational • Allogeneic HSCT has not been effective in the treatment of Hunter, Sanfilippo or Morquio syndromes and is considered investigational because the evidence is insufficient in demonstrating improved net health outcomes. • Allogeneic HSCT is considered investigational for the treatment of genetic diseases not indicated above because the evidence is insufficient in demonstrating improved net health outcomes.
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Hematopoietic Stem Cell Transplantation (HSCT): Solid Tumors

Indication	Hematopoietic Stem Cell Transplantation (HSCT) Coverage Criteria
	Note: When considered medically necessary allogeneic transplantation must be from an appropriately HLA matched donor (related, unrelated matched, cord blood or haploidentical)
Central Nervous System (CNS) Tumors CNS cancers including but not limited to the following: • Glioma (WHO grade 1, oligodendroglioma [1p19q codeleted, IDH-mutant], IDH-mutant astrocytoma, glioblastoma), • Intracranial and spinal ependymomas • Medulloblastoma • Limited and extensive brain metastases • Leptomeningeal metastases	Medically Necessary Autologous HSCT may be considered medically necessary for the treatment of central nervous system (CNS) tumors for the following indications: • As consolidation therapy for embryonal tumors of the central nervous system (e.g. medulloblastoma, medulloepithelioma, supratentorial PNETs [sPNETs; pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma], ependymoblastoma, atypical teratoid/rhabdoid tumor) that show partial or complete response to induction chemotherapy, or stable disease after induction therapy. • To treat recurrent embryonal tumors of the central nervous system (e.g., medulloblastoma, medulloepithelioma, supratentorial PNETs [sPNETs; pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma], ependymoblastoma, atypical teratoid/rhabdoid tumor). Investigational *Tandem autologous HSCT is considered investigational for the treatment of central nervous (CNS) tumors because the evidence is insufficient in demonstrating improved net health outcomes

• Non–AIDS-related primary CNS lymphomas (PCNSLs) • metastatic spine tumors • Meningiomas • Primary spinal cord tumors.	<i>*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.</i> Autologous HSCT is considered investigational for the treatment of central nervous (CNS) tumors, including but not limited to the following because the evidence is insufficient in demonstrating improved net health outcomes: • Central nervous system (CNS) tumors <i>not meeting the above criteria</i> • Astrocytomas • Oligodendrogliomas • Anaplastic gliomas and glioblastoma • Ependymomas • Meningiomas • Primary spinal cord tumors Allogeneic HSCT is considered investigational for the treatment of central nervous system (CNS) tumors for all indications because the evidence is insufficient in demonstrating improved net health outcomes. Notes: • <i>Classification of brain tumors is based on both histopathologic characteristics of the tumor and location in the brain. Central nervous system (CNS) embryonal tumors are more common in children and are the most common brain tumor in childhood. CNS embryonal tumors are primarily composed of undifferentiated round cells, with divergent patterns of differentiation.</i> ▪ <i>Embryonal tumors of central nervous system (CNS) include medulloblastoma, medulloepithelioma, supratentorial PNETs (sPNETs; pineoblastoma, cerebral neuroblastoma, ganglioneuroblastoma), ependymblastoma, atypical teratoid/rhabdoid tumor.</i> ▪ <i>Ependymoma is a neuroepithelial tumor that arises from the ependymal lining cell of the ventricles and is, therefore, usually continuous with the ventricular system. An ependymoma tumor typically arises intracranially in children, while in adults a spinal cord location is more common. Ependymomas have access to the cerebrospinal fluid and may spread throughout the neuroaxis.</i>
Germ Cell Tumors Current Version of NCCN Guideline: WHO Histological Classification Germ Cell Tumors	Medically Necessary Testicular Germ Cell Tumors Single autologous HSCT is considered medically necessary for the treatment of testicular germ cell tumors following prior conventional chemotherapy as second- line therapy for the following indication: • An individual with relapsed or recurrent disease.

• Teratoma benign • Immature teratoma NOS • Dysgerminoma • Yolk sac tumor NOS • Embryonal carcinoma NOS • Choriocarcinoma NOS • Mixed germ cell tumor Germ Cell-Sex Cord-Stromal Tumors • Gonadoblastoma ▪ Dissecting gonadoblastoma ▪ Undifferentiated gonadal tissue • Mixed germ cell-sex cord-stromal tumor, NOS	Single autologous HSCT is considered medically necessary for the treatment of testicular germ cell tumors as third-line therapy for the following indication: • An individual with relapsed or recurrent disease treated with prior first and second-line conventional dose chemotherapy and no prior autologous stem cell transplant. *Tandem Autologous Hematopoietic Stem Cell Transplantation Tandem autologous HSCT or transplant with sequential high dose chemotherapy may be considered medically necessary for the treatment of testicular tumors either as salvage therapy or with platinum-refractory disease. <i>*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.</i> Ovarian Metastatic Germ Cell Tumors Medically Necessary Single autologous HSCT may be considered medically necessary for the treatment of metastatic ovarian germ cell tumors for the following indications: • For the treatment of relapsed/recurrent or persistent disease that have failed previous course of conventional dose chemotherapy. Investigational • Autologous HSCT is considered investigational for the treatment of germ cell tumors not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. • All other uses of tandem autologous HSCT are considered investigational except as indicated above because the evidence is insufficient in demonstrating improved net health outcomes. • Allogeneic HSCT is considered investigational to treat germ cell tumors, including but not limited to its use as therapy after a prior failed autologous hematopoietic stem cell transplant (HSCT) because the evidence is insufficient in demonstrating improved net health outcomes. Notes: • <i>Germ cell tumors are composed primarily of testicular neoplasms (seminomas or nonseminomatous tumors) as well as ovarian and extragonadal germ cell tumors (e.g., retroperitoneal or mediastinal tumors). Germ cell tumors are classified according to their histology, stage, prognosis, and response to chemotherapy.</i> • <i>Individuals with favorable prognostic factors include those with a testis or retroperitoneal primary site, a complete response to initial</i>
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	chemotherapy, low levels of serum tumor markers, and low volume disease. - Individuals with unfavorable prognostic factors are those with an extra testicular primary site, an incomplete response to initial therapy, high levels of serum tumor markers, high-volume disease or relapsing mediastinal nonseminomatous germ cell tumors. Definitions Salvage therapy is treatment that is given after the cancer has not responded to other treatment. Sequential chemotherapy is a chemotherapy regimen consisting of several (2 to 4) sequential monochemotherapies with only one chemotherapeutic agent per course. The idea behind this approach is that when using single-agent chemotherapy, the physician can easily escalate the dose of the drug to the maximum tolerable dose by the patient, avoiding hematological toxicity from chemotherapeutic combinations.
Small Cell Carcinoma Ovary, Hypercalcaemic Type (SCCHOT) Current NCCN Guideline WHO Histologic Classification – Miscellaneous Tumors - Small cell carcinoma, hypercalcaemic type - Small cell carcinoma, large cell variant	Small Cell carcinoma of the ovary, hypercalcaemic type (SCCHOT) is a rare disease with a poor prognosis that is associated with SMARC4A gene mutations as well as molecular and genetic similarities to malignant rhabdoid tumors. (NCCN current guideline) Medically Necessary - Single autologous HSCT is considered medically necessary for consolidation in the treatment of Stage IA-III small cell carcinoma ovary, hypercalcaemic type (SCCOHT) with response to systemic primary therapy. Investigational - Autologous HSCT is considered investigational for the treatment of small cell carcinoma ovary, hypercalcaemic type (SCCOHT) not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. - Allogeneic HSCT is considered investigational for small cell carcinoma ovary, hypercalcaemic type (SCCOHT), including its use as therapy after a prior failed autologous hematopoietic stem cell transplant (HSCT) because the evidence is insufficient in demonstrating improved net health outcomes.
Solid Tumors in Adults	Investigational Autologous or allogeneic HSCT is considered investigational for the treatment of the following malignancies in adults, including, but not limited to the following: - Lung cancer (any histology) - Colon cancer - Rectal cancer - Pancreatic cancer - Stomach cancer - Esophageal cancer - Gallbladder cancer - Cancer of the bile duct - Renal cell cancer - Breast cancer

	• Cervical cancer • Uterine cancer • Cancer of the fallopian tubes • Ovarian cancer <i>except for ovarian metastatic germ cell tumors and small cell carcinoma ovary, hypercalcaemic type (SCCOHT) as indicated above</i> • Prostate cancer • Nasopharyngeal cancer • Paranasal sinus cancer • Neuroendocrine tumors • Soft tissue sarcomas • Thyroid cancer • Tumors of the thymus • Tumors of unknown primary origin • Malignant melanoma Based upon the review of the peer reviewed medical literature treatment with autologous and allogeneic HSCT for solid tumors in adults has not been medically proven outside the investigational setting for these patients. Current National Comprehensive Cancer Network (NCCN) guidelines do not discuss HSCT as a treatment option. Available evidence is insufficient and does not demonstrate improved net health outcomes. Additional controlled trials (with appropriate comparator therapies) that report on clinical outcomes are needed to demonstrate efficacy. The evidence is insufficient to determine the safety and/or efficacy of autologous or allogeneic HSCT for the treatment of solid tumors in adults.
Solid Tumors in Childhood	Autologous HSCT Medically Necessary Single Autologous Hematopoietic Stem Cell Transplantation Single autologous HSCT may be considered medically necessary for the following indications: • Ewing sarcoma ▪ Initial treatment of high-risk Ewing's sarcoma ▪ Relapsed or refractory Ewing's sarcoma • Neuroblastoma ▪ Initial treatment of high-risk neuroblastoma ▪ Relapsed or refractory high-risk neuroblastoma • Retinoblastoma ▪ In the treatment of metastatic retinoblastoma Note: <i>For ovarian cancer small cell carcinoma ovary, hypercalcaemic type (SCCOHT) see criteria above.</i> *Tandem Autologous Hematopoietic Stem Cell Transplantation (HSCT) A maximum of three tandem autologous HSCTs may be considered medically necessary for the treatment of high-risk neuroblastoma. Note: <i>Treatment options for recurrent or refractory neuroblastoma in individuals initially classified as high risk may also include the following:</i> • <i>131I-MIBG (MIBG therapy-infusion) alone, in combination with other therapy, or followed by stem cell rescue.</i>

	<i>*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.</i> Investigational Autologous HSCT is considered investigational when the above criteria is not met and for the following indications below because the evidence is insufficient in demonstrating improved net health outcomes: • Initial treatment of low or intermediate risk Ewing sarcoma • Initial treatment of low or intermediate risk neuroblastoma • For other solid tumors of childhood including, but not limited, to the following: ▪ Rhabdomyosarcoma ▪ Osteosarcoma ▪ Retinoblastoma without metastases ▪ Ovarian cancer except for small cell carcinoma ovary, hypercalcaemic type (SCCOHT) as indicated above. ▪ Wilms Tumor *Tandem autologous HSCT is considered investigational when the criteria above are not met and for the treatment of all other types of solid tumors of childhood, including but not limited to the following indications because the evidence is insufficient in demonstrating improved net health outcomes: • Ewing Sarcoma • Neuroblastoma <i>except as indicated above</i> • Rhabdomyosarcoma • Wilms Tumor • Osteosarcoma • Retinoblastoma • Ovarian cancer including small cell carcinoma ovary, hypercalcaemic type (SCCOHT)/small cell carcinoma of the ovary. Allogeneic HSCT Allogeneic (myeloablative or non-myeloablative) HSCT is considered investigational for the treatment of childhood solid tumors, including but not limited to the following indications because the evidence is insufficient in demonstrating improved net health outcomes: • Ewing Sarcoma • Neuroblastoma • Rhabdomyosarcoma • Wilms Tumor • Osteosarcoma • Retinoblastoma Salvage allogeneic HSCT for solid tumors of childhood, including but not limited to the following, that relapse after autologous HSCT or fail to
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respond is considered **investigational** because the evidence is insufficient in demonstrating improved net health outcomes:

- Ewing Sarcoma
- Neuroblastoma
- Rhabdomyosarcoma
- Wilms Tumor
- Osteosarcoma
- Retinoblastoma
- Ovarian cancer including small cell carcinoma ovary, hypercalcaemic type (SCCOHT)/small cell carcinoma of the ovary.

Definitions

- **Refractory** is a cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant to treatment. Also called resistant cancer.
- **Relapse** is a cancer that recurs after prior complete response
- **Salvage therapy** is treatment that is given after the cancer has not responded to other treatment.

International Neuroblastoma Staging System

Note: INSS takes into account the results of surgery to remove the tumor it cannot help determine a stage before any treatment has started.

Stage	Description
I	Localized tumor with complete gross excision, with or without microscopic residual disease; lymph nodes negative for tumor
2A	Localized tumor with incomplete gross excision; lymph nodes negative for tumor
2B	Localized tumor with or without complete gross excision, with ipsilateral lymph nodes positive for tumor
3	Unresectable unilateral tumor infiltrating across the midline, with or without regional lymph node involvement; or localized unilateral tumor with contralateral regional lymph node involvement; or midline tumor with bilateral extension by infiltration or by lymph node involvement
4	Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, and/or other organs, except as defined for stage 4S
4S	Localized primary tumor as defined for stage 1, 2A, or 2B, with dissemination limited to skin, liver, and/or bone marrow (marrow involvement less than 10%), limited to children younger than 1 year of age

International Neuroblastoma Risk Group Staging System

Note: The INRGSS system uses image defined risk factors (IDFRs), which are factors seen on imaging tests that might mean the tumor will be harder

	to remove. This includes things like the tumor growing into a nearby vital organ or growing around important blood vessels. <table border="1"> <thead> <tr> <th>Stage</th><th>Description</th></tr> </thead> <tbody> <tr> <td>L1</td><td>Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment</td></tr> <tr> <td>L2</td><td>Locoregional tumor with presence of one or more image defined risk factors</td></tr> <tr> <td>M</td><td>Distant metastatic disease (except stage MS)</td></tr> <tr> <td>MS</td><td>Metastatic disease in children younger than 18 months with metastasis confined to skin, liver, and/or bone marrow</td></tr> </tbody> </table> In the INRG classification system, a combination of clinical, pathologic, and genetic markers is used to predict whether the tumor will grow and how it will respond to treatment. These markers are used to define risk. Using the following factors, neuroblastoma is classified into 1 of 4 categories: very low-risk, low-risk, intermediate-risk, or high risk. • The stage of the disease according to the INRG staging system • Age at the time of diagnosis • Histologic category such as maturing ganglioneuroma versus ganglioneuroblastoma, intermixed versus ganglioneuroblastoma or nodular versus neuroblastoma • Grade or how cells of the tumor are differentiated • MYCN gene status (presence or absence of MYCN amplification) • Chromosome 11q status • Tumor cell ploidy, which is the DNA content of tumor cells High risk neuroblastoma is characterized by age older than 1 year, disseminated disease, MYCN oncogene amplification, and unfavorable histopathologic findings. Low-risk neuroblastoma includes individuals younger than 1 year of age with stage 1, 2 or 4S disease with favorable histopathologic findings and no MYCN oncogene amplification.	Stage	Description	L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment	L2	Locoregional tumor with presence of one or more image defined risk factors	M	Distant metastatic disease (except stage MS)	MS	Metastatic disease in children younger than 18 months with metastasis confined to skin, liver, and/or bone marrow
Stage	Description										
L1	Localized tumor not involving vital structures as defined by the list of image-defined risk factors and confined to one body compartment										
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Hematopoietic Stem Cell Transplantation (HSCT): Blood Cancers

Indication	Hematopoietic Stem Cell Transplantation Coverage Criteria <i>Note: When considered medically necessary allogeneic transplantation must be from an appropriately HLA matched donor (related, unrelated matched, cord blood or haploidentical)</i>
Acute Lymphoblastic Leukemia (ALL) Adult B-ALL: B-cell acute	Autologous HSCT Investigational • Autologous HSCT is considered investigational for the treatment of adult B-ALL and T-ALL because the evidence is insufficient in demonstrating improved net health outcomes.

lymphoblastic leukemia T-ALL: T-cell acute lymphoblastic leukemia	Allogeneic HSCT B-ALL Medically Necessary Ph- B-ALL - Allogeneic HSCT may be considered medically necessary to treat adult Ph- B-ALL with poor risk mutations (<i>see table below</i>) with MRD positive disease following first CR - Allogeneic HSCT may be considered medically necessary to treat adult Ph- B-ALL regardless of genotype for those individuals with persistent MRD who received immunologic consolidation or if immunologic consolidation was not available. - Allogeneic HSCT may be considered medically necessary to treat adult Ph- B-ALL Ph- B-ALL for relapsed or refractory disease after prior allogeneic HCT in CR2 or greater. - Allogeneic HSCT may be considered medically necessary for relapsed or refractory disease as consolidation therapy to treat adult Ph- B-ALL if in second CR and patient has not had a prior allogeneic HSCT. Ph+ B-ALL - Allogeneic HSCT may be considered medically necessary for to treat adult Ph+ B-ALL in first CR in individuals that have achieved MRD negativity post-consolidation therapy. - Allogeneic HSCT may be considered medically necessary to treat adult Ph+ B-ALL for relapse at any point in time or in the setting of MRD positivity post-consolidation T-ALL - Allogeneic HSCT may be considered medically necessary to treat adult T-ALL with high-risk features (ETP-phenotype or RAS/PTEN and/or NOTCH1/FBXW7 wild-type classifier regardless of MRD response. - Allogeneic HSCT may be considered medically necessary to treat adult T-ALL for non-ETP (early T-cell precursor) disease with persistent or recurrent MRD after consolidation therapy. Reduced Intensity HSCT Allogeneic HSCT reduced intensity conditioning (non-myeloablative) may be considered medically necessary as a treatment for adult ALL in individuals who are in complete marrow and extramedullary first or second remission, and who, for medical reasons, would be unable to tolerate a standard myeloablative conditioning regimen. <i>Note: Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation but would not tolerate the standard myeloablative conditioning regimen. This may include the individual's fitness, comorbidities, and end-organ reserve (e.g., liver or kidney dysfunction, generalized-debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).</i> Investigational Allogeneic HSCT is considered investigational not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. Definitions Complete response (<i>also known as complete remission</i>) is the disappearance of all signs of cancer in response to treatment; this does not always mean the cancer has been cured. Karnofsky Performance Status Score is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0
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to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in a clinical trial.

- 100 – normal no complaints
- 90 – able to carry on normal activities. Minor signs or symptoms of disease
- 80 – normal activity with effort
- 70 – care for self, unable to carry on normal activity or do active work
- 60 – requires occasional assistance, but able to care for most of his or her needs
- 50 – requires considerable assistance and frequent medical care
- 40 – disabled requires special care and assistance
- 30 – severely disabled, hospitalization indicated though death not imminent
- 20 – very sick, hospitalization necessary, active supportive treatment necessary
- 10 - moribund (approaching death, deepening stupor and coma)
- **Myeloablative** is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments.
- **Non-myeloablative** (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.
- **Refractory** is a cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant to treatment. Also called resistant cancer.
- **Relapse** is a cancer that recurs after prior complete response.

Response Assessment

Response Criteria for Blood and Bone Marrow ^a	
Complete Remission (CR)	• No circulating blasts or extramedullary disease ▪ No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement • Trilineage hematopoiesis (TLH) and < 5% blasts • absolute neutrophil count (ANC) > 1000/microL • platelets > 100,000/microL
CR with partial hematologic recovery CRh)	• Meets all criteria for CR except with partial recovery of peripheral blood counts (platelets $\geq$ 50,000/microL and ANC $\geq$ 500/microL
CR with incomplete hematologic recovery (CRi)	• Meets all criteria for CR except without recovery of platelet count or without recovery of ANC (platelets < 100,000/microL and ANC $\geq$ 1000/microL or platelets $\geq$ 100,000/microL and ANC < 1000/microL
	Response Assessment for Those Not Achieving Complete Response
Morphologic leukemia-free state (MLFS)	• Leukemic Blasts < 5% and no measurable extramedullary leukemia • ANC < 500/microL and platelets < 50/microL • The marrow shows $\geq$ 10% cellularity, with at least 200 cells enumerated from an aspirate that contains spicules

	Aplastic marrow ^b	All criteria for MLFS are met, but with <10% cellularity and/or an aspirate with <200 cells that be enumerated
	Refractory disease	CR not achieved at the end of induction
	Progressive disease (PD)	Appearance of circulating leukemic blasts or an increase of at least 25% in the absolute number of circulating or bone marrow blast or development of extramedullary disease
	Relapsed disease	Reappearance of blasts in the blood or bone marrow (>5%) or in extramedullary site after a CR
	^a MRD assessment is not included in a morphologic assessment and should be obtained.	
	^b This entity may be consistent with a response.	
	Response Criteria for CNS Disease	
	CNS remission	Achievement of CNS1 status in a patient with CNS-2 or CNS-3 status of diagnosis
	CNS relapse	New development of CNS-2 or CNS-3 status (including CNS parenchymal relapse) or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without other explanation
	Response Criteria for Lymphomatous Extramedullary Disease	
CT of neck/chest/abdomen/pelvis with IV contrast and PET/CT if lymphomatous involvement is suspected and/or confirmed by CT, imaging should be performed to assess response for extramedullary disease		
CR	Complete resolution of lymphomatous enlargement by CT. For patients with a previous PET scan, a post-treatment residual mass of any size is considered a CR as long as it is PET negative	
Partial remission (PR)	>50% decrease in the sum of the product of the greatest perpendicular diameters (SPD) of the lymphomatous enlargement.	
PD	> 25% increase in the SPD of the mediastinal enlargement. For patients with a previous positive PET scan, post-treatment PET must be positive in at least one previously involved site.	
No response (NR)	Does not meet criteria for either PR or PD	
Relapse	Recurrence of lymphomatous enlargement after achieving CR	
Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL		
Risk Groups		Cytogenetics and Molecular Aleterations
Standard risk		- Hyperdiploidy (51-65 chromosomes) - Cases with trisomy of chromosomes 4, 10, and 17 appear to have the most favorable outcome:

		• t(12;21) (p13;q22): ETV6::UNX1ⁱ • t(1;19)(q23;p13.3): TCF3::PBX1 • DUX4 rearranged • PAX5 P80R • t(9;22)(q34;q11.2): BCR::ABL:1^j without IKZF1 plus^k and without antecedent chronic myeloid leukemia (CML)	
	Poor risk	• Hypodiploidy^{l,m} (< 44 chromosomes) • Low hypodiploidy (30-39 chromosomes) • Near triploidy (30-39 chromosomes) • TP53 mutation • KMT2A rearranged (t[4;11] or others) • IgH rearranged^o • HLF rearranged • ZNF384 rearranged • MEF2D rearranged • MYC rearranged • BCR::ABL1-like (Philadelphia chromosome [Ph]-like) ALL ➢ JAK-STAT (CRLF2r, EPORr, JAK 1/2/3r, TYKR2r, mutations of SH2B3, IL7R, JAK 1/2/3) ➢ ABL class (rearrangements of ABL1, ABL2, PDGFRA, PDGFRB, FBFR) ➢ Other (NTRK 1/2/3r, FLT3r, LYNr, PTK2Br) • PAX5alt • t(9;22)(q34;q11.2): BCR::ABL1^j with IKZF1 plus^k and/or antecedent CML • Intrachromosomal amplification of chromosome 21 (AMP21) • Alterations of IKZF1^k • Complex karyotype (5 or more chromosomal abnormalities)	
		Footnotes: ⁱ The translocation t(12;21)(p13;q22) is typically cryptic by conventional chromosome analysis and requires FISH or PCR to identify. ^j Interphase FISH for the detection of BCR::ABL1 transcript on blood granulocytes is recommended to differentiate between de novo blast phase CML (BP-CML) and de novo Ph-positive ALL. ^k IKZF1 deletions with co-occurring deletions in CDKN2A, CDKN2B, PAX5, or PAR1 in the absence of ERG deletion, which are called IKZF1 plus, as well as those with concomitant 22q11.22 deletions, are especially associated with worse outcomes in pediatric patients with B-ALL.	

		^l There are other results that are not < 44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hypodiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. ^m Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone. Patients with hypodiploid ALL should be considered for germline testing, as hypodiploid ALL may be associated Li-Fraumeni syndrome. ^o Includes IGH::IL3 gene fusion ^r Emerging evidence suggests DUX4r ALL is favorable. Additionally in cases of DUX4r, IKZF1 alterations do not confer poor prognosis.	
Acute Lymphoblastic Leukemia (ALL) – Pediatric Per Current NCCN Guideline: “The NCCN Panel considers the term “Pediatric” to include any patient aged ≤18 years and certain patients >18 years of age. These guidelines are intended to apply to adolescent and young adult (AYA) patients treated in pediatric oncology setting and may include patients up to age 30 years.” B-ALL: B-cell acute lymphoblastic leukemia T-ALL: T-cell acute lymphoblastic leukemia	Autologous HSCT Investigational Autologous HSCT is considered investigational for the treatment of childhood B-ALL and T-ALL because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary B-ALL - Allogeneic HSCT may be considered medically necessary to treat childhood ALL in infants < 6 months of age with unfavorable cytogenetics (MLL/KMT2A mutation) with high-risk features (<i>see table below for Infant Risk Group Definitions</i>) in first CR. - Allogeneic HSCT may be considered medically necessary to treat childhood ALL (BCR:ABL+/BCR::ABL-/Like B-ALL) if MRD ≥0.01% post consolidation (week 9-12 from diagnosis following first CR) - Allogeneic HSCT may be considered medically necessary to treat childhood ALL (BCR:ABL+/BCR::ABL-/Like B-ALL) with induction failure (M3 ≥ 25% blasts) after achieving MRD-negative status. - Allogeneic HSCT may be considered medically necessary to childhood ALL (BCR:ABL+/BCR::ABL-/Like B-ALL) for relapsed or refractory disease following CR2 based upon timing and leukemic phenotype meeting one of the following: - Medullary (isolated or combined) <36 months from initial diagnosis following response with reinduction therapy ≥36 months from initial diagnosis if following reinduction therapy the MRD ≥0.1% within 4-8 weeks of reinduction - Extramedullary (isolated) <18 months from initial diagnosis following response to reinduction therapy - Allogeneic HSCT may be considered medically necessary to treat childhood ALL for relapsed or refractory disease in CR3 or greater following complete response to reinduction therapy. T-ALL - Allogeneic HSCT may be considered medically necessary to treat childhood T-ALL in individuals with very high-risk disease (MRD positivity >0.1%) at completion of consolidation therapy.		

- Allogeneic HSCT may be considered **medically necessary** to treat childhood T-ALL with induction failure (M3 $\geq$ 25% blasts).
- Allogeneic HSCT may be considered **medically necessary** to treat childhood T-ALL in individuals with medullary or extramedullary relapse at any time point.
- Allogeneic HSCT may be considered **medically necessary** to treat childhood T-ALL with very high-risk disease (MRD positivity $>0.1\%$) following a first relapse after achieving CR as consolidation therapy.
- Allogeneic HSCT may be considered **medically necessary** to treat childhood T-ALL with very high-risk disease (MRD positivity $>0.1\%$) for refractory or multiple relapse disease in CR 2 or greater as consolidation therapy.

Investigational

- Allogeneic HSCT is considered **investigational** not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes.

Definitions

- **Complete response** (also known as complete remission) is the disappearance of all signs of cancer in response to treatment; this does not always mean the cancer has been cured.
- **Refractory** is a cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment, or it may become resistant to treatment. Also called resistant cancer.
- **Relapse** is a cancer that recurs after prior complete response.

Response Assessment

Response Criteria for Blood and Bone Marrow	
Complete Response (CR)	No circulating blasts or extramedullary disease • No lymphadenopathy, splenomegaly, skin/gum infiltration/testicular mass/CNS involvement Marrow with trilineage hematopoiesis (TLH) and $< 5\%$ (M1) or $<1\%$ by low or molecular testing^a With blood count recovery = absolute neutrophil count (ANC) $> 1000/\mu\text{L}$ and platelets $> 100,000/\mu\text{L}$ No recurrence in 4 weeks
CR with Incomplete Blood Count Recovery (Cri)	Meets all criteria for CR except platelet count and/or ANC.
Overall response Rate (ORR = CR + Cri)	Note: MRD assessment is not included in morphologic assessment and should be obtained
Refractory Disease	CR not achieved at the end of induction (EOI)

	Progressive Disease (PD)	Increase at least 25% in the absolute number of circulating or bone marrow blasts or development of extramedullary disease
	Relapsed Disease	Reappearance of blasts in the blood or bone marrow > 5% (M2 or greater) or >1% with previous/supportive molecular findings or any extramedullary site after a CR
	Response Criteria for CNS Disease	
	CNS Remission	Achievement of CNS1 status in a patient with CNS-2 or CNS-3 status of diagnosis
	CNS Relapse	New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome without another explanation. New development of CNS-2 status on 2 consecutive lumbar punctures (between 2-4 weeks apart) with confirmation by immunophenotyping or with molecular testing methods.
	Genetic Risk Groups for B-ALL	
	Risk Groups	Genetics
	Favorable risk features	- High hyperdiploidy (51-67 chromosomes) - Double trisomy (DT) of chromosomes 4, 10 or triple trisomy of chromosomes 4, 10, and 17 are among trisomies that have the most favorable outcome - Cryptic t(12;21)(p13;q22): ETV6::RUNX1 fusion - DUX4r - NUTM1r
	Intermediate risk features	MEF2Dr, ZNF384r, PAX5alt, PAX5 P80R, ETV6::RUNX1-like, t(1;19): TCF::PBX1
	Unfavorable risk features	- Hypodiploidy (<44 chromosomes)^{c,d} - KMTZAr (t[4;11] or others - t(9;22)(q34;q11.2): BCR::ABL1 - BCR::ABL1-like ALL - JAK-STAT (CRLF2r^e, EPORr, JAK1/2/3r, TYK2r, mutations of SH2B3, IL7R, JAK1/2/3) - ABL class (rearrangements of ABL1, ABL2, PDGFRA, PDGFRB, FGFR1) - Other (NTRKr, FLT3r, LYNr, PTL2Br) - t(17;19); TCF3::HLF and t(17;18): TCF4::HLF - Intrachromosomal amplification of chromosome 21 (iAMP21) - Alterations of IKZF1^f

	^c Alternatively defined as DNA index less than protocol-defined threshold or other clear evidence of hypodiploid clone: near-haploid (24–31 chromosomes); low-hypodiploid (32–39 chromosomes); or high-hypodiploid (40–43 chromosomes). Low hypodiploid ALL is also often associated with TP53 loss-of-function somatic mutations in which half are observed to be germline pathogenic variants associated with Li-Fraumeni syndrome. ^d There are other results that are not <44 chromosomes that may be equivalent to hypodiploidy and have the same implications. It is important to distinguish true hyperdiploidy from masked hypodiploidy, which results from the doubling of hypodiploid clones. Single nucleotide polymorphism (SNP) array or whole genome sequencing to look for loss of heterozygosity (LOH) can distinguish true hyperdiploidy from masked hypodiploidy. ^e Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. ^f IKZF1 deletions with deletions in CDKN2A, CDKN2B (homozygous), PAX5, or PAR1 region in the absence of ERG deletion, which are called IKZF1plus, as well as those with concomitant 22q11.22 deletions are especially associated with worse outcomes. However, DUX4 rearrangements with IKZF1 alterations do not confer poor prognosis. Infant Risk Groups Definitions <table border="1"> <thead> <tr> <th>Risk Group</th><th>Features</th></tr> </thead> <tbody> <tr> <td>High</td><td>KMT2A rearranged; and Age <3 months with any WBC or age <6 months with WBC count $\geq 300,000$; or remains MRD+ after intensive consolidation therapy (any age/WBC count)</td></tr> <tr> <td>Intermediate</td><td>KMT2A - rearranged and not high risk</td></tr> <tr> <td>Standard</td><td>KMT2A not rearranged</td></tr> </tbody> </table> T-ALL Post-Induction Risk Group Definitions <table border="1"> <thead> <tr> <th>Risk Group</th><th>Features²</th></tr> </thead> <tbody> <tr> <td>Very High</td><td>End consolidation MRD >0.1%</td></tr> <tr> <td>High</td><td>Absence of standard- and very-high risk features</td></tr> <tr> <td>Standard</td><td>Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment</td></tr> </tbody> </table> ²The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used.	Risk Group	Features	High	KMT2A rearranged; and Age <3 months with any WBC or age <6 months with WBC count $\geq 300,000$; or remains MRD+ after intensive consolidation therapy (any age/WBC count)	Intermediate	KMT2A - rearranged and not high risk	Standard	KMT2A not rearranged	Risk Group	Features ²	Very High	End consolidation MRD >0.1%	High	Absence of standard- and very-high risk features	Standard	Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment
Risk Group	Features																
High	KMT2A rearranged; and Age <3 months with any WBC or age <6 months with WBC count $\geq 300,000$; or remains MRD+ after intensive consolidation therapy (any age/WBC count)																
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Standard	Day 29 MRD <0.01% and CNS-1 and absence of testicular disease and no steroid pretreatment																
Acute Myeloid Leukemia (AML)	<i>Acute myeloid leukemia includes the following: acute promyelocytic Leukemia (APL), acute myeloid leukemia (AML) and Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)</i> Autologous HSCT Medically Necessary Autologous HSCT may be considered medically necessary for the treatment of acute myeloid leukemia (AML): • In individuals in first complete remission (CR1) or beyond. • Individuals with relapsed AML if responsive to intensified induction chemotherapy in individuals who are not candidates for allogeneic HSCT.																

	Investigational - Autologous HSCT is considered investigational for the treatment of AML not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary Allogeneic HSCT using a myeloablative conditioning regimen may be considered medically necessary for the treatment of individuals with AML with one of the following: - Poor to intermediate-risk (see <i>tables below</i>) Acute myeloid leukemia (AML) in individuals first complete remission (CR1). - Acute myeloid leukemia (AML) that is refractory to standard induction chemotherapy (induction failure) but can be brought into complete remission (CR) with intensified induction therapy. - Acute myeloid leukemia (AML) in individuals with relapsed disease following chemotherapy induced complete remission (CR1) but can be brought into CR2 or beyond with intensified induction chemotherapy. - Acute myeloid leukemia (AML) who have relapsed disease and is following a prior autologous hematopoietic stem cell transplantation, and the patient can be brought into complete remission with intensified induction chemotherapy and are medically able to tolerate the procedure. Reduced Intensity HSCT Allogeneic HSCT reduced intensity conditioning regimen (non-myeloablative) as a treatment for AML may be considered medically necessary when the above criterion for an allogeneic HSCT is met and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Note: <i>Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation but would not tolerate standard myeloablative conditioning regimen. This may include the individual's fitness, comorbidities, and end-organ reserve (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).</i> Investigational - Allogeneic HSCT is considered investigational not meeting above criteria because the evidence is insufficient in demonstrating improved net health outcomes. Definitions Karnofsky Performance Status is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in the clinical trial. 100 – normal no complaints 90 – able to carry on normal activities. Minor signs or symptoms of disease 80 – normal activity with effort 70 – care for self, unable to carry on normal activity or do active work 60 – requires occasional assistance, but able to care for most of his or her needs 50 – requires considerable assistance and frequent medical care 40 – disabled requires special care and assistance
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- 30 – severely disabled, hospitalization indicated though death not imminent
- 20 – very sick, hospitalization necessary, active supportive treatment necessary
- 10 - moribund (approaching death, deepening stupor and coma)
- **Myeloablative** is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments.
- **Non-myeloablative** (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.
- **Primary refractory acute myeloid leukemia (AML)** is defined as leukemia that does not achieve a complete remission after conventionally dosed (non-marrow ablative) chemotherapy.

Clinical features that predict poor outcomes of AML therapy include, but are not limited to, the following:

- Treatment-related AML (secondary to prior chemotherapy and/or radiotherapy for another malignancy)
- AML with antecedent hematologic disease (e.g., myelodysplasia)
- Presence of circulating blasts at the time of diagnosis
- Difficulty in obtaining first complete remission with standard chemotherapy
- Leukemias with monocytoid differentiation (French-American-British classification M4 or M5).

ELN Risk Stratification by Biological Disease Factor for Patients with Non-APL AML Treated with Intensive Induction Chemotherapy

Risk Category	Genetic Abnormality
Favorable	t(8;21)(q22;q22.1); <i>RUNX1::RUNX1T1</i> ^{b,c} inv(16)(p13.1;q22) or t(16;16)(p13.1;q22)/ <i>CBFB::MYH11</i> ^{b,c} Mutated <i>NPM1</i> ^{b,d} without <i>FLT3</i> -ITD bZIP in-frame mutated <i>CEBPA</i> ^e
Intermediate	Mutated <i>NPM1</i> ^{b,d} and <i>FLT3</i> -ITD Wild-type <i>NPM1</i> without <i>FLT3</i> -ITD (without adverse-risk genetic lesions) t(9;11)(p21.3;q23.3)/ <i>MLL</i> :: <i>KMT2A</i> ^{b,f} Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Poor /Adverse	t(6;9)(p23;q34.1)/ <i>DEK::NUP214</i> t(v;11q23.3)/ <i>KMT2A</i> rearranged ^g t(9;22)(q34.1;q11.2)/ <i>BCR::ABL1</i> t(8;16)(p11.2;p13.3)/ <i>KAT6A::CREBBP</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2,MECOM(EV11)</i> t(3q26.2;v)/ <i>MECOM(EV11)</i> -rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype ^h , monosomal karyotype ⁱ Mutated <i>ASXL1</i> , <i>BCOR</i> , <i>EZH2</i> , <i>RUNX1</i> , <i>SF3B1</i> , <i>SRSF2</i> , <i>STAG2</i> , <i>U2AF1</i> , and/or <i>ZRSR2</i> ^j Mutated <i>TP53</i> ^k

AML: acute myeloid leukemia; ITD: internal tandem duplication.

^b Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of MRD.

^c Concurrent *KIT* and/or *FLT3* gene mutation does not alter risk categorization.

^d AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.

^e Only in-frame mutations affecting the bZIP region of CEBPA, irrespective of whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.

^f The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

^g Excluding KMT2A partial tandem duplication (PTD).

^h Complex karyotype: ≥ 3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.

ⁱ Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding CBF-AML). ^j For the time being, these markers should not be used as an adverse prognostic marker if they cooccur with favorable-risk AML subtypes.

^j For the time being, these markers should not be used as an adverse marker if they co-occur with favorable-risk AML subtypes.

^k TP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype

Response Criteria Definitions for AML

Morphologic Leukemia-Free State (MFLS)	BM <5% blasts in an aspirate with spicules; at least 200 cells must be enumerated No blasts with Auer rods or persistence of extramedullary disease If there is a question of residual leukemia, a BM aspirate/biopsy should be repeated in one week A BM biopsy/aspirate should be performed.
Complete Remission (CR)	Morphologic CR - ANC $\geq 1 \times 10^9/L$ (blasts <5%) - Platelets $\geq 100 \times 10^9/L$ (blasts <5%)
CR without MRD (CR _{MRD})	If studied pretreatment, CR with negativity for a genetic marker by reverse transcriptase PCR (RT-PCR) or CR with negativity by MFC^a Sensitivity varies by marker and method used; analyses should be done in experienced laboratories Molecular CR – molecular studies negative
CR with Partial Hematological Recovery (CRh)	Defined as <5% blasts in the BM, no evidence of disease (NED), and partial recovery of peripheral blood counts (platelets $\geq 50 \times 10^9/L$ and ANC $\geq 0.5 \times 10^9/L$)²
CRi	All CR criteria and transfusion independence but with persistence of neutropenia (<1 X 10⁹/L) or thrombocytopenia (<100 x 10⁹/L) Responses less than CR may still be meaningful depending on the therapy
Partial Remission (PR)	Decrease of at least 50% in the percentage of blasts to 5% to 25% in the BM aspirate and meeting hematologic criteria for CR, as noted above

	Relapse Following CR	Reappearance of leukemic blasts in the peripheral blood or the finding of >5% blasts in the BM, not attributable to another cause (e.g., BM regeneration after consolidation therapy) or extramedullary relapse
	Primary Refractory	Inability to attain CR, CRh, or CRi following exposure to at least 2 courses of intensive induction therapy
	MRD Relapse	Conversion from MRD negativity to MRD positivity, independent of method of testing
^a This is clinically relevant in APL and Ph+ leukemia, and inability to achieve a significant reduction (e.g. >3 log) in molecular evidence of t(8;21) or inv(16) has a very high predictive value of relapse. Molecular remission for APL should be performed after consolidation, not after induction as in non-APL AML. NPM1 is a target that can be included in the molecular response assessment.		
Amyloidosis (Systemic Light Chain)	Autologous HSCT) Medically Necessary - Autologous HSCT may be considered medically necessary as part of the primary treatment for systemic amyloidosis. Investigational - Autologous HSCT is considered investigational not meeting the above because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Investigational - Allogeneic HSCT is considered investigational for all indications because the evidence is insufficient in demonstrating improved net health outcomes.	
Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	Autologous HSCT Investigational - Autologous HSCT is considered investigational to treat individuals with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) for all indications because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) - Allogeneic HSCT may be considered medically necessary meeting one of the following: - To treat CLL or SLL in individuals with markers of poor risk (<i>see table below Cytogenetics and Gene Mutations – DNA Sequencing</i>). - In relapsed or refractory disease after prior therapy with cBTKi or ncBTKi and BCL2i containing regimens (<i>see below table</i>). Richter's Transformation (Diffuse large B-cell lymphoma): Transformed Chronic Lymphocytic Leukemia (Richter's Syndrome) - Allogeneic HSCT may be considered medically necessary for histologic transformed CLL or SLL (i.e., Richter's transformation into diffuse large B-cell lymphoma [DLBCL]) in response to Non-CIT (<i>see below table</i>) regimens in complete remission (CR). - An autologous HSCT may be considered medically necessary when the above criteria is met and the individual has no suitable donor available.	

Investigational

- Allogeneic HCST is considered **investigational** when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes.

Reduced Intensity HSCT

Allogeneic HSCT reduced intensity conditioning regimen (non-myeloablative) as a treatment for CLL or SLL may be considered **medically necessary** when the above criterion for an allogeneic HSCT is met and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.

Note: *Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation but would not tolerate standard myeloablative conditioning regimen. This may include the individual's fitness, comorbidities, and end-organ reserve (e.g., liver or kidney dysfunction, prior intensive chemotherapy, generalized debilitation, low Karnofsky Performance Status score).*

Definitions

- Karnofsky Performance Status** is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in the clinical trial.
 - 100 – normal no complaints
 - 90 – able to carry on normal activities. Minor signs or symptoms of disease
 - 80 – normal activity with effort
 - 70 – care for self, unable to carry on normal activity or do active work
 - 60 – requires occasional assistance, but able to care for most of his or her needs
 - 50 – requires considerable assistance and frequent medical care
 - 40 – disabled requires special care and assistance
 - 30 – severely disabled, hospitalization indicated though death not imminent
 - 20 – very sick, hospitalization necessary, active supportive treatment necessary
 - 10 - moribund (approaching death, deepening stupor and coma)
- Myeloablative** is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments.
- Non-myeloablative** (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.

Non-CIT Based Regimens

ICI-Based Regimens	BTKi (monotherapy)	Bispecific Antibody Therapy	CAR-T Cell Therapy (CD-directed; after at least 1 prior systemic prior regimen)
Venetoclax* + Atezolizumab + Obinutuzumab	Pirtobrutinib** Acalabrutinib+ (Category 2B)	Epcoritamab-bysp Glofitamab-gxbm	Axicabtagene ciloleucel

	Nivolumab + Ibrutinib Pembrolizumab + Ibrutinib Zanubrutinib* + Tislelizumab-jsgr			Lisocabtagene maraleucel Tisagenlecleucel																		
*BCL-2 inhibitor (BCL2i)																						
**Noncovalent (reversible) BTKi (ncBTKi)																						
*Covalent BTKi (cBTKi)																						
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CLL Staging Systems																						
RAI System																						
<table><tr><th>Stage</th><th>Description</th><th>Modified Risk Status</th></tr><tr><td>0</td><td>Lymphocytes in blood > 5 x 10⁹/L clonal B cells and >40% lymphocytes in the bone marrow</td><td>Low</td></tr><tr><td>I</td><td>Stage 0 with enlarged node(s)</td><td>Intermediate</td></tr><tr><td>II</td><td>Stage 0-1 with splenomegaly, hepatomegaly, or both</td><td>Intermediate</td></tr><tr><td>III</td><td>Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit <33%</td><td>High</td></tr><tr><td>IV</td><td>Stage 0-III with platelets <100,000/mm³</td><td>High</td></tr></table>					Stage	Description	Modified Risk Status	0	Lymphocytes in blood > 5 x 10 ⁹ /L clonal B cells and >40% lymphocytes in the bone marrow	Low	I	Stage 0 with enlarged node(s)	Intermediate	II	Stage 0-1 with splenomegaly, hepatomegaly, or both	Intermediate	III	Stage 0-II with hemoglobin < 11.0 g/dL or hematocrit <33%	High	IV	Stage 0-III with platelets <100,000/mm ³	High
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SLL staging System																						
Lugano Modification of Ann Arbor Staging System ^c																						
<table><tr><th>Stage^d</th><th>Involvement^f</th><th>Extranodal (E) Status</th></tr><tr><td>Limited</td><td></td><td></td></tr><tr><td>Stage I</td><td>One node or a group of adjacent nodes</td><td>Single extranodal lesions without nodal involvement</td></tr><tr><td>Stage II</td><td>Two or more nodal groups on the same side of the diaphragm</td><td>Stage I or II by nodal extent with limited</td></tr></table>					Stage ^d	Involvement ^f	Extranodal (E) Status	Limited			Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement	Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited						
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			contiguous extranodal involvement
Stage II bulky ^e	II as above with “bulky” disease ^e Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.		Not applicable
Advanced			
Stage III	Nodes on both sides of the diaphragm		Not applicable
	Nodes above the diaphragm with spleen involvement		
Stage IV	Additional non-contiguous extra lymphatic involvement		Not applicable

^eExtent of disease is determined by FDG-PET/CT for avid lymphomas and CT for non-avid histologies.

^cCategorization of A versus B has been removed from Lugano Modification for Ann Arbor Staging System.

^f Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

Prognostic Variables in Patients with CLL/SLL

Cytogenetics and Gene Mutations

Method of Detection	Prognostic Variable	Clinical Association
Interphase cytogenetics (FISH)		
	Del(13q) as a sole abnormality	Favorable prognosis: longest median overall survival (OS) in patients treated with chemoimmunotherapy (CIT)
	Trisomy 12	Intermediate prognosis for time-to-first treatment (TTFT) in patients with newly diagnosed CLL; and intermediate OS in patients treated with chemoimmunotherapy
	None	Intermediate prognosis for TTFT in patients with newly diagnosed CLL; and intermediate OS in patients treated with chemoimmunotherapy
	Del(11q)	Shortened TTFT, and shorter median OS with chemoimmunotherapy
	Del(17p) ^b	Inferior response, shorter treatment-free interval, and

			inferior survival with chemoimmunotherapy Good responses but shorter progression-free survival (PFS) and OS with time-limited venetoclax-based regimens and covalent BTK inhibitor (cBTKI)
	DNA sequencing		
		IGHV^c Mutated: >2% mutation or <98% homology with germline gene sequence Unmutated: ≤2% of mutation or ≥98% homology with germline gene sequence)	Unmutated IGHV is associated with shorter TTFT and PFS with chemoimmunotherapy and time-limited venetoclax-based regimens, compared to mutated IGHV Overall response rates are not correlated with IGHV mutation status in patients treated with cBTKi or time-limited venetoclax-based regimens PFS and OS are not correlated with IGHV mutation status in patients treated with cBTKi
		TP53 mutation^d with del(17p)	Shorter PFS and OS with chemoimmunotherapy,^e time-limited venetoclax-based regimens and cBTK Increased resistance to chemoimmunotherapy and targeted therapies; significantly shortened TTFT and time to next treatment (TTNT) and potentially increased risk for Richter transformation Low burden variant allele frequencies (VAF, <10%) may behave similar to wild type (WT)
		TP53 mutation^d without del(17p)	TP53 mutation in the absence of del(17p) is associated with shortened PFS and OS. However, PFS and OS outcomes on treatment with TP53 mutation but in absence of del(17p) may be more favorable than with

			concurrent TP53 mutation and del(17p)
	CpG-stimulated metaphase karyotype^f	Complex karyotype (CK) (≥3 unrelated clonal chromosome abnormalities in more than one cell on karyotype)	Inferior survival and shorter time to disease progression with chemoimmunotherapy, time-limited venetoclax based regimens, and cBTKi High CK (≥5 unrelated chromosomal abnormalities) is an adverse prognostic factor independent of clinical stage, IGHV mutation status, del(17p) and/or TP53 mutation
	Serum Testing	Beta-2 Microglobulin (B2M) (can be affected by renal dysfunction in a CLL-independent manner)	Correlates with CLL/SLL disease burden and retains independent prognostic significance in multivariate models Elevated levels are associated with overall response, treatment free intervals, and OS in patients treated with frontline chemoimmunotherapy Reduction in levels associated with prolonged PFS in patients treated with ibrutinib
^bPrognostic significance may be dependent on the percentage of malignant cells with the deletion; prognosis is more favorable when the percentage of cells with del(17p) is low. ^cIGHV gene usage involving VH3-21 is considered higher risk regardless of the IGHV mutation status. IGHV4–39 usage is associated with a higher risk for Richter's transformation. ^dPatients can have TP53 mutations independent of del(17p). TP53 mutation status also provides additional prognostic information in addition to the cytogenetic abnormalities detected by FISH. ^eHazard ratios (HR) for PFS and OS with TP53 mutation on treatment versus TP53 WT are higher with chemoimmunotherapy compared to targeted therapies. ^fConventional metaphase FISH is difficult in CLL due to the very low in vitro proliferative activity of the leukemic cells. CK is based on results of metaphase karyotyping of CpG-stimulated CLL cells. Interphase FISH is the standard method to detect specific chromosomal abnormalities that may have prognostic significance. CpG oligonucleotide stimulation can be utilized to enhance metaphase cytogenetics. ^gCutoff values vary between institutions and studies. CLL-IPI utilizes a cutoff of >3.5 mg/L; other studies use a cutoff of 4 mg/L in patients treated with chemoimmunotherapy			
Chronic Myeloid Leukemia (CML)	Autologous HSCT Investigational Autologous HSCT is considered investigational for the treatment of chronic myeloid leukemia (CML) because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT		

	Medically Necessary - Allogeneic HSCT using a myeloablative conditioning regimen may be considered medically necessary for the treatment of CML. Reduced Intensity HSCT Allogeneic HSCT using a reduced intensity conditioning regimen (non-myeloablative) may be considered medically necessary for the treatment of CML who meet the above criterion for an allogeneic HSCT but who are not considered candidates for a myeloablative conditioning allogeneic HSCT. Note: <i>Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation but would not tolerate standard myeloablative conditioning regimen. This may include the individual's fitness, comorbidities, and end-organ reserve (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).</i> Investigational - Allogeneic HSCT is considered investigational when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes. Definitions Karnofsky Performance Status is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in the clinical trial. 100 – normal no complaints 90 – able to carry on normal activities. Minor signs or symptoms of disease 80 – normal activity with effort 70 – care for self, unable to carry on normal activity or do active work 60 – requires occasional assistance, but able to care for most of his or her needs 50 – requires considerable assistance and frequent medical care 40 – disabled requires special care and assistance 30 – severely disabled, hospitalization indicated though death not imminent 20 – very sick, hospitalization necessary, active supportive treatment necessary 10 – moribund (approaching death, deepening stupor and coma) Myeloablative is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments. Non-myeloablative (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells. Definitions of Advanced Phase CML Clinical trials in the TKI era have mostly utilized the modified MD Anderson Cancer Center (MDACC) criteria or the International Bone Marrow Transplant Registry (IBMTR) criteria. The use of the International Consensus Classification (ICC)4 or the World Health Organization (WHO) criteria for the diagnosis of AP-CML and BP-CML is not recommended. <table border="1"> <tr> <td>AP-CML^a</td><td>BP-CML</td></tr> <tr> <td>Modified MDACC Criteria</td><td>IBMTR criteria</td></tr> </table>	AP-CML^a	BP-CML	Modified MDACC Criteria	IBMTR criteria
AP-CML^a	BP-CML				
Modified MDACC Criteria	IBMTR criteria				

	- Peripheral blood myeloblasts $\geq 15\%$ and $< 30\%$ - Peripheral blood myeloblasts and promyelocytes combined $\geq 30\%$ - Peripheral blood basophils $\geq 20\%$ - Platelet count $\leq 100 \times 10^9 /L$ unrelated to therapy - Additional clonal cytogenetic abnormalities in Ph+ cells^b Myeloid BP-CML $\geq 30\%$ blasts in the blood, marrow, or both - Extramedullary infiltrates of leukemic cells Lymphoid BP-CML - Any increase I lymphoblasts in peripheral blood or bone marrow ^aSokal criteria and IBMTR criteria are historically used when allogeneic HCT is the recommended treatment option. ^bThe prognostic significance of ACAs in Ph-positive cells (ACA/Ph+) is related to the specific chromosomal abnormality and often other features of accelerated phase. The presence of "major route" ACA/Ph+ (trisomy 8, isochromosome 17q, second Ph, trisomy 19, and chromosome 3 abnormalities) at diagnosis may have a negative prognostic impact on survival.
Hodgkin Lymphoma	Autologous HSCT Medically Necessary - Autologous HSCT may be considered medically necessary for the treatment Hodgkin lymphoma (HL) in individuals with primary refractory or relapsed disease. Note: <i>Primary refractory disease refers to inability to achieve complete remission (CR) following front-line therapy.</i> Investigational - Autologous HSCT is considered investigational for the treatment of HL not meeting the above criteria and including but not limited to, the following indications because the evidence is insufficient in demonstrating improved net health outcomes: - A second autologous HSCT for relapsed disease after a prior autologous HSCT. - Tandem autologous HSCT Allogeneic HSCT Medically Necessary Allogeneic HSCT using either myeloablative or reduced intensity conditioning regimens (non-myeloablative) may be considered medically necessary for the following: - Individuals with HL for the treatment of primary refractory or relapsed disease. - Individuals with relapsed HL after prior autologous HSCT that was used to treat primary refractory or relapsed disease. Note: <i>Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic HSCT, but would not tolerate standard myeloablative conditioning regimen. This may include the individuals fitness, comorbidities and end-organ reserve (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).</i> Investigational - Allogeneic HSCT for the treatment of HL is considered investigational when the above criteria is not met, and including but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission because the evidence is insufficient in demonstrating improved net health outcomes. Definitions

Karnofsky Performance Status is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status

- may be used to determine the individual's prognosis, to measure changes in an individual's ability to function or to decide whether an individual could be included in a clinical trial.
 - 100 – normal no complaints
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- **Myeloablative** is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments.
- **Non-myeloablative** (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.
- **Poor-risk relapsed Hodgkin lymphoma** may be defined as 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites.
- **Primary refractory Hodgkin lymphoma** may be defined as disease regression less than 50% after 4 to 6 cycles of doxorubicin-containing chemotherapy or disease progression during induction or within 90 days after the end of the first-line treatment.

Staging and Risk Classification of Classic Hodgkin Lymphoma (CHL)^m

Stage	Bulky Mediastinal Disease ^m or >10 cm Adenopathy	# of Nodal Regions	ESR ≥ 50 mm/hr	E-Lesion(s)	Type
IA/IIA					
	No	≤2	No	No	Favorable Disease by GHSG Criteria
	No	≤3	No	Yes/No	Favorable Disease by EORTC Criteria
	Yes	Any	Yes/No	Yes/No	Unfavorable Disease
IB/IIB	Yes/No	Any	Yes/No	Yes/No	Unfavorable Disease
III-IV	Yes/No	Any	N/A	Yes/No	Advanced Disease

^mFor definitions of bulky disease see table below

	Unfavorable Risk Factors for Stage I-II Hodgkin Lymphoma <table><tr><th>Risk Factor</th><th>GHSG</th><th>EORTC</th><th>NCCN</th></tr><tr><td>Age</td><td></td><td>≥50 years</td><td></td></tr><tr><td>ESR and B symptoms</td><td>>50 mm/hr if A; >30 mm/hr if B</td><td>>50 mm/hr if A; >30 mm/hr if B</td><td>≥50 mm/hr or any B symptoms</td></tr><tr><td>Mediastinal massⁿ</td><td><u>MMR >0.33</u></td><td>MTR >0.35</td><td>MMR >0.33</td></tr><tr><td># Nodal regions</td><td>≥3*</td><td>≥4*</td><td>≥4</td></tr><tr><td>E lesion</td><td>Any</td><td></td><td></td></tr><tr><td>Bulkyⁿ</td><td></td><td></td><td>>10 cm</td></tr></table> *Note that the EORTC includes the infraclavicular/subpectoral area with axilla while the GHSG includes it with the cervical. Both EORTC and GHSG combine the mediastinum and bilateral hila as a single region. ⁿThe definition of mediastinal bulk is best assessed with a standard CXR, as practice-changing studies utilized this staging modality. If a staging CXR is not obtained, disease bulk can also be assessed with CT. In this scenario a single mass or nodal conglomerate measuring (in any direction) >1/3 the maximum transverse diameter of the chest, or any tumor mass or nodal conglomerate > 10cm (also measured in any direction) should be considered “bulky”	Risk Factor	GHSG	EORTC	NCCN	Age		≥50 years		ESR and B symptoms	>50 mm/hr if A; >30 mm/hr if B	>50 mm/hr if A; >30 mm/hr if B	≥50 mm/hr or any B symptoms	Mediastinal mass ⁿ	<u>MMR >0.33</u>	MTR >0.35	MMR >0.33	# Nodal regions	≥3*	≥4*	≥4	E lesion	Any			Bulky ⁿ			>10 cm
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Multiple Myeloma	Autologous HSCT Medically Necessary - A single autologous HSCT may be considered medically necessary for the treatment of multiple myeloma (MM) following primary therapy. - Autologous HSCT may be considered medically necessary for the treatment of progressive or relapsed MM who did not receive an autologous HSCT as part of their initial treatment. - A repeat autologous HSCT may be considered medically necessary to treat responsive MM that has relapsed after a complete response (CR) or very good partial response (VGPR) following an initial autologous HSCT. Investigational - Autologous HSCT is considered investigational for the treatment of MM not meeting the above criteria to include a third autologous HSCT for salvage therapy. The evidence is insufficient in demonstrating improved net health outcomes. *Tandem Autologous Transplantation Medically Necessary *Tandem autologous HSCT may be considered medically necessary to treat multiple myeloma after primary therapy. *Tandem autologous HSCT with an initial round of autologous HSCT followed by non-marrow-ablative conditioning regimen and allogeneic hematopoietic stem cell transplantation (i.e., reduced intensity conditioning transplant) may be considered medically necessary to treatment individuals with newly diagnosed multiple myeloma. *Tandem autologous HSCT may be considered medically necessary in individuals who fail to achieve at least a near complete response (CR) or very good partial response (VGPR) after the first transplant in the tandem sequence. <i>*Tandem transplantation refers to a planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat</i>																												

	<i>transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.</i> Investigational *Tandem autologous HSCT is considered investigational for the treatment of MM when the above criteria is not met to include a third HSCT for salvage therapy because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary - Allogeneic HSCT may be considered medically necessary for the treatment of MM following a single or tandem autologous hematopoietic stem cell transplantation for the treatment of progressive disease (PD). Note: Myeloablative allogeneic HSCT is preferred but if based on the individuals fitness, comorbidities and end-organ reserve (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, Karnofsky Performance Status score) a non-myeloablative conditioning regimen allogeneic HSCT (i.e., reduced-intensity conditioning regimen) may be utilized and considered medically necessary if meets the above criteria for HSCT. Investigational - Allogeneic HSCT myeloablative or non-myeloablative is considered investigational not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. Definitions Myeloablative is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments. Non-myeloablative (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells. Response criteria for multiple myeloma by International Myeloma Working Group (IMWG) (Revised based on the new criteria by International Working Group [IMWG]) <table border="1"> <thead> <tr> <th colspan="2">IMWG Criteria for Response Assessment Including Criteria for Minimal Residual Disease (MRD)</th></tr> <tr> <th>Response Category</th><th>Response Criteria</th></tr> </thead> <tbody> <tr> <td colspan="2">IMWG MRD Criteria (requires a complete response as defined below)</td></tr> <tr> <td>Sustained MRD-negative</td><td>MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years).^b</td></tr> <tr> <td>Flow MRD-negative</td><td>Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent</td></tr> </tbody> </table>	IMWG Criteria for Response Assessment Including Criteria for Minimal Residual Disease (MRD)		Response Category	Response Criteria	IMWG MRD Criteria (requires a complete response as defined below)		Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years). ^b	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent
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		method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
	Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher.
	Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG-PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue.
	Standard IMWG Response Criteria	
	Stringent complete response	Complete response as defined below plus normal FLC ratio ^g and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ / λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ patients, respectively, after counting ≥ 100 plasma cells). ^h
	Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates.
	Very good partial response (VGPR)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h.
	Partial response	$\geq 50\%$ reduction of serum M-protein please reduction in 24 h urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$. In addition to these criteria if present at baseline, a $\geq 50\%$ reduction in the size (sum of the products of the maximal perpendicular diameters (SPD) of measure lesions) of soft tissue plasmacytomas is also required.

	Minimal response	≥ 25% but ≤49% reduction of serum M-protein and reduction in 24 h urine M-protein by 50%-89%. In addition to the above listed criteria, if present at baseline, a 25%-49% reduction in SPD of soft tissue plasmacytomas is also required.
	Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
	Progressive disease	Any one or more of the following criteria: • Increase of 25% from lowest confirmed response value in one or more of the following criteria: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL); • Serum M-protein increase ≥ 1g/dL, if the lowest M component was ≥ 0.5 g/dL; • Urine M-protein (absolute increase must be ≥ 200 mg/24 h. • In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL); • In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥ 10%); • Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion > 1 cm in short axis; • 50% increase in circulating plasma cells (minimum of 200 cells per uL) if this is the only measure of disease.
	Clinical relapse	Clinical relapse requires one or more of the following criteria: • Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features] related to the underlying clonal plasma-cell

		proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and $\geq 1\text{cm}$) increase as measured serially by the SPD of the measurable lesion; • Hypercalcemia ($>11\text{ mg/dL}$); • Decrease in hemoglobin of $\geq 2\text{ g/dL}$ not related to therapy or other non-myeloma related conditions; • Rise in serum creatinine by 2 mg/dL or more from the start of therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein.
	Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one of the following criteria: • Reappearance of serum or urine M-protein by immunofixation or electrophoresis;ⁱ • Developmental of $\geq 5\%$ plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above).
	Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: • Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; • Development of $\geq 5\%$ clonal plasma cells in the bone marrow; • Appearance of any other sign of progression (i.e. new plasmacytoma, lytic bone lesion; or hypercalcemia).
	^bSustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative)	

	^hPresence/absence of clonal cells on immunohistochemistry is based upon the κ / λ ratio. An abnormal κ / λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is $\kappa / \lambda \geq 4:1$ or $<1:2$ ⁱSpecial attention should be given to the emergence of a difference monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patient receiving monoclonal antibodies should be differentiated from the therapeutic antibody.
Myeloid/ Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes	WHO classification in both 2022 International Consensus Classification (ICC) and 2022 5th Edition of the WHO classification the major category name for these diseases has changed to myeloid/lymphoid neoplasms with eosinophilia with tyrosine kinase gene fusions. It now includes gene rearrangements PDGFRA, FGFR1, Jak2, FLT3 and ETV6::ABL1. The WHO 5th Edition additional includes other defined fusions including, ETV6::FGFR2; ETV6::LYN; ETV6::NTRK3; RANBP2::ALK; BCR::RET; and FGFR1OP::RET. Clonal eosinophilia associated with tyrosine kinase (TK) gene fusions (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 phenotype acute leukemias/lymphomas. Diagnosis and Staging Considerations in Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions^{e,p}: - Chronic phase may present in the BM (bone marrow) or peripheral blood (PB) as an MPN as an MPN (myeloproliferative neoplasm) or MDS (myelodysplastic syndrome)/MPN with or without eosinophilia, and the BM may exhibit an atypical mast cell proliferation, often in an interstitial pattern (not typical aggregates found in SM [systemic mastocytosis]). - Blast phase ($\geq 20\%$ blasts) may present in the BBM or PB as AML, ALL,^o or mixed phenotype acute leukemias. EMD (extramedullary disease) presents a blast phase component. Blast phase may also present as EMD with an “MPN-like” picture in the blood and marrow. - There is no current definition for “accelerated phase” disease; similar to myeloid neoplasms such as CML, 10%-19% blasts in the BM or PB have been used to define “accelerated phase.” - EMD may present extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemias. EMD may present alone, or with chronic or blast phase disease involving the BM or PB. Lineage involvement of the EMD may be different from the lineage involving the BM or PB. - The clinical presentation of these disease partly reflects the fusion partner gene for the TK. This is best exemplified by the diverse phenotypes in FGFR1-rearranged diseases. Step 1. Disease Extent: Does disease involvement includes BM, PB or EMD or ALL? If clinical suspected, imaging to identify EMD Step 2. Disease Stage: Is chronic phase or blast phase disease present in the BM or PB? (If present, EMD represents a blast phase component): Staging of BM or PB to determine if chronic vs. blast phase^o Step 3. Disease Lineage(s): What are the disease lineage(s) of the BM or PB and EMD components? Immunophenotyping to determine lineage in BM or BP and/or EMD

	^eThe diagnosis requires a combination of histopathologic, clinical, laboratory, and cytogenetic/molecular analyses. ^oThe differential diagnosis of JAK2 and ABL1 fusions with a phenotype of ALL includes Ph-like ALL ^pEosinophilia is not always present. Autologous HSCT Investigational - Autologous HSCT is considered investigational for the treatment of myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase fusion genes because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary - Allogeneic HSCT may be considered medically necessary for the treatment of myeloid/lymphoid neoplasms with eosinophilia in blast phase* with one of the following rearrangements FGFR1, JAK2, FLT3 or ABL1 for relapsed or disease progression. <i>(Blast Phase $\geq$ 20% blasts in bone marrow and/or peripheral blood (may present as AML, ALL or mixed phenotype acute leukemias) and/or extramedullary myeloid sarcoma, T-cell or B-cell lymphoblastic lymphoma, or myeloid/T-cell or B-cell lymphoid mixed phenotype acute leukemia. Blast phase may also present as an EMD [extra medullary disease] with an “myeloproliferative neoplasm-like” picture in blood and marrow) receiving TKI induction chemotherapy to be followed by allogeneic hematopoietic stem cell transplantation.)</i> - Allogeneic HSCT may be considered medically necessary for the treatment of myeloid/lymphoid neoplasms with eosinophilia with one of the following rearrangements PDGFRA or PDGFRB for relapsed disease following a complete hematologic response ([CHR] – defined as the normalization of peripheral blood counts and eosinophilia) and complete cytogenetic response (CCyR). Investigational - Allogeneic HSCT is considered investigational for indications not meeting the criteria above because the evidence is insufficient in demonstrating improved net health outcomes.
Myelodysplastic Syndromes (MDS) and Myeloproliferative Neoplasms	Myelodysplastic Syndromes (MDS) Note: Information is from NCCN Current Guideline 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 of MDS to evolve into acute myeloid leukemia (AML). The category of myelodysplastic/myeloproliferative neoplasm (MDS/MPN) was added to the 2008 update of the WHO classification of myeloid neoplasm. In the 2022 updated, this category chronic myelomonocytic leukemia (CMML)-1 and CMML-2, MDS/MPN and neutrophilia (previously aCML), MDS/MPN with SF3B1 mutation and thrombocytosis (previously MDS/MPN with ring sideroblasts [RS] and thrombocytosis), and MDS/MPN NOS (previously MDS/MPN unclassifiable). Juvenile myelomonocytic leukemia (JMML) is classified as a myeloproliferative neoplasm. (See also below table for 2022 WHO Classification)

	Myelofibrosis (MF) Note: Information is from NCCN Current Guideline Myelofibrosis (MF) can present as a de novo disorder primary myelofibrosis (PMF), or it can develop from the progression of polycythemia vera (PV) and essential thrombocythemia (ET) (Post-PV MF or Post ET MF). Autologous HSCT Investigational - Autologous HSCT is considered investigational for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms (e.g., myelofibrosis) because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary - Allogeneic HSCT may be considered medically necessary for the treatment of juvenile myelomonocytic leukemia (JMML). - Allogeneic HSCT may be considered medically necessary for the treatment of chronic myelomonocytic leukemia (CMML). - Allogeneic HSCT may be considered medically necessary for the treatment of individuals who have myelodysplastic disease with an intermediate IPSS (International Prognostic Scoring System) overall score of 1.5 to 2.0 or high IPPS overall score of ≥ 2.5; or an intermediate IPSS-R (Revised International Prognostic Scoring System) overall score of $>3.0 - \leq 4.5$ or high IPSS-R overall score of $>4.5 - \leq 6.0$, or very high IPSS-R overall score of > 6.0; or an intermediate WHO-Based Prognostic Scoring System (WPSS) overall score of 2, or high WPSS overall score 3-4, or a very high WPSS overall score of 5-6 and have not responded to prior therapy. - A second allogeneic HSCT may be considered medically necessary for the treatment of relapsed myelodysplastic disease after a remission following the first allogeneic HSCT. - Allogeneic HSCT may be considered medically necessary for the treatment of myeloproliferative neoplasms (e.g., myelofibrosis (MF) in intermediate and high-risk individuals. (IPSS [International Prognostic Scoring System: intermediate-risk 1-2 or high-risk ≥ 3] DIPSS [Dynamic International Prognostic Scoring System] intermediate risk 1-4 points; high-risk ≥ 5 points]) Reduced Intensity HSCT Reduced intensity (non-myeloablative) conditioning allogeneic HSCT may be considered medically necessary for the treatment of myelodysplastic syndromes and myeloproliferative neoplasms (e.g., myelofibrosis) meeting the above criteria for allogeneic HSCT for medical reasons would be unable to tolerate a myeloablative conditioning regimen. Note: Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) but would not tolerate standard myeloablative conditioning regimen. This may include the individuals fitness, comorbidities and end-organ reserve (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) Investigational - Allogeneic HSCT is considered investigational for indications not meeting the criteria above because the evidence is insufficient in demonstrating improved net health outcomes. Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) Classification
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WHO 2016	WHO 2022	ICC	Features
Chronic myelomonocytic leukemia (CMML)	CMML-1 ^k CMML-2 ^l	CMML-myelodysplastic (CMML-MD) ^m CMML-myeloproliferative (CMML-MP) ^m	≥0.5 absolute monocyte count (AMC) ≥10% monocytes Clonality ^p
Atypical chronic myeloid leukemia (aCML) (BCR::ABL negative)	MDS/MPN and neutrophilia	aCML	WBC ≥13K, dysplastic granulocytosis, ≥10% granulocytic precursor cells ^q mSETBP1 ± mASXL1
MDS/MPN with ring sideroblasts (RS) and thrombocytosis (T)	MDS/MPN with mSF3B1 and thrombocytosis	MDS/MPN-T-SF3B1 ⁿ MDS/MPN-RS-T, NOS	Platelets ≥450K
MDS/MPN unclassifiable (MDS/MPN-U)	MDS/MPN not otherwise specified (NOS)	MDS/MPN NOS	Platelets ≥450K or WBC ≥13K
		MDS/MPN with i(17q) ^o	WBC ≥13K, dysgranulopoiesis
Juvenile myelomonocytic leukemia (JMML)	JMML (now MPN)	Pediatric disorder and/or germline mutation-associated disorders	>90% RAS pathway activation abnormality ^r

^k< 10% bone marrow blasts or blast equivalent;

^l10% to <20% bone marrow blasts or blast equivalents;

^m CMML-MD=WBC ≤ 13K, CMML-MP=WBC >13K; ⁿ VAF >10%;

^p 80%–90% with ≥ 1 mutation in SRSF2, TET2, and/or ASXL1. Substantial frequency of SETBP1, NRAS/KRAS, RUNX1, CBL, and EZH2 mutations;

^qCraniofacial RAS pathway mutations in NRAS, KRAS, PTPN11, NF1, CBL, or RAS-related genes in >95% patients; no KMT2A rearrangement or -7 cytogenetic abnormality;

WHO 5th Edition Diagnostic Criteria for Polycythemia Vera and Essential Thrombocythemia

Polycythemia Vera (PV)

(Diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion)

- Major criteria
 - Hemoglobin > 16.5 g/dL in men, >16.0 g/dL in women; **OR**
 - Hematocrit > 49% in men, > 48% in women; **OR**
 - Increased cell mass (RCM)

	▪ Bone marrow biopsy showing hypercellularity for age with trilineage growth (pathmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)* ▪ Presence of JAK2V617F or JAK2 exon 12 mutation** • Minor criteria ▪ Subnormal serum erythropoietin (EPO) level *A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin >18.5 g/dl in men or >16.5 g/dl in women) and the presence of a JAK2 V617F or JAK2 exon 12 mutation. However, Initial MF (present in as many as 20% of patients) can only be detected by BM, and this finding may predict a more rapid progression to overt myelofibrosis (post-PV myelofibrosis). **It is recommended to use highly sensitive assays for JAK2 V617F (sensitivity level <1%) and CALR and MPL (sensitivity level 1%-3%) in negative cases, consider searching for non-canonical JAK2 mutations. WHO 5th Edition Diagnostic Criteria for Essential Thrombocythemia (ET) (Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and one minor criteria) • Major criteria ▪ Platelet count $\geq 450 \times 10^9/L$ ▪ Bone marrow (BM) biopsy proliferation with mature cytology, hyperlobulated nuclei and in loose clusters, BM fibrosis absent or $\leq$ grade 1 ▪ Not meeting International Consensus Classification (ICC) criteria for other myeloid neoplasms including PV, Prefibrotic and CML ▪ Presence of JAK2, CALR, or MPL mutated • Minor criterion ▪ Other clonal marker present ▪ No evidence of reactive thrombocytosis IWG-MRT Diagnostic Criteria for Post-Polycythemia Vera (PV) and Post-Essential (ET) Myelofibrosis Criteria for Post-PV Myelofibrosis • Required criteria ▪ Documentation of a previous diagnosis of PV as defined by the WHO criteria ▪ Bone marrow fibrosis grade $\geq 2^b$ ^bDiffuse often coarse fiber network with or without evidence of collagenization (trichrome stain). • Additional criteria (two are required) ▪ Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytes ▪ A leukoerythroblastic peripheral blood picture ▪ Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly ▪ Development of $\geq 1\%$ of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5 degrees Celsius)
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	Criteria for Post-ET Myelofibrosis • Required criteria ▪ Documentation of a previous diagnosis of ET as defined by WHO criteria ▪ Bone marrow fibrosis grade $\geq 2^b$ • Additional criteria (two are required) ▪ Anemia and $\geq 2\text{g/dl}$ decrease from baseline hemoglobin level ▪ A leucoerythroblastic peripheral blood smear ▪ Increasing splenomegaly defined as either an increase in palpable splenomegaly of $\geq 5\text{cm}$ (distance of the tip of the spleen from the left cost margin) or the appearance of a newly palpable splenomegaly ▪ Increased LDH (above reference level) ▪ Development of ≥ 1 of 3 constitutional symptoms: $> 10\%$ weight loss in 6 months, night sweats, unexplained fever (37.5 degrees Celsius) ^bDiffuse often coarse fiber network with or without evidence of collagenization (trichrome stain). 2022 WHO Classification for Myeloid Neoplasm and Histiocytic/Dendritic Neoplasms <table><tr><td>Clonal Hematopoiesis (CH) • CH of indeterminate potential (CHIP) • Clonal cytopenia of undetermined significance (CCUS) </td></tr><tr><td>Myeloproliferative Neoplasms (MPN) • Chronic myeloid leukemia (CML), BCR-ABL1⁺ • Chronic neutrophilic leukemia (CNL) • Polycythemia vera • Primary myelofibrosis (PMF) • Essential thrombocythemia • Chronic eosinophilic leukemia • MPN, not otherwise specified • Juvenile myelomonocytic leukemia </td></tr><tr><td>Mastocytosis • Cutaneous mastocytosis • Systemic mastocytosis • Mast cell sarcoma </td></tr><tr><td>Childhood Myelodysplastic Syndrome (MDS) • Childhood MDS with low blasts ▪ Hypocellular ▪ Not otherwise specified • Childhood MDS with increased blasts </td></tr><tr><td>Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions (MLN-TK)</td></tr><tr><td>Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) • Chronic myelomonocytic leukemia (CMML) • MDS/MPN with neutrophilia • MDS/MPN with <i>SF3B1</i> mutation and thrombocytosis • MDS/MPN, not otherwise specified </td></tr><tr><td>Myelodysplastic Neoplasms (MDS)</td></tr></table>	Clonal Hematopoiesis (CH) • CH of indeterminate potential (CHIP) • Clonal cytopenia of undetermined significance (CCUS)	Myeloproliferative Neoplasms (MPN) • Chronic myeloid leukemia (CML), BCR-ABL1⁺ • Chronic neutrophilic leukemia (CNL) • Polycythemia vera • Primary myelofibrosis (PMF) • Essential thrombocythemia • Chronic eosinophilic leukemia • MPN, not otherwise specified • Juvenile myelomonocytic leukemia	Mastocytosis • Cutaneous mastocytosis • Systemic mastocytosis • Mast cell sarcoma	Childhood Myelodysplastic Syndrome (MDS) • Childhood MDS with low blasts ▪ Hypocellular ▪ Not otherwise specified • Childhood MDS with increased blasts	Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions (MLN-TK)	Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) • Chronic myelomonocytic leukemia (CMML) • MDS/MPN with neutrophilia • MDS/MPN with <i>SF3B1</i> mutation and thrombocytosis • MDS/MPN, not otherwise specified	Myelodysplastic Neoplasms (MDS)
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Myelodysplastic Neoplasms (MDS)								

	• MDS with defining genetic abnormalities ▪ MDS with low blasts and isolated 5q deletion (MDS-5q) ▪ MDS with low blasts and <i>SF3B1</i> mutation (MDS-<i>SF3B1</i>), or MDS with low blasts and ring sideroblasts ▪ MDS with biallelic <i>TP53</i> inactivation (MDS-bi<i>TP53</i>)																																			
	MDS, Morphologically Defined • MDS with low blasts (MDS-LB) • MDs, hypoplastic (MDS-h) • MDs with increased blasts (MDS-IB) ▪ MDS-IB1 ▪ MDS-IB2 ▪ MDS with fibrosis (MDS-f)																																			
	Acute Myeloid Leukemia (AML) • AML with defining genetic abnormalities • AML, defined by differentiation																																			
	Secondary Myeloid Neoplasms • Myeloid neoplasms post cytotoxic therapy • Myeloid neoplasms associated with germline predisposition																																			
	Dendritic Cell and Histiocytic Neoplasms • Plasmacytoid dendritic cell neoplasms • Langerhans cell and other dendritic cell neoplasms • Histiocytic neoplasms																																			
	Acute Leukemias of Ambiguous Lineage (ALAL) • ALAL with defining genetic abnormalities • ALAL, immunophenotypically defined																																			
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	Prognostic Scoring Systems																																			
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	<table><tr><th colspan="6">Survival and AML Evolution</th></tr><tr><th></th><th colspan="5">Score Value</th></tr><tr><th>Prognostic variable</th><th>0</th><th>0.5</th><th>1.0</th><th>1.5</th><th>2.0</th></tr><tr><td>Marrow blasts (%)^b</td><td><5</td><td>5-10</td><td></td><td>11-20</td><td>21-30</td></tr><tr><td>Karyotype^c</td><td>Good</td><td>intermediate</td><td>Poor</td><td></td><td></td></tr><tr><td>Cytopenia^d</td><td>0/1</td><td>2/3</td><td></td><td></td><td></td></tr></table>		Survival and AML Evolution							Score Value					Prognostic variable	0	0.5	1.0	1.5	2.0	Marrow blasts (%) ^b	<5	5-10		11-20	21-30	Karyotype ^c	Good	intermediate	Poor			Cytopenia ^d	0/1	2/3	
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^a IPSS should be used for initial prognostic and planning purposes. WPSS permits dynamic estimation of prognosis at multiple time points during the course of MDS																																				
^b Patients with 20%-29% blasts may be considered to have MDs (FAB) or AL (WHO)																																				

	^cCytogenetics: Good=normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (>3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. [This excludes karyotypes t(8,21), inv16, and t(15;17), which are considered to AML and not MDS.] ^dCytopenias: neutrophil count <1800/mcL, platelets <100,000/mcL, hb ,10 g/dL Revised International Prognostic Scoring System (IPSS-R) <table><tr><th></th><th colspan="7">Score Value</th></tr><tr><th>Prognostic variable</th><th>0</th><th>0.5</th><th>1</th><th>1.5</th><th>2</th><th>3</th><th>4</th></tr><tr><td>Cytogenetic^e</td><td>Very good</td><td></td><td>Good</td><td></td><td>Intermediate</td><td>Poor</td><td>Very poor</td></tr><tr><td>Marrow blasts %</td><td>≤2</td><td></td><td>>2-<5</td><td></td><td>5-10</td><td>>10</td><td></td></tr><tr><td>Hemoglobin</td><td>≥10</td><td></td><td>8-<10</td><td><8</td><td></td><td></td><td></td></tr><tr><td>Platelets</td><td>≥100</td><td>50-<100</td><td><50</td><td></td><td></td><td></td><td></td></tr><tr><td>ANC</td><td>≥0.8</td><td><0.8</td><td></td><td></td><td></td><td></td><td></td></tr></table> ^eCytogenetic risks: Very good = - Y, del(11q); Good = normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate – del(7q) +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; very poor = complex: >3 abnormalities Definitions • Karnofosky Performance Status is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in a clinical trial. ▪ 100 – normal no complaints ▪ 90 – able to carry on normal activities. Minor signs or symptoms of disease ▪ 80 – normal activity with effort ▪ 70 – care for self, unable to carry on normal activity or do active work ▪ 60 – requires occasional assistance, but able to care for most of his or her needs ▪ 50 – requires considerable assistance and frequent medical care ▪ 40 – disabled requires special care and assistance ▪ 30 – severely disabled, hospitalization indicated though death not imminent ▪ 20 – very sick, hospitalization necessary, active supportive treatment necessary ▪ 10 - moribund (approaching death, deepening stupor and coma) • Myeloablative is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments. • Non-myeloablative (also knowns as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.		Score Value							Prognostic variable	0	0.5	1	1.5	2	3	4	Cytogenetic ^e	Very good		Good		Intermediate	Poor	Very poor	Marrow blasts %	≤2		>2-<5		5-10	>10		Hemoglobin	≥10		8-<10	<8				Platelets	≥100	50-<100	<50					ANC	≥0.8	<0.8					
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Non-Hodgkin Lymphoma	Modified REAL Classification of Lymphoproliferative Diseases (NCI, 2021): Non-Hodgkin Indolent lymphoma/leukemia																																																								

- A. Follicular lymphoma (follicular small cleaved cell [grade 1], follicular mixed small cleaved and large cell [grade 2], diffuse small cleaved cell)
- B. Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) (**Note: Do not utilize the NHL criteria for Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) refer to specific criteria above for this indication**)
- C. Lymphoplasmacytic lymphoma (Waldenström's macroglobulinemia) (**Note: this is for Waldenström's macroglobulinemia transformed to lymphoplasmacytic lymphoma**)
- D. Extranodal marginal zone B-cell lymphoma (MALT lymphoma)
- E. Nodal marginal zone B-cell lymphoma (monocytoid B-cell lymphoma)
- F. Splenic marginal zone lymphoma (splenic lymphoma with villous lymphocytes)
- G. Hairy cell leukemia
- H. Mycosis fungoides/Sézary syndrome
- I. T-cell granular lymphocytic leukemia
- J. Primary cutaneous anaplastic large cell lymphoma/lymphomatoid papulosis (CD30+)
- K. Nodular lymphocyte predominant Hodgkin lymphoma

Aggressive lymphoma/leukemia

- A. Diffuse large cell lymphoma (includes diffuse mixed cell, diffuse large cell, immunoblastic, T-cell rich large B-cell lymphoma)
Distinguish:
 - 1. Mediastinal large B-cell lymphoma
 - 2. Follicular large cell lymphoma (grade 3)
 - 3. Anaplastic large cell lymphoma (CD30+)
 - 4. Extranodal NK/T-cell lymphoma, nasal type/aggressive NK-cell leukemia/blastic NK-cell lymphoma
 - 5. Lymphomatoid granulomatosis (angiocentric pulmonary B-cell lymphoma)
 - 6. Angioimmunoblastic T-cell lymphoma
 - 7. Peripheral T-cell lymphoma, unspecified
 - a. Subcutaneous panniculitis-like T-cell lymphoma
 - b. Hepatosplenic T-cell lymphoma
 - 8. Enteropathy-type T-cell lymphoma
 - 9. Intravascular large B-cell lymphoma
- B. Burkitt's lymphoma/Burkitt's cell leukemia/Burkitt's-like lymphoma
- C. Precursor B- or T-cell lymphoblastic lymphoma/leukemia
- D. Primary central nervous system (CNS) lymphoma
- E. Adult T-cell leukemia/lymphoma (HTLV 1+)
- F. Mantle cell lymphoma
- G. Polymorphic post-transplantation lymphoproliferative disorder
- H. AIDS-related lymphoma
- I. True histiocytic lymphoma
- J. Primary effusion lymphoma
- K. B- or T-cell prolymphocytic leukemia
- L. Plasmablastic lymphoma

Allogeneic HSCT

A. Allogeneic myeloablative HSCT may be considered **medically necessary** to treat individuals with non-Hodgkins lymphoma (NHL) subtypes classified by the National Cancer Institute (NCI) modified REAL classification system as "Indolent" for any one of the following:

- As salvage therapy for individuals who do not achieve complete remission (CR) after first-line therapy (induction) with a full course of standard-dose chemotherapy.
- To achieve or consolidate CR for those individuals in a first or subsequent chemosensitive relapse, whether or not their lymphoma has transformed to a higher grade.

B. Allogeneic myeloablative HSCT may be considered **medically necessary** to treat individuals with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL classification system as "Aggressive" (except Mantle Cell Lymphoma, Mature T-Cell Or Natural Killer Cell Neoplasms to include Peripheral T-cell Neoplasms) for any one of the following:

	• As salvage therapy for individuals who do not achieve a CR after first-line treatment (induction) with a full course of standard-dose chemotherapy. • To achieve or consolidate a CR for those in chemosensitive first or subsequent relapse. • To consolidate a first CR in individuals with diffuse large B-cell lymphoma (DLBCL), with an age adjusted International Prognostic Index Score (<i>see below</i>) that predicts high or high-intermediate risk of relapse. Autologous HSCT Autologous HSCT may be considered medically necessary to treat individuals with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL classification system as “Indolent” for any one of the following: • As salvage therapy for individuals who do not achieve complete remission (CR) after first line therapy (induction) with a full course of standard dose chemotherapy. • To achieve or consolidate CR for those individuals in a first or subsequent chemosensitive relapse, whether or not their lymphoma has transformed to a higher grade. Mature T-cell or Natural Killer Cells/Peripheral T-Cell Neoplasms Allogeneic HSCT • Allogeneic myeloablative HSCT may be considered medically necessary for individuals with “Aggressive” NHL subtypes mature T-cell or natural killer cell/peripheral T-cell neoplasms classified by the National Cancer Institute (NCI) modified REAL classification system as salvage therapy (<i>see definition below</i>). Autologous HSCT • Autologous HSCT may be considered medically necessary for individuals with “Aggressive” NHL subtypes (includes ALCL, ALK positive) mature T-cell or natural killer cell/peripheral T-cell neoplasms classified by the National Cancer Institute (NCI) modified REAL classification system to consolidate a first CR. • Autologous HSCT may be considered may be considered medically necessary for individuals with “Aggressive” NHL subtypes mature T-cell or natural killer cell/peripheral T-cell neoplasms classified by the National Cancer Institute (NCI) modified REAL classification system as salvage therapy (<i>see definition below</i>). Hepatosplenic T-Cell Allogeneic HSCT • Allogeneic HSCT may be considered medically necessary to consolidate first CR or partial response (PR). Autologous HSCT • Autologous HSCT may be considered medically necessary to consolidate first CR or partial response (PR) if a suitable donor is not available or for individuals who are ineligible for allogeneic HSCT. Mantle Cell Lymphoma Allogeneic HSCT • Allogeneic HSCT may be considered medically necessary for individuals with mantle cell lymphoma as salvage therapy (<i>see definition below</i>). Autologous HSCT
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- Autologous HSCT may be considered **medically necessary** for individuals with mantle cell lymphoma to consolidate first CR.

Reduced Intensity HSCT

Reduced intensity conditioning (non-myeloablative) allogeneic hematopoietic stem cell transplantation (HSCT) may be considered **medically necessary** for the treatment of non-Hodgkin lymphoma B-cell lymphomas in individuals who meet the criteria for an allogeneic hematopoietic stem cell transplantation (HSCT) above and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen.

***Note:** Reduced intensity conditioning regimens (non-myeloablative allogeneic transplantation) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) but would not tolerate standard myeloablative conditioning regimen. This may include the following age typically > 60 years or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).*

Investigational Allogeneic and Autologous HSCT

Allogeneic and autologous HSCT is considered **investigational** for individuals with NHL for any of the following, because the evidence is insufficient in demonstrating improved net health outcomes:

- When the above criteria is not met.
- As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL.
- To consolidate a first CR for individuals with diffuse large B-cell lymphoma (DLBCL) and an International Prognostic Index Score that predicts low – or low-intermediate risk of relapse (see below).
- To consolidate a first CR for those with NHL subtypes classified by the National Cancer Institute (NCI) modified REAL classification system as “Indolent”.
- Tandem transplants to treat individuals with any stage, grade or subtype of NHL

International Prognostic Index (IPI)

International Prognostic Index: Low Risk = IPI score of zero or one (0-1 points); Low Intermediate Risk = IPS score of two (2 points); High Intermediate Risk = IPI score three (3 points); High Risk = IPI score of four or five (4-5 points)

In this system, one point is given for each of the below characteristics present in the individual, for a total score ranging from 0-5, representing increasing degrees to risk:

- Age greater than 60 years
- Serum lactate dehydrogenase (LDH) concentration greater than normal
- ECOG performance status equal to 2
- Ann Arbor Clinical Stage III or IV (see below)
- Number of involved extranodal disease sites greater than 1.

Age Adjust International Prognostic Index

For this score, all the prognostic factors above, with the exception of age and number of extranodal sites, were given one point, for a score ranging from zero to three, representing increased degrees of risk:

- Low Risk: Age-adjusted IPI Score of Zero (0)
- Low Intermediate Risk: Age-adjusted IPI Score of One (1)
- High Intermediate Risk: Age-adjusted IPI Score of Two (2)
- High Risk: Age-adjusted IPI Score of Three (3)

Eastern Cooperative Oncology Group (ECOG) Performance Status

- 0 – Fully active able to carry on all pre-disease performance without restriction
- 1 – Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
- 2 – Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
- 3 – Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.
- 4 – Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
- 5 – Dead

Staging Lugano Modification of Ann Arbor Staging System (for Primary Nodal Lymphomas) * (NCCN)

Stage	Involvement	Extranodal I Status
Limited Stage I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
Stage II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II Bulky**	II as above with "bulky" disease	Not applicable
Advanced		
Stage III	Nodes on both sides of the diaphragm Nodes above the diaphragm with spleen involvement	Not applicable
Stage IV	Additional non-contiguous extralymphatic involvement	Not applicable

*Extent of disease is determined by PET/CT for avid lymphomas, and CT for non-avid histologies.

Note: Tonsils, Waldeyer's ring, and spleen are considered nodal tissue

**Whether II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors.

Definitions

- **Chemosensitive relapse** is defined as relapsed non-Hodgkin's lymphoma that does not progress during or immediately after standard dose chemotherapy (i.e., achieve stable disease or a partial response).
- **Complete response** (also known as complete remission) is the disappearance of all signs of cancer in response to treatment; this does not always mean the cancer has been cured.

- **Karnofsky Performance Status** is a standard way of measuring the ability of individuals with cancer to perform ordinary tasks. The scores on the scale range from 0 to 100. A higher score means the individual is better able to carry out daily activities. The Karnofsky Performance Status may be used to determine an individual's prognosis, to measure changes in an individual's ability to function, or to decide whether an individual could be included in the clinical trial.
 - 100 – normal no complaints
 - 90 – able to carry on normal activities. Minor signs or symptoms of disease
 - 80 – normal activity with effort
 - 70 – care for self, unable to carry on normal activity or do active work
 - 60 – requires occasional assistance, but able to care for most of his or her needs
 - 50 – requires considerable assistance and frequent medical care
 - 40 – disabled requires special care and assistance
 - 30 – severely disabled, hospitalization indicated though death not imminent
 - 20 – very sick, hospitalization necessary, active supportive treatment necessary
 - 10 – moribund (approaching death, deepening stupor and coma)
- **Myeloablative** is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments.
- **Non-myeloablative** (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.
- **Salvage therapy** is a treatment that is given after the cancer has not responded to other treatments, i.e., refractory or relapsed disease. For individuals with peripheral T-cell lymphoma, salvage therapy may be indicated in individuals who do not achieve a complete response (e.g., achieve only a partial response, have no response, or have progressive disease) with first-line induction chemotherapy (refractory disease) or who relapse after achieving a complete response with first-line induction chemotherapy. For mantle cell lymphoma, salvage therapy may be indicated in individuals with progressive disease with first-line induction chemotherapy (refractory disease) or in individuals who relapse after a complete or partial response after initial induction chemotherapy, or individuals who fail a previous autologous HCT.
- **Transformation describes** a lymphoma whose histologic pattern has evolved to a higher-grade lymphoma. Transformed lymphomas typically evolve from a nodular pattern to a diffuse pattern.

Non-Hodgkin Lymphoma Pediatric Aggressive Mature B-cell Lymphomas Per Current NCCN Guideline: "The NCCN Panel considers the term "Pediatric" to include any patient aged ≤18 years and certain patients >18 years of age. These guidelines are intended to apply to adolescent and young adult (AYA) patients treated in pediatric oncology setting and may include patients up to age 30 years."	The most common types of aggressive mature B-cell lymphomas in children and adolescents are Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL). Medically Necessary - Autologous HSCT or allogeneic HSCT may be considered medically necessary for the treatment of pediatric aggressive non-Hodgkin Lymphoma (pediatric Burkitt lymphoma or pediatric diffuse large B-cell lymphomas) for relapsed or refractory disease. Notes: <i>There is no data to support autologous versus allogeneic HSCT; therefore, the decision to regarding transplant should be based on physician preference.</i> Investigational - Autologous HSCT or allogeneic HSCT is considered investigational for the treatment of pediatric aggressive non-Hodgkin Lymphoma (pediatric Burkitt lymphoma or pediatric diffuse large B-cell lymphomas) when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes. Risk Group Definitions <table border="1" data-bbox="418 814 1429 1455"> <thead> <tr> <th colspan="2">Group Classification</th></tr> </thead> <tbody> <tr> <td>Group A</td><td>Completely resected stage I or Completely resected abdominal stage II</td></tr> <tr> <td>Group B (Low Risk)</td><td>Unresected stage I and non-abdominal stage II or stage III with low LDH (≤ 2 times the upper limit of normal [UNN])</td></tr> <tr> <td>Group B (High Risk)</td><td>Stage III with high LDH (>2 times ULN) , or all non-central nervous system (CNS) stage IV with bone marrow involvement (,25% lymphoma cells)</td></tr> <tr> <td>Group C^x</td><td>Any CNS involvement^u and/or Bone marrow involvement (≥25% lymphoma cells)</td></tr> </tbody> </table> ^u The CNS is considered involved if one or more of the following applies: - Any lymphoma cells by cytology in CSF - Any CNS tumor mass by imaging - Cranial nerve palsy (if not explained by extracranial tumor) - Clinical spinal cord compression - Parameningeal extension: cranial and/or spinal	Group Classification		Group A	Completely resected stage I or Completely resected abdominal stage II	Group B (Low Risk)	Unresected stage I and non-abdominal stage II or stage III with low LDH (≤ 2 times the upper limit of normal [UNN])	Group B (High Risk)	Stage III with high LDH (>2 times ULN) , or all non-central nervous system (CNS) stage IV with bone marrow involvement (,25% lymphoma cells)	Group C ^x	Any CNS involvement ^u and/or Bone marrow involvement (≥25% lymphoma cells)
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Group C ^x	Any CNS involvement ^u and/or Bone marrow involvement (≥25% lymphoma cells)										
POEMS Syndrome (Polyneuropathy, Organomegaly, Endocrinopathy , Monoclonal Gammopathy and Skin Abnormalities)	Autologous HSCT Medically Necessary - Autologous HSCT may be considered medically necessary for the treatment of disseminated POEMS syndrome. Note: <i>Individuals with disseminated POEMS syndrome may have diffuse sclerotic lesions or disseminated bone marrow involvement.</i> Investigational - Autologous HSCT is considered investigational not meeting the above criteria because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)										

	Investigational Allogeneic hematopoietic stem cell transplantation (HSCT) is considered investigational for the treatment of POEMS syndrome because the evidence is insufficient in demonstrating improved net health outcomes. Tandem HSCT Tandem HSCT is considered investigational to treat POEMS syndrome because the evidence is insufficient in demonstrating improved net health outcomes.
Systemic Mastocytosis	Autologous HSCT Investigational - Autologous HSCT is considered investigational for the treatment of any subtype of systemic mastocytosis because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Medically Necessary Aggressive Systemic Mastocytosis (ASM) Allogeneic HSCT may be considered medically necessary for the treatment of aggressive systemic mastocytosis (ASM) after adequate response first line treatment. Allogeneic HCT may be considered medically necessary for ASM when there is inadequate response or loss of response as a second-line therapy. Systemic Mastocytosis with an Associated Hematologic Neoplasm (SM-AHN) - Allogeneic HSCT may be considered medically necessary for the treatment of systemic mastocytosis with an associated hematologic neoplasm (SM-AHN) when any of the following criteria is met: - After adequate response to initial treatment. - Progression of associated hematologic neoplasm (AHN). - Inadequate response or loss of response as a second-line therapy. Mast Cell Leukemia (MCL) with or without Associated Hematologic Neoplasm (AHN) - Allogeneic HSCT may be considered medically necessary for the treatment of mast cell leukemia (MCL) with or without associated hematologic neoplasm (AHN) when any of the following criteria are met: - After adequate response first line treatment. - Progression of AHN or transformation to acute myeloid leukemia (AML) - Inadequate response or loss of response meeting as a second-line therapy. Investigational - Allogeneic HSCT is considered investigational when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes. Diagnostic Criteria for Systemic Mastocytosis

	Major	Multifocal dense infiltrates of mast cells (≥15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs(s). ^a
	Minor	Atypical mast cell morphology, including spindle shape or immature morphology, present in >25% of all mast cells on bone marrow smears or in other extracutaneous organ(s). ^b Mast cells aberrantly express one or more of the following antigens: CD2, CD25, CD30. KIT p.D816V mutation or other activating KIT mutation ^c detected in peripheral blood, bone marrow, or other extracutaneous organ(s). Baseline serum tryptase concentration of >20 ng/mL in the absence of an associated myeloid neoplasm; in the case of a known HαT, the tryptase level could be adjusted. ^{d, e}

WHO 5 th Edition	ICC ^f
1 major + 1 minor criteria	1 major criterion
OR	OR
≥3 minor criteria	≥3 minor criteria

^a The ICC also requires demonstration of CD117 (often strong) and mast cell (MC) tryptase expression (often weaker and may be partial) to confirm the MC infiltrate. Per the ICC, with the support of IHC, the major criterion on its own can be sufficient for diagnosing SM, when myeloid and/or lymphoid neoplasm with eosinophilia (MLNE) is carefully excluded.

^b Well-differentiated round cell morphology may be seen in a small subset of cases; mast cells in such cases are usually positive for CD30 and negative for CD2 and CD25.

^c Any type of KIT mutation counts as a minor systemic mastocytosis criterion when published solid evidence for its transforming behaviour is available.

^dThe basal tryptase level may be divided by 1 plus the number of extra copies of the α-tryptase gene. For example, if the tryptase level is 30 ng/mL and two extra copies of the α-tryptase gene are found in a patient with HαT, the HαT-corrected tryptase level is 10 ng/mL (30/3 = 10), thereby not meeting the level of a minor systemic mastocytosis criterion.

^eOther causes for an elevated serum tryptase level (e.g. renal disease) should be considered.

^fThe identification of one of the tyrosine kinase gene fusions associated with MLNE excludes a diagnosis of SM. Rare cases with both a gene fusion associated with MLNE and a KIT mutation have been reported, and the MLNE represents the AMN.

Diagnostic Criteria for Variants of Systematic Mastocytosis

WHO Diagnostic Criteria

Systemic Mastocytosis with an Associated Hematological Neoplasm

- Systemic mastocytosis criteria fulfilled
- Criteria for a WHO-defined hematological neoplasm; both disease compartments are classified according to WHO definitions

Aggressive Systemic Mastocytosis^d

- Systemic mastocytosis criteria fulfilled
- At least 1 C finding^e

Mast Cell Leukemia

- Systemic mastocytosis criteria fulfilled
- Bone marrow aspirate smears show $\geq 20\%$ mast cells^f
- In peripheral blood smears: $\geq 10\%$ mast cells in classic MCL, $< 10\%$ MCs in aleukemic MCL
- In acute MCL, C-findings are detectable; chronic MCL (n C-findings) has a more favorable prognosis

Footnotes:

^dASM with 5%-19% mast cells in bone marrow aspirate is referred to as ASM in transformation (ASM-t).

^e B- and C-findings indicate organ involvement without and with organ dysfunction, respectively.

^f Atypical immature mast cells include promastocytes, metachromatic blast-like cells, or highly pleomorphic mast cells. Thus, the ICC restricts MCL to "acute" MCL which presents with C-findings. For example "chronic" MCL which is typically seen with spindle-shaped mast cells would not be included in this definition. The ICC also notes that in the presence of an inadequate aspirate smear, MCL may be diagnosed by a diffuse, dense infiltration of atypical immature mast cells on bone marrow biopsy.

Criteria for B-Findings in Patients with Systemic Mastocytosis^a

WHO	ICC
High mast cell burden: Infiltration in bone marrow $\geq 30\%$ and/or serum total tryptase ≥ 200 ng/mL ^b and/or KIT p.D816V variant allele frequency $\geq 10\%$ in bone marrow or peripheral blood leukocytes	$>30\%$ mast cells on bone marrow biopsy and serum total tryptase >200 ng/mL
Signs of myeloproliferation and/or myelodysplasia not fulfilling criteria for AHN ^c	Cytopenia not meeting criteria for C-findings or -cytosis. Reactive causes are excluded and criteria for myeloid neoplasms are not met.
Hepatomegaly on palpation or imaging (ultrasound, CT, or MRI) without ascites or other signs of organ damage and/or splenomegaly on palpation or imaging without hypersplenism and/or lymphadenopathy on palpation or imaging (>20 mm)	Hepatomegaly without impaired liver function, palpable splenomegaly without hypersplenism and/or lymphadenopathy >1 cm (palpation or imaging)

^a In patients with SM in whom less than 2 B-findings and no C-findings are detected, the diagnosis is ISM. The diagnosis of BMM requires no B- or C-findings. When 2 or more B-findings but no C-findings are present, the diagnosis is SSM. When 1 or more C-findings (with or without additional B-findings) are detected, the final diagnosis is ASM ($<20\%$ MCs in bone marrow smears).

^b In the case of a known H α T, the basal serum tryptase level can be adjusted. The optimal method of adjustment is not definitively defined. A common method is to divide the basal tryptase level by 1 plus the number of extra copies of the α -tryptase gene. For example, with a tryptase level of 300 and 2 extra copies of the α -tryptase gene in a patient with H α T, the H α T-corrected tryptase level is 100 ($300/3 = 100$) and therefore does not qualify as a B finding.

^c Signs of myeloproliferation and/or myelodysplasia must be discrete and stable and must not meet diagnostic criteria for an MPN, MDS, or MDS/MPN, excluding SMAHN. The presence of a myeloid AHN excludes B findings and SSM by definition.

Criteria for C-Findings in Patients with Systemic Mastocytosis^a

C-Findings
≥ 1 cytopenia(s) found:

- Absolute neutrophile count $< \times 10^9/L$
- Hemoglobin $<10 \text{ g/dL}$
- Platelet count $<1 \times 10^9/L$

Hepatopathy: Ascites and elevated liver enzymes^b $\pm$ hepatomegaly or cirrhotic liver $\pm$ portal hypertension

Spleen: Palpable splenomegaly with hypersplenism $\pm$ weight loss $\pm$ hypoalbuminemia

Gastrointestinal tract: Malabsorption with hypoalbuminemia $\pm$ weight loss

Bone: Large sized osteolysis ($\geq 20 \text{ mm}$) $\pm$ pathologic fracture $\pm$ bone pain

^a In patients with SM in whom less than 2 B-findings and no C-findings are detected, the diagnosis is ISM. The diagnosis of BMM requires no B- or C-findings. When 2 or more B-findings but no C-findings are present, the diagnosis is SSM. When 1 or more C-findings (with or without additional B-findings) are detected, the final diagnosis is ASM ($<20\%$ MCs in bone marrow smears).

^b Alkaline phosphatase levels are typically elevated in patients with advanced SM and SM-induced liver damage. In some of these patients, only elevated liver enzymes are found, without (clinically relevant) ascites.

IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response

Nonhematologic

Organ Damage	Organ Damage Eligible for CI Response	CI Response Criteria
Ascites or pleural effusions	(1) Symptomatic ascites or pleural effusion requiring medical intervention such as use of diuretics (grade 2), OR (2) ≥ 2 therapeutic paracenteses or thoracenteses at least 28 days apart over 12 weeks prior to study entry (grade 3), and one of the procedures is performed during the 6 weeks prior drug start	(1) Complete resolution of symptomatic ascites or pleural effusion AND no longer in need of diuretic(s) for ≥ 12 weeks, OR (2) No therapeutic paracentesis or thoracentesis for ≥ 12 weeks
Liver function abnormalities	$\geq$ Grade 2 abnormalities in direct bilirubin, AST, ALT, AP in the presence of ascites, and/or clinically relevant portal hypertension, and/or liver MC infiltration that is a biopsy-proven or other causes for abnormal liver function are not identified	Reversion of 1 or more liver function tests to normal range for ≥ 12 weeks
Hypoalbuminemia	$\geq$ Grade 2 hypoalbuminemia ($<3.0 \text{ g/dL}$)	Reversion of albumin to normal range for ≥ 12 weeks
Symptomatic marked splenomegaly	Symptomatic marked splenomegaly: a spleen that is palpable $> 5 \text{ cm}$ below that left	$\geq 50\%$ reduction in palpable splenomegaly and no endorsement of discomfort

	costal margin and the patient endorses symptoms of discomfort and/or early satiety	and/or early satiety for ≥ 12 weeks (3D computed tomography/magnetic resonance imaging evaluation may also be undertaken)
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IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response

Hematologic

Organ Damage	Organ Damage Eligible for CI Response	CI Response Criteria
ANC	Baseline grade $\geq$ ANC ($<1 \times 10^9/L$)	A minimum 100% increase in the ANC and an ANC of at least $0.5 \times 10^9/L$ for ≥ 12 weeks
Anemia (transfusion-independent)	Grade ≥ 2 anemia (Hb < 10 g/dL)	An increase in Hb level of at least 2 g/dL that is maintained for ≥ 12 weeks
Anemia (transfusion dependent)	Transfusion of a minimum of 6 units of PRBC in the 12 weeks before the start of treatment with the most recent transfusion occurring in the previous 4 weeks. RBC transfusions are only considered as part of the baseline criteria if they are administered for an Hb level ≤ 8.5 g/dL and not associated with bleeding, hemolysis, or therapy	Transfusion independence for ≥ 12 weeks and maintenance of a minimum Hb level of 8.5 g/dL at the end of the 12-week period of response duration
Thrombocytopenia (transfusion-independent)	Grade ≥ 2 thrombocytopenia ($<75 \times 10^9/L$)	A minimum of 100% increase in the platelet count and an absolute platelet count increase of at least $50 \times 10^9/L$ and no need for platelet transfusions for ≥ 12 weeks
Thrombocytopenia (transfusion-dependent)	1) Transfusion of a minimum of 6 units of apheresed platelets during the 12 weeks preceding treatment; and 2) at least 2 units transfused in the previous 4 weeks; and	Transfusion independence for a minimal period of 12 - weeks and maintenance of a platelet count of $\geq 20 \times 10^9/L$

IWG-MRT-ECNM Criteria for Eligible Organ Damage to Assess Clinical Improvement (CI) and Treatment Response

Organ Damage	Organ Damage Eligible for CI Response	CI Response Criteria
ANC	Baseline grade $\geq$ ANC ($<1 \times 10^9/L$)	A minimum 100% increase in the ANC and an ANC of at least $0.5 \times 10^9/L$ for ≥ 12 weeks
Anemia (transfusion-independent)	Grade ≥ 2 anemia (Hb < 10 g/dL)	An increase in Hb level of at least 2 g/dL that is maintained for ≥ 12 weeks
Anemia (transfusion dependent)	Transfusion of a minimum of 6 units of PRBC in the 12 weeks before the start of treatment with the most recent transfusion occurring in the previous 4 weeks. RBC transfusions are only considered as part of the baseline criteria if they are administered for an Hb level ≤ 8.5 g/dL and not associated with bleeding, hemolysis, or therapy	Transfusion independence for ≥ 12 weeks and maintenance of a minimum Hb level of 8.5 g/dL at the end of the 12-week period of response duration
Thrombocytopenia (transfusion-independent)	Grade ≥ 2 thrombocytopenia ($<75 \times 10^9/L$)	A minimum of 100% increase in the platelet count and an absolute platelet count increase of at least $50 \times 10^9/L$ and no need for platelet transfusions for ≥ 12 weeks
Thrombocytopenia (transfusion-dependent)	1)Transfusion of a minimum of 6 units of apheresed platelets during the 12 weeks preceding treatment; and 2)at least 2 units transfused in the previous 4 weeks; and	Transfusion independence for a minimal period of 12 - weeks and maintenance of a platelet count of $\geq 20 \times 10^9/L$

		3)transfusions are administered only for a platelet count < 20 x 10 ⁹ /L	
Waldenstrom Macroglobulinemia	Autologous HSCT Medically Necessary - Autologous HSCT may be considered medically necessary for relapsed Waldenstrom macroglobulinemia (WM). Investigational - Autologous HSCT is considered investigational when the above criteria is not met because the evidence is insufficient in demonstrating improved net health outcomes. Allogeneic HSCT Investigational - Allogeneic HSCT is considered investigational for the treatment to treat WM for all indications because the evidence is insufficient in demonstrating improved net health outcomes.		

POLICY GUIDELINES

Definitions

Ablative: A very high dose of a treatment, calculated to kill a tumor.

Allogeneic stem cells: Stem cells harvested from a histocompatible donor.

Autologous stem cells: Stem cells harvested from the individual's own bone marrow or peripheral blood.

Bone marrow: A spongy tissue located within flat bones, including the hip and breast bones and the skull. This tissue contains stem cells, the precursors of platelets, red blood cells, and white cells.

Chemosensitive: Showing tumor response to the most recent chemotherapy regimen.

Chemotherapy: The medical treatment of a disease, particularly cancer, with drugs or other chemicals. Chemotherapy may vary by disease and stage.

Chimerism: Cell populations derived from different individuals; may be mixed or complete.

Complete response/remission (CR): The disappearance of all signs of cancer in response to treatment; this does not always mean the cancer has been cured; also called a complete response.

Cytotoxic: Destructive to cells.

ECOG (Eastern Cooperative Oncology Group) Performance Status: A scale used to determine the individual's level of functioning; this scale may also be referred to as the WHO (World Health Organization) or Zubrod score; based on the following scale:

- 0 Fully active, able to carry on all pre-disease performance without restriction

- 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
- 2 Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- 3 Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- 4 Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- 5 Deceased

Failure to engraft: When the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Graft versus host disease: A life-threatening complication of bone marrow transplants in which the donated marrow causes an immune reaction against the recipient's body.

Hematopoietic stem cells: Primitive cells capable of replication and formation into mature blood cells in order to repopulate the bone marrow.

High-dose or myeloablative chemotherapy (HDC): The administration of cytotoxic agents using doses several times greater than the standard therapeutic dose.

HLA (human leukocyte antigen): A group of protein molecules located on bone marrow cells that can provoke an immune response.

Karnofsky Score: A measure of the individual's overall physical health, judged by their level of activity; the score uses the following scale:

- | | |
|------|---|
| 100% | Normal, no complaints, no signs of disease |
| 90% | Capable of normal activity, few symptoms or signs of disease |
| 80% | Normal activity with some difficulty, some symptoms or signs |
| 70% | Caring for self, not capable of normal activity or work |
| 60% | Requiring some help, can take care of most personal requirements |
| 50% | Requires help often, requires frequent medical care |
| 40% | Disabled, requires special care and help |
| 30% | Severely disabled, hospital admission indicated but no risk of death |
| 20% | Very ill, urgently requiring admission, requires supportive measures or treatment |
| 10% | Moribund, rapidly progressive fatal disease processes |
| 0% | Death |

Lansky Score: A measure of the individuals overall physical health, judged by their level of activity; the score uses the following scale:

- | | |
|-----|---|
| 100 | Fully active, normal |
| 90 | Minor restrictions in physically strenuous activity |
| 80 | Active, but tires more quickly |
| 70 | Both greater restriction of and less time spent in play activity |
| 60 | Up and around, but minimal active play; keeps busy with quieter activities |
| 50 | Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities |
| 40 | Mostly in bed; participates in quiet activities |
| 30 | In bed; needs assistance even for quiet play |
| 20 | Often sleeping; play entirely limited to very passive activities |
| 10 | No play; does not get out of bed |
| 0 | Unresponsive |

Non-myeloablative chemotherapy: Less intense chemotherapy conditioning regimens, which rely more on immunosuppression than cytotoxic effects to permit engraftment of donor cells.

Partial response: Showing at least a 50% reduction in tumor burden.

Primary graft failure: Occurs when the bone marrow infused during a bone marrow transplant does not take or is not accepted by the recipient.

Refractory: Tumors that show less than 50% reduction in tumor burden in response to chemotherapy upon or during the course(s) of chemotherapy.

Relapse: The return of signs and symptoms of cancer after a period of improvement.

Tandem transplant: Planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Coding

See the [Codes](#) table for details.

BACKGROUND

Hematopoietic Stem Cell Transplant (HSCT)

The hematopoietic stem cell transplant (HSCT) is an adjunctive therapy and follows the administration of high-dose chemotherapy and/or whole-body or localized radiotherapy prior to the transplant. The transplantation of hematopoietic stem cells (HSCT) has been found to increase the efficacy of high-dose chemotherapy and/or radiotherapy in the treatment of certain non-cancer (acquired or inherited) or cancer related conditions.

High-dose chemotherapy (HDC) involves the administration of cytotoxic agents using doses several times greater than the standard therapeutic dose. In some cases, whole body or localized radiotherapy is also given and is included in the term HDC when applicable. The rationale for HDC is that many cytotoxic agents act according to a steep dose-response curve. Thus, small increments in dosage will result in relatively large increases in tumor cell kill. Increasing the dosage also increases the incidence and severity of adverse effects related primarily to bone marrow ablation (for example, opportunistic infections, hemorrhage, or organ failure). Bone marrow ablation is the most significant side effect of HDC. As a result, HDC is accompanied by a re-infusion of hematopoietic stem cells, which are primitive cells capable of replication and formation into mature blood cells, in order to repopulate the marrow. The potential donors of stem cells include:

1. Allogeneic - Stem cells harvested from another individual, a matched related to include haploidentical donor or unrelated donor or donor without a complete match.
2. Autologous - Stem cells can be harvested from the individual's own bone marrow or peripheral blood.
3. Syngeneic- Stem cells from his or her identical twin.

Stages of Transplantation

Hematopoietic stem cell transplantation (HSCT) involves the mobilization, harvesting, and transplantation of hematopoietic stem cells (HCT) that have been collected from bone marrow or peripheral blood.

- **Mobilization:** Preparing for hematopoietic stem cell transplantation first requires stem cell mobilization. Mobilization makes harvesting more efficient and occurs when the accumulation of stem cells has reached its highest level.
 - **Autologous:** Prior to harvesting, autologous blood stem cell donors are occasionally given a course of chemotherapy to destroy some of the malignant tumors in their body. This low-dose chemotherapy reduces the risk for tumor contamination and facilitates the filtering of stem cells for collection. Autologous donors may also receive injections of a colony-stimulating factor. Colony-stimulating factors are groups of proteins that cause blood cells to grow and mature, which facilitates mobilization. In some cases, a combination of chemotherapy and colony-stimulating factor is used.
 - **Allogeneic:** In allogeneic donors, mobilization is accomplished through a series of subcutaneous injections of colony-stimulating factors (i.e., granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]). Typically, the colony-stimulating factor is administered for 4 to 5 days, followed by apheresis, which generally occurs over the next day or two. Apheresis, also called pheresis, is a procedure in which blood is collected, the stem cells are removed, and the remaining blood is given back to the donor. The stem cells are frozen until they are given to the recipient.
- **Harvesting:** After mobilization, hematopoietic stem cells (HCT) can be harvested from bone marrow and/or peripheral blood.
 - Harvesting from bone marrow involves inserting a hollow needle into the pelvic (hip) bone or, in rare cases, the sternum (breastbone), under general or regional anesthesia. The procedure takes about 1 hour. The cells are harvested prior to myeloablative therapy.
 - In individuals undergoing peripheral blood stem cell transplantation, stem cells are removed from the bloodstream via apheresis. In apheresis, blood is removed through a large vein in the arm or a central venous catheter (a flexible tube that is placed in a large vein in the neck, chest, or groin area) and sent to sterile equipment, where it is separated into various components, such as red cells, white cells, and plasma. Healthy parts of the blood are then returned to the individual. Apheresis typically takes 4 to 6 hours. For 4 or 5 days before apheresis, the donor may be given a medication to increase the number of stem cells released into the bloodstream.
- **Transplantation:** Upon entering the bloodstream, the stem cells travel to the bone marrow, where they begin to produce new white blood cells, red blood cells, and platelets in a process known as engraftment. Engraftment typically occurs within 2 to 4 weeks after transplantation and is monitored by blood counts. Following the transplant, full recovery of the immune system may take several months for autologous transplantation recipients and as much as 1 to 2 years for individuals receiving allogeneic transplantation. A bone marrow aspiration may also be performed to determine the progress of the new marrow.

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic hematopoietic stem cell transplantation (HSCT) involves using hematopoietic stem cells (HCT) harvested from another individual. They can be from a matched related or unrelated donor or a donor without a complete match. The success of the transplant depends in part on how well the HLAs of the donor's stem cells match those of the recipient's stem cells. HLAs are a set of proteins that are found on the surface of cells and are identifiable by a special blood test, the higher the number of matching HLAs between the individuals, the greater the chance that the recipient will accept the donor's stem cells. Close relatives, especially siblings, are more likely than unrelated individuals to be HLA-matched (6/6 HLA match); however, only 25 to 35 percent of transplant candidates have a sibling who is an HLA match.

Allogeneic hematopoietic stem cell transplantation (HSCT) consists of the following conditioning regimens:

- Myeloablative is a severe form of myelosuppression. Myelosuppression is a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets. It is a side effect of some cancer treatments prior to receiving the donor's marrow or stem cells.
- Non-myeloablative (also known as reduced intensity conditioning) is a bone marrow transplant in which the individual's marrow is not completely destroyed prior to receiving the donor's marrow or stem cells.

Reduced intensity conditioning regimens (non-myeloablative) would be considered for individuals who would otherwise qualify for a myeloablative allogeneic hematopoietic stem cell transplantation (HSCT) but would not tolerate standard myeloablative conditioning regimen. This may include the following: age typically > 60 years or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score).

Autologous Hematopoietic Stem Cell Transplantation

In autologous hematopoietic stem cell transplantation (HSCT), the individual receives his or her own stem cells, which were harvested prior to myeloablative therapy and are relatively cancer-free. Myeloablative chemotherapy is performed to eradicate cancerous cells from the blood and bone marrow, thereby permitting subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic progenitor cells or cells that allow themselves to differentiate from other cells. Advantages of autologous transplants include the reduced toxicity that is associated with treatment and an extended, disease-free survival time, most often without the need for additional treatment.

Tandem Transplantation

Tandem high-dose or non-myeloablative chemotherapy with autologous or allogeneic stem cell support is the planned administration of two cycles of high-dose chemotherapy, alone or with total body irradiation, each of which is followed by re-infusion of stem cells. Despite treatment with high-dose chemotherapy, many individuals with advanced malignancies eventually relapse, indicating the presence of residual neoplastic cells. The hypothesis is that eradication of residual tumor cells can be achieved using multiple cycles of myeloablative or non-myeloablative chemotherapy with stem cell support.

- Planned infusion (transplant) of previously harvested hematopoietic stem cells with a repeat hematopoietic stem cell infusion (transplant) that is performed within 6 months of the initial

transplant. This is distinguished from a repeat transplantation requested or performed more than 6 months after the first transplant and is used as salvage therapy after failure of initial transplantation or relapsed disease.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under the Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic cells are included in these regulations.

RATIONALE

This evidence review was created in April 2018 and has been updated regularly with searches of the PubMed database. The most recent literature update was performed through June 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Therapy Purpose

The purpose of allogenic and autologous hematopoietic stem cell transplant (HSCT) in individuals with non-cancer disorders: autoimmune disease, genetic disorders (acquired anemias and other bone marrow failure syndromes [inherited]). Oncologic indications: solid tumors and blood cancers is to provide a treatment option that is an alternative to or an improvement in existing therapies.

The following PICO was used to Select literature to inform this review.

Populations

The relevant population of interest is individuals with non-cancer disorders: autoimmune disease, genetic disorders (acquired anemias and other bone marrow failure syndromes [inherited]). Oncologic indications: solid tumors and blood cancers

Interventions

The therapy being considered is allogenic and autologous HSCT.

Comparators

The following therapies are currently being used to treat individuals with non-cancer disorders: autoimmune disease, genetic disorders (acquired anemias and other bone marrow failure syndromes [inherited]): conventional medical therapy.

The following therapies are currently being used to treatment individuals with oncologic indications solid tumors and blood cancers: standard of care which may include chemotherapy and/or immunotherapy.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity. Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

For individuals who receive HSCT for the various oncologic and non-oncologic indications addressed in this policy, there exists a large body of available evidence which varies widely across populations in type, findings, and sufficiency.

For example, for individuals who have aggressive B-cell NHL, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first CR, the evidence includes RCTs and a systematic review. While the data from the randomized trials offer conflicting results, some data have revealed an OS benefit in patients with aggressive B-cell lymphomas (at high- or high-intermediate risk of relapse) who receive HCT to consolidate a first CR. Randomized studies of HCT for relapsed aggressive B-cell lymphomas have also shown an OS benefit with the previously described approach. Results of a retrospective study comparing autologous and allogenic HCT for relapsed or refractory B-cell NHL showed more positive outcomes for autologous HCTs.

In contrast, for individuals receiving allogenic HCT for renal cell carcinoma, the evidence is limited to multiple noncomparative case series studies. In the absence of RCTs, current evidence is insufficient to conclude whether allogenic HCT results in improved OS among renal cell carcinoma patients.

For those indications in which the type of transplant and the individual's condition meets the criteria outlined in Policy above, the available evidence has shown that the transplant (autologous/allogeneic) improves overall survival (OS) and the evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For those indications in which the type of transplant and the individual's condition does not meet the criteria outlined in Policy below, the available evidence is insufficient and does not demonstrate improved net health outcomes and would be considered investigational.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society for Transplantation and Cellular Therapy (ASTCT)

Note: *The American Society for Blood and Marrow Transplantation is now known as the American Society for Transplantation and Cellular Therapy (ASTCT).*

In 2019, the American Society of Blood and Marrow Transplantation issued a position statement on autologous hematopoietic cell transplantation (AHCT) for treatment-refractory relapsing multiple sclerosis (MS).

POSITION STATEMENT: "The ASBMT Task Force recommends revising the recommended indication for AHCT in MS to "standard of care, clinical evidence available", for patients with relapsing forms of MS (RRMS or progressive MS with superimposed activity) who have prognostic factors that indicate a high risk of future disability, including ongoing clinical relapse or MRI lesion activity despite treatment with available DMTs, especially if disease activity continues despite treatment with high-efficacy DMTs and/or worsening disability. This revision of our previous "developmental" guideline is based on the evidence from retrospective studies, clinical trials, and meta-analyses/systematic reviews summarized above."

Patient Selection and Transplantation Regimen

"Collaboration of neurologists with expertise in treating MS and transplantation physicians with experience performing AHCT for autoimmune disease is crucial for appropriate patient selection and optimizing transplant procedures to improve patient outcomes. Patients most likely to benefit from AHCT include those of relatively younger age with relatively short disease duration, a relapsing form of MS (RRMS or progressive MS with superimposed activity), accumulating disability but still ambulatory, and ongoing disease activity despite DMT. Patients with progressive MS without recent inflammatory disease activity (i.e., clinical relapse or MRI lesion activity within the previous 1 to 2 years) are less likely to benefit. Some patients with other demographic or disease characteristics (e.g., patients with early MS who have failed only a limited number of DMTs but are considered at high risk for future disability or some patients with progressive disease without recent activity) may benefit from AHCT, but there is less supportive evidence for AHCT in those populations."

“This position paper does not provide recommendations on preferred methods for mobilization and stem cell collection, graft manipulation (e.g., CD34⁺ selection), cell dose, conditioning regimen, or post-transplantation supportive care.”

Conclusion: “In summary, the ASBMT endorses AHCT as a “standard of care, clinical evidence available” for treatment-refractory relapsing MS. This document is not a treatment guideline, but is intended to provide guidance to physicians, patients, payers, policy makers, and other stakeholders on coverage decisions and the appropriate use of this procedure for MS.”

In 2020, the American Society for Transplantation and Cellular Therapy (ASTCT), formerly known as the American Society of Blood and Marrow Transplantation updated their guideline-indications for autologous and allogeneic hematopoietic stem cell transplantation.

Definitions for Classifying Indications

- **Standard of Care (S):** This category includes indications that are well defined and generally supported by evidence in the form of high-quality clinical trials and/or observational studies (e.g., through CIBMRT or European Society for Blood and Marrow Transplantation).
- **Standard of Care, Clinical Evidence Available (C):** This category includes indications for which large clinical trials and observational studies are not available. However, HCT/IECT has been shown to be an effective therapy with acceptable risk or morbidity or mortality in sufficiently large single or multicenter cohort studies. HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risk and benefits. As more evidence becomes available, some indications may be reclassified as “Standard of care”.
- **Standard of Care, Rare Indication (R):** Indications included in this category are rare disease for which clinical trials and observational studies with sufficient number of patients are not currently feasible because of their very low incidence. However, single, or multicenter or registry studies in relatively small cohorts of patients have shown HCT/IECT to be effective treatment with acceptable risks of morbidity and mortality. For patients with diseases in this category, HCT/IECT can be considered as a treatment option for individual patients after careful evaluation of risks and benefits.
- **Developmental (D):** Developmental indications include diseases where preclinical and/or early phase clinical studies show HCT/IECT to be a promising treatment option. HCT/IECT is best pursued for these indications as part of a clinical trial. As more evidence becomes available, some indications may be reclassified as “Standard of care, clinical evidence available” or “Standard of care”.
- **Not Generally Recommended (N):** Is currently not recommended for these indications where evidence and clinical practice do not support the routine use of HCT/IECT as a potential treatment and may be pursued within the context of a clinical trial.

Indications for Hematopoietic Cell Transplant (HCT) in Pediatric Patients (Generally Age < 18 years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1 low risk	N	N
CR1 intermediate risk	C	N
CR1 high risk	S	N
CR2 ⁺	S	N
Not in remission	S	N

Acute promyelocytic leukemia, relapse	R	R
Acute lymphoblastic leukemia		
CR1 standard risk	N	N
CR1 high risk	S	N
CR2	S	N
CR3+	C	N
Not in remission	C*	N
Chronic myeloid leukemia		
Chronic phase	C	N
Accelerated phase	C	N
Blast phase	C	N
Myelodysplastic syndromes		
Low risk	C	N
High risk	S	N
Juvenile myelomonocytic leukemia	S	N
Therapy related	S	N
T-cell non-Hodgkin's Lymphoma		
CR1 standard risk	N	R
CR1 high risk	R	R
CR2	S	C
CR3+	C	C
Not in remission	C	N
Burkitt's lymphoma		
First remission	N	N
First or greater relapse, sensitive	C	C
First or greater relapse resistant	C	N
Hodgkin lymphoma		
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	C	N
First relapse, sensitive	N	S
First relapse, resistant	C	N
Second or greater relapse	C	C
Solid tumors		
Germ cell tumor, relapse	D	C

Germ cell tumor, refractory	D	C
Ewing's sarcoma, high risk or relapse	D	D
Soft tissue sarcoma, high risk or relapse	D	D
Neuroblastoma, high risk or relapse	D	S †
Wilm's tumor, relapse	N	C
Osteosarcoma, high risk	N	C
Medulloblastoma, high risk	N	C
Other malignant brain tumors	N	C
Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Other bone marrow failure syndrome ‡	R	N
Sickle cell disease	C	N
Thalassemia	S	N
Congenital amegakaryocytic thrombocytopenia	R	N
Severe combined immunodeficiency (SCID)	R	N
T-cell immunodeficiency, SCID variants	R	N
Wiskott-Aldrich syndrome	R	N
Hemophagocytic disorders	S	N
Severe congenital neutropenia	R	N
Chronic granulomatous disease	R	N
Other phagocytic cell disorders	R	N
IPEX syndrome	R	N
Juvenile rheumatoid arthritis	D	R
Systemic sclerosis	D	R
Other Autoimmune and immune dysregulation disorders		
Mucopolysaccharidosis I (severe; Hurler syndrome)	R	N
Other mucopolysaccharidosis (II, IV, VI)	D	N
Other lysosomal metabolic diseases	D	N

Osteopetrosis (severe, recessive)	R	N
Osteopetrosis (intermediate)	D	N
Globoid cell leukodystrophy	R	N
Metachromatic leukodystrophy	R	N
Cerebral X-linked adrenoleukodystrophy	R	N

Standard of care (S); Standard of care, clinical evidence available (C); Standard of care, rare indication (R); Developmental (D); Not generally recommended (N). CR, complete remission; IPEX, Immune dysregulation, polyendocrinopathy, enteropathy, x-linked syndrome.

*Used in Clinical practice but associated with high failure rates; hence, recommended clinical trial enrollment and nontransplant strategies when available.

† Tandem autologous HCT recommended (randomized, phase III trial showed superiority of tandem autologous stem cell transplant compared with sing transplant)

‡ Include dyskeratosis congenita, Shwachman-Diamond syndrome, congenital sideroblastic anemia, GATA gene has no further expansion 2 (GATA₂) associate marrow failure, sterile alpha motif motif containing 9 (SAMD₉) or SAMD ligand 9 (SAMD_{L9}) disorder, paroxysmal nocturnal hemoglobinuria (PNH), etc.

Indications for Hematopoietic Cell Transplant (HCT) in Adults (Generally Age ≥ 18 years)

Indication and Disease Status	Allogeneic HCT	Autologous HCT
Acute myeloid leukemia		
CR1, low risk	N	C
CR1, intermediate risk	S	C
CR1, high risk	S	N
CR2	S	C
CR3 ⁺	C	N
Not in remission	C	N
Acute promyelocytic leukemia		
CR1	N	N
CR2, molecular remission	C	S
CR2, not in molecular remission	S	N
CR3 ⁺	C	N
Not in remission	C	N
Relapse after autologous transplant	C	N
Acute lymphoblastic leukemia		
CR1, standard risk	S	N
CR1, high risk	S	N
CR2	S	N
CR3 ⁺	C	N
Not in remission	C	N
Chronic myeloid leukemia		

Chronic phase I, TKI intolerant	C	N
Chronic phase I, TKI refractory	C	N
Chronic phase 2+	S	N
Accelerated phase	S	N
Blast phase	S	N
Myelodysplastic syndromes		
Low/intermediate – 1 risk	C	N
Intermediate -2/high risk	S	N
Therapy related acute myeloid leukemia (AML)/myelodysplastic syndromes (MDS) CR1	S	N
Myelofibrosis and myeloproliferative diseases		
Primary low risk	C	N
Primary intermediate/high risk	C	N
Secondary	C	N
Hypereosinophilic syndromes, refractory	R	N
Miscellaneous		
Systemic mastocytosis	R	N
Blastic plasmacytoid dendritic cell neoplasm	R	R
Plasma cell disorders		
Myeloma, initial response	D	S
Myeloma, sensitive relapse	S	S
Myeloma, refractory	C	C
Plasma cell leukemia	S	C
Amyloid light-chain amyloidosis	N	S
POEMS syndrome	N	C
Relapse after autologous transplant	C	C
Hodgkin lymphoma		
CR1 (positron emission tomography negative)	N	N
Primary refractory, sensitive	C	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse, resistant	C	N
Second or greater relapse	S	S
Relapse after autologous transplant	S	N

Diffuse large B cell lymphoma		
CR1 (positron emission tomography negative)	N	N
Primary refractory, sensitive	S	S
Primary refractory, resistant	S	N
First relapse, sensitive	S	S
First relapse, resistant	S	N
Second or greater relapse	S	N
Relapse after autologous transplant		
High-grade B-cell lymphoma, with MYC and BCL₂ and/or BCL₆ rearrangements		
CR1 (positron emission tomography negative)	N	C
Primary refractory, sensitive	R	C
Primary refractory, resistant	R	N
First relapse, sensitive	R	C
First relapse, resistant	R	N
Second or greater relapse	R	C
Relapse after autologous transplant	R	N
Primary central nervous system lymphoma		
CR1/first partial remission (consolidation)	N	C
Relapse, sensitive	N	C
Follicular lymphoma		
CR1	N	N
Primary refractory, sensitive	S	S
Primary refractory, resistant	S	N
First relapse, sensitive (including POD ₂₄)	N	S
First relapse, resistant	S	N
Second or greater relapse	S	S
Transformation to high grade lymphoma	C	S
Relapse after autologous transplant	S	N
Mantle cell lymphoma		
CR1/first partial remission	S	S
Primary refractory, sensitive	S	S

Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse resistant	C	N
Second or greater relapse	S	S
Relapse after autologous transplant	S	N
T-cell lymphoma		
CR1/first partial remission	S	S
Primary refractory, sensitive	S	S
Primary refractory, resistant	C	N
First relapse, sensitive	S	S
First relapse resistant	C	N
Second or greater relapse	S	C
Relapse after autologous transplant	S	N
Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia		
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	R	N
First or greater relapse, sensitive	C	S
First or greater relapse resistant	R	N
Relapse after autologous transplant	C	N
Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia		
CR1	N	N
Primary refractory, sensitive	N	C
Primary refractory, resistant	R	N
First or greater relapse, sensitive	C	S
First or greater relapse, resistant	R	N
Relapse after autologous transplant	C	N
Burkitt's lymphoma		
CR1	N	N
First or greater relapse, sensitive	C	C
First or greater relapse, resistant	C	N
Relapse after autologous transplant	C	N
Cutaneous T-cell lymphoma		
Relapse	S	C

Plasmablastic lymphoma		
CR1	R	R
Relapse	R	C
Chronic lymphocytic leukemia		
High risk, first or greater remission	S	N
T-cell prolymphocytic leukemia	S	R
B cell, prolymphocytic leukemia	R	R
Transformation to high grade lymphoma	C	S
Solid Tumors		
Germ cell tumor, relapse	N	S
Germ cell tumor refractory	N	S
Ewing's sarcoma, high risk	D	C
Breast cancer, adjuvant high risk	N	N
Breast cancer, metastatic	D	N
Renal cancer, metastatic	D	N
Nonmalignant diseases		
Severe aplastic anemia, new diagnosis	S	N
Severe aplastic anemia, relapse/refractory	S	N
Fanconi's anemia	R	N
Dyskeratosis congenita	R	N
Sickle cell disease	S	N
Thalassemia	D	N
Hemophagocytic syndromes, refractory	S	N
Common variable immunodeficiency	R	N
	C	N
Wiskott-Aldrich syndrome	R	N
Chronic granulomatous disease	N	C
Multiple sclerosis	N	S
Systemic sclerosis	N	D
Rheumatoid arthritis	N	D
Systemic lupus erythematosus	N	D
Crohn's disease	N	D
	N	D
Polymyositis-dermatomyositis		

Osteopetrosis (intermediate)	D	N
Cerebral X-linked adrenoleukodystrophy	R	N

Standard of care (S); Standard of care, clinical evidence available (C); Standard of care, rare indication (R); Developmental (D); Not generally recommended (N). TKI, tyrosine kinase inhibitor; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes, POD₂₄, progress of disease in <24 months from initial therapy.

In 2008, the American Society for Blood and Marrow Transplantation issued a position statement regarding collection and preservation of cord blood for personal use. The recommendations include the following:

- Expectant parents are encouraged to donate their newborn's UCB (umbilical cord blood) for public banking when that option is available. Donation makes the CB (cord blood), which is rich in HSCs (hematopoietic stem cells), available for life-saving treatments when there is a suitable match with a patient.
- Private storage of CB for future use by a newborn is not routinely recommended. The likelihood of the stored blood being used for HSCT (hematopoietic stem cell transplantation) is very small, probably as low as 0.04% to 0.001% in the first 20 years of life. If later in life a transplant is required, there likely will be superior sources of suitable stem cells than the child's own CB.
- Family member banking (collecting and storing CB for a family member) may be recommended for a newborn who has a sibling with a disease that can be successfully treated with HSCT. Family member banking on behalf of a parent with a disease that may be treated successfully with allogeneic transplant is only recommended when there are shared HLA-antigens between the parents.
- Accurate and complete information about UCB collection and banking should be available to expectant parents so that they can make informed decisions. Parents who choose to store CB for personal use should carefully review their contract and financial responsibilities, and inquire about quality standards, median nucleated cell dose of stored units and accreditation of the CB bank.

The committee acknowledges the potential for an expansion of indications for CB in the future, and these recommendations will be reviewed periodically so that they remain consistent with current medical knowledge.

National Comprehensive Cancer Network (NCCN)

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat, and manage patients with cancer. These guidelines evolve continuously as new treatments and diagnostics emerge and may be utilized by Wellmark BlueCross BlueShield when determining medical necessity and investigational according to this medical policy.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review can be located at clinicaltrials.gov.

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337. National Comprehensive Cancer Network (NCCN) Ampullary Adenocarcinoma Version 2.2026 Also available at <https://www.nccn.org>
338. National Comprehensive Cancer Network (NCCN) Anal Carcinoma Version 2.2026 Also available at <https://www.nccn.org>

339. National Comprehensive Cancer Network (NCCN) Biliary Tract Cancers (Gallbladder Cancer, Intrahepatic Cholangiocarcinoma, Extrahepatic Cholangiocarcinoma) Version 1.2026. Also available at <https://www.nccn.org>
340. National Comprehensive Cancer Network (NCCN) Bladder Cancer Version 1.2026 Also available at <https://www.nccn.org>
341. National Comprehensive Cancer Network (NCCN) Bone Cancer Version 2.2026 Also available at <https://www.nccn.org>
342. National Comprehensive Cancer Network (NCCN) Breast Cancer Version 3.2026 Also available at <https://www.nccn.org>
343. National Comprehensive Cancer Network (NCCN) Castleman Disease Version 2.2026 Also available at <https://www.nccn.org>
344. National Comprehensive Cancer Network (NCCN) Central Nervous System Cancers Version 1.2026 Also available at <https://www.nccn.org>
345. National Comprehensive Cancer Network (NCCN) Cervical Cancer Version 2.2026 Also available at <https://www.nccn.org>
346. National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Version 2.2026 Also available at <https://www.nccn.org>
347. National Comprehensive Cancer Network (NCCN) Chronic Myeloid Leukemia Version 1.2026 Also available at <https://www.nccn.org>
348. National Comprehensive Cancer Network (NCCN) Colon Cancer Version 2.2026 Also available at <https://www.nccn.org>
349. National Comprehensive Cancer Network (NCCN) Dermatofibrosarcoma Protuberans Version 2.2026 Also available at <https://www.nccn.org>
350. National Comprehensive Cancer Network (NCCN) Rectal Cancer Version 1.2024 Also available at <https://www.nccn.org>
351. National Comprehensive Cancer Network (NCCN) Esophageal and Esophagogastric Junction Cancers Version 2.2026 Also available at <https://www.nccn.org>
352. National Comprehensive Cancer Network (NCCN) Gastric Cancer Version 2.2026 Also available at <https://www.nccn.org>
353. National Comprehensive Cancer Network (NCCN) Gastrointestinal Stromal Tumors (GISTs) Version 1.2026 Also available at <https://www.nccn.org>
354. National Comprehensive Cancer Network (NCCN) Gestational Trophoblastic Neoplasia Version 2.2026 Also available at <https://www.nccn.org>
355. National Comprehensive Cancer Network (NCCN) Hairy Cell Leukemia Version 2.2026 Also available at <https://www.nccn.org>
356. National Comprehensive Cancer Network (NCCN) Head and Neck Cancers Version 2.2026 Also available at <https://www.nccn.org>
357. National Comprehensive Cancer Network (NCCN) Hepatobiliary Cancers Version 1.2023 Also available at <https://www.nccn.org>. This guideline is no longer applicable has been broken out into separate guidelines
358. National Comprehensive Cancer Network (NCCN) Hepatocellular Carcinoma Version 1.2026. Also available at <https://www.nccn.org>

- 359. National Comprehensive Cancer Network (NCCN) Histiocytic Neoplasms Version 1.2026
Also available at <https://www.nccn.org>
- 360. National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma Version 1.2026
Also available at <https://www.nccn.org>
- 361. National Comprehensive Cancer Network (NCCN) Hodgkin Lymphoma (Pediatric) Version 1.2026 Also available at <https://www.nccn.org>
- 362. National Comprehensive Cancer Network (NCCN) Kidney Cancer Version 2.2026 Also available at <https://www.nccn.org>
- 363. National Comprehensive Cancer Network (NCCN) Mesothelioma: Peritoneal Version 2.2026 Also available at <https://www.nccn.org>
- 364. National Comprehensive Cancer Network (NCCN) Mesothelioma: Pleural Version 2.2026 Also available at <https://www.nccn.org>
- 365. National Comprehensive Cancer Network (NCCN) Merkel Cell Carcinoma Version 2.2026 Also available at <https://www.nccn.org>
- 366. National Comprehensive Cancer Network (NCCN) Cutaneous Melanoma Version 2.2026 Also available at <https://www.nccn.org>
- 367. National Comprehensive Cancer Network (NCCN) Uveal Melanoma Version 2.2026 Also available at <https://www.nccn.org>
- 368. National Comprehensive Cancer Network (NCCN) Multiple Myeloma Version 5.2026 Also available at <https://www.nccn.org>
- 369. National Comprehensive Cancer Network (NCCN) Systemic Light Chain Amyloidosis Version 2.2026 Also available at <https://www.nccn.org>
- 370. National Comprehensive Cancer Network (NCCN) Myelodysplastic Syndromes Version 3.2026 Also available at <https://www.nccn.org>
- 371. National Comprehensive Cancer Network (NCCN) Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes Version 1.2026 Also available at <https://www.nccn.org>
- 372. National Comprehensive Cancer Network (NCCN) Myeloproliferative Neoplasms Version 1.2026 Also available at <https://www.nccn.org>
- 373. National Comprehensive Cancer Network (NCCN) Neuroblastoma Version 2.2026 Also available at <https://www.nccn.org>
- 374. National Comprehensive Cancer Network (NCCN) Neuroendocrine and Adrenal Tumors Version 1.2026 Also available at <https://www.nccn.org>
- 375. National Comprehensive Cancer Network (NCCN) B-Cell Lymphomas Version 4.2026 Also available at <https://www.nccn.org>
- 376. National Comprehensive Cancer Network (NCCN) Pediatric Aggressive Mature B-Cell Lymphomas Version 1.2026 Also available at <https://www.nccn.org>
- 377. National Comprehensive Cancer Network (NCCN) Pediatric Soft Tissue Sarcoma Version 1.2026 Also available at <https://www.nccn.org>
- 378. National Comprehensive Cancer Network (NCCN) Pediatric Central Nervous System Cancer Version 1.2026 Also available at <https://www.nccn.org>

- 379. National Comprehensive Cancer Network (NCCN) Cutaneous Lymphomas Version 2.2026 Also available at <https://www.nccn.org>
- 380. National Comprehensive Cancer Network (NCCN) T-Cell Lymphomas Version 2.2026 Also available at <https://www.nccn.org>
- 381. National Comprehensive Cancer Network (NCCN) Squamous Cell Skin Cancer Version 2.2026 Also available at <https://www.nccn.org>
- 382. National Comprehensive Cancer Network (NCCN) Non-Small Cell Lung Cancer. Version 5.2026 Also available at <https://www.nccn.org>
- 383. National Comprehensive Cancer Network (NCCN) Occult Primary (Cancer of Unknown Primary) Version 2.2026 Also available at <https://www.nccn.org>
- 384. National Comprehensive Cancer Network (NCCN) Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer Version 4.2026 Also available at <https://www.nccn.org>
- 385. National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma Version 2.2026 Also available at <https://www.nccn.org>
- 386. National Comprehensive Cancer Network (NCCN) Penile Cancer Version 1.2026 Also available at <https://www.nccn.org>
- 387. National Comprehensive Cancer Network (NCCN) Prostate Cancer Version 5.2026 Also available at <https://www.nccn.org>
- 388. National Comprehensive Cancer Network (NCCN). Small Bowel Adenocarcinoma Version 2.2026 Also available at <https://www.nccn.org>
- 389. National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer Version 2.2026 Also available at <https://www.nccn.org>
- 390. National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma Version 3.2026 Also available at <https://www.nccn.org>
- 391. National Comprehensive Cancer Network (NCCN) Systemic Mastocytosis Version 2.2026 Also available at <https://www.nccn.org>
- 392. National Comprehensive Cancer Network (NCCN) Testicular Cancer Version 1.2026 Also available at <https://www.nccn.org>
- 393. National Comprehensive Cancer Network (NCCN) Thymomas and Thymic Carcinomas Version 2.2026 Also available at <https://www.nccn.org>
- 394. National Comprehensive Cancer Network (NCCN) Thyroid Carcinoma Version 1.2026 Also available at <https://www.nccn.org>
- 395. National Comprehensive Cancer Network (NCCN) Uterine Neoplasms Version 2.2026 Also available at <https://www.nccn.org>
- 396. National Comprehensive Cancer Network (NCCN) Vaginal Cancer Version 2.2026 Also available at <https://www.nccn.org>
- 397. National Comprehensive Cancer Network (NCCN) Vulvar Cancer Version 2.2026 Also available at <https://www.nccn.org>
- 398. National Comprehensive Cancer Network (NCCN) Wilms Tumor (Nephroblastoma) Version 1.2026 Also available at <https://www.nccn.org>

399. National Comprehensive Cancer Network (NCCN) Waldstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma Version 2.2026. Also available at <https://www.nccn.org>
400. National Comprehensive Cancer Network Adolescent and Young Adult Oncology Version 2.2026 Also available at <https://www.nccn.org>
401. UpToDate. Hematopoietic Cell Transplantation for Non-SCID Inborn Errors of Immunity. Topic last updated May 2026. Also available at <https://www.uptodate.com>
402. UpToDate. Hematopoietic cell transplantation cell transplantation for severe combined immunodeficiencies. Topic last updated May 2025. Also available at <https://www.uptodate.com>
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CODES

To report provider services, use appropriate CPT codes, HCPCS codes, Revenue codes, and/or ICD diagnosis codes.

Codes	Number	Description
CPT		
	38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
	38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	None	
Type of Service	Therapy	
Place of Service	Inpatient/Outpatient	

POLICY HISTORY

Date	Action	Action
June 2026	Annual Review	Policy Revised
April 2025	Annual Review	Policy Revised
April 2024	Annual Review	Policy Revised
March 2023	Annual Review	Policy Revised
April 2022	Annual Review	Policy Revised
April 2021	Annual Review	Policy Revised
November 2020	Interim Review	Policy Revised
August 2020	Interim Review	Policy Revised
July 2020	Interim Review	Policy Revised
April 2020	Annual Review	Policy Revised
September 2019	Interim Review	Policy Revised
July 2019	Interim Review	Policy Revised
April 2019	Annual Review	Policy Revised
April 2018		New Medical Policy

APPENDIX

Clinical Input

2026 Clinical Input

Objective

Clinical input was sought to help determine whether the use of autologous hematopoietic cell transplantation for individuals with multiple sclerosis would provide a clinically meaningful improvement in net health outcome and represents generally accepted medical practice in selected patients. In response to requests, clinical input was received from 3 physician-level respondents, all identified by the American Academy of Neurology.

Respondents

Clinical input was provided by the following physician members identified by a specialty society:

1. Jeffrey A. Cohen, MD – Cleveland Clinic (identified by AAN)
2. Mark S. Freedman, MSc MD – University of Ottawa and the Ottawa Hospital Research Institute (identified by AAN)
3. John R. Corboy, MD – University of Colorado, School of Medicine (identified by AAN)

Ratings

All responses to Question 1 regarding whether evidence supports improved health outcomes and whether clinical use is in accordance with generally accepted medical practice were "Yes."

			Regarding the use of Hematopoietic Cell Transplantation:									
			Confidence Level that Evidence Supports Improved Health Outcomes					Confidence Level that Clinical Use is in Accordance with Generally Accepted Medical Practice				
			Low Intermediate High					Low Intermediate High				
Clinical Indication	Respondent	Identified By	1	2	3	4	5	1	2	3	4	5
Individuals with multiple sclerosis.	Dr. Cohen	AAN										
	Dr. Freedman	AAN										
	Dr. Corboy	AAN										

AAN: American Academy of Neurology.

Respondent Profile

#	Respondent	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
1	Dr. Jeffrey A. Cohen	Cleveland Clinic	Neurology	Neurology, Neuroimmunology
2	Dr. Mark S. Freedman	University of Ottawa and the Ottawa Hospital Research Institute	Neurology/Neuroimmunology	RCPSC; FAAN; FANA; Fellowship training at Montreal Neurological Institute

3	Dr. John R. Corboy	University of Colorado, School of Medicine	Neurology	ABPN; Neurovirology at Johns Hopkins, 1989-1992
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Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than \$1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than \$350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	Yes	I am Protocol Chair and site PI for the BEAT-MS trial, sponsored by NIAID/NIH and conducted by the Immune Tolerance Network	No		Yes	Personal compensation for consulting for Astoria, AstraZeneca, Bristol-Myers Squibb, Convelo, Kite Pharma, Legend Biotech, Novartis, polTreg, PSI, and Shionogi, and Chairing a DSMB for Celltrion - all related to multiple sclerosis.	No	
2	Yes	I have run 2 large projects funded by MS Canada and continue to have funding regarding HSCT for MS from other sources as well	Yes	I am part of the faculty of the University of Ottawa and a Sr. Scientist at the Ottawa Hospital Research Institute where are studies are being carried out.	No	I have many sources of consulting fees and honoraria with various industry partners, but none related to the topic of HSCT	No	
3	Yes	The BEAT-MS clinical trial,	No		No		No	

		supported by the Immune Tolerance Network. I am the site PI at the University of Colorado.						
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Detailed Responses

Question 1:

We are seeking your rationale on whether using the intervention for the above indication provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience. Please address these points in your response:

- Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
- Specific outcomes that are clinically meaningful;
- Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
- Key supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	There is a subset of patients with highly active relapsing MS and high risk of worsening disability who do not achieve adequate disease control with the available disease modifying medications. Autologous HCT is an appropriate option for treatment of such patients. HCT has potent and durable efficacy on relapses, MRI lesion activity and brain volume loss, disability progression, disability improvement. Potential adverse effects related to HCT are well-recognized and similar in patients with MS as in other indications. The risks and financial cost of HCT are largely front-loaded. Because most patients do not require restarting disease medication, HCT becomes cost effective in 3-4 years. Characteristics of patients most likely to benefit include young, relatively recent disease onset, still ambulatory, highly active MS with recent clinical relapses and/or MRI lesion activity, continued activity despite disease therapy, and without comorbidities that increase risk. The References summarize the literature supporting utility of HCT in MS. Published position statements from the American Society of Blood and Marrow Transplantation, European Blood and Marrow Transplantation, and National MS Society support HCT as a reasonable option for highly active relapsing MS and an inadequate response to the available therapies.
2	We have been using aHSCT as a regular treatment for patients deemed to have "aggressive early MS", based one or more criteria: - Disease onset typically within 5-10 years - Failure to obtain adequate disease control with 1 or more approved DMT - Rapid accumulation of irreversible deficits (EDSS typically 2 or 3)

	- Continued clinical relapses (>3 per year) with residual deficits - High burden of disease on MRI with continued evidence of inflammation (i.e. new lesion formation or persistent enhancing lesions) - No medical co-morbidity that would pose an excess risk to aHSCT In a few select cases, we have gone to aHSCT as a "first line" treatment given the sense that a rapid accumulation of irreversible deficits has transpired as the patient first presents to us and the patient meets one or more of the above criteria. It was our experience that such patients would be highly likely to fail any current DMT. We have several published papers concerning our experience and will be reporting our 20 year follow up later this year. We have treated >120 MS patients with aHSCT. Given that our healthcare system is universal coverage for all Canadians, the cost of the single procedure is a pittance compared to the long term costs of maintaining a DMT. It is estimated that the average cost for the procedure in Ontario is <\$50K CAD. Not a single patient has required DMT after aHSCT. We continue to see a few patients who continue to progress by EDSS following the treatment, but not a single patient has experienced any further relapses or developed any new MRI lesions consistent with new MS inflammation going on some 25 years. Lancet 2016; 388: 576–85. DOI.org/10.1016/S0140-6736(16)30169-6 Multiple Sclerosis Journal 1–7 DOI: 10.1177/1352458520985238 Current Protocols, 2, e437. DOI: 10.1002/cpz1.437 Multiple Sclerosis Journal 2021, Vol. 27(2) 167–173 DOI: 10.1177/1352458520917936
3	1. Scenarios: The data from multiple trials and meta-analyses shows that younger patients with active MS, who are still ambulatory and have recent disease activity that was not responsive to routine immunotherapy, have the best response to aHSCT. This is especially true if they have failed highly effective therapy. Failure would include, while on therapy, recent relapses, new MRI lesions, significant disability in a young person 2. Meaningful outcomes: Significantly reduced/no new MS relapses, new MRI lesions, and worsening of disability; disease stability or improvement; improved functionality with activities of daily living; and enhanced quality of life. 3. Inclusion/Exclusion. See above, #1, under scenarios. 4. Evidence: The relevant research papers are noted in the references, and might also include several additional publications as noted below under question 3.

- Respond YES or NO whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

Clinically Meaningful Improvement in Net Health Outcome			Low Confidence		Intermediate Confidence		High Confidence
#	YES	NO	1	2	3	4	5
1	X						X
2	X						X
3	X						X

- Respond YES or NO whether this intervention is consistent with generally accepted medical practice; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

Generally Accepted Medical Practice			Low Confidence		Intermediate Confidence		High Confidence
#	YES	NO	1	2	3	4	5
1	X					X	
2	X						X
3	X					X	

Question 2:

Would you agree that the following criteria for identifying individuals with multiple sclerosis for hematopoietic cell transplantation are clinically appropriate?

Autologous hematopoietic cell transplantation (AHCT) is considered medically necessary for the treatment of multiple sclerosis when the following criteria are met:

- Relapsing-remitting multiple sclerosis (RRMS); OR
- Secondary progressive multiple sclerosis with evidence of ongoing inflammatory disease activity defined by any of the following:
 - Two or more clinical relapses in the previous 12 months; OR
 - One or more clinical relapses in the 24 months AND MRI evidence of disease activity (new/enlarging T2 lesions or gadolinium-enhancing lesions) at a different time point; OR
 - Confirmed EDSS (Expanded Disability Status Scale) worsening of ≥ 1 point over the preceding 12 months;

AND

- Disease progression or continued activity despite treatment with disease-modifying therapy (DMT), evidenced by both of the following:
 - Prior DMT exposure, evidenced by:
 - Failure of ≥ 1 disease-modifying therapy at therapeutic doses for adequate duration; OR
 - Documented intolerance to disease-modifying therapy; AND
 - Evidence of treatment failure, evidenced by:
 - Continued clinical relapse activity while on DMT; OR
 - New or enlarging MRI lesions (T2-hyperintense or gadolinium-enhancing) while on DMT; OR
 - Confirmed disability progression (EDSS increase ≥ 1.0 point) while on DMT;

AND

- At high risk for future disability, evidenced by any of the following:
 - ≥ 2 relapses per year despite treatment; OR
 - Incomplete recovery from relapses with residual deficits; OR
 - Early accumulation of disability (EDSS increase ≥ 1.0 point within 12 months); OR

- High T2 lesion burden on MRI; OR
- Presence of gadolinium-enhancing lesions despite DMT; OR
- Spinal cord involvement on MRI; OR
- Poor response to high-efficacy disease-modifying therapies;

AND

- The individual is between 18 to 55 years old with a disease duration ≤15 years;

AND

- Has a functional status meeting both of the following:
 - EDSS score between 2.0 to 6.5; AND
 - The individual is ambulatory (with or without an assistive device).

#	YES	NO
1	X	
2	X	
3	X	

Please provide any supporting comments below:

#	Comments
1	Several publications have proposed similar criteria.
2	Variations of these criteria have been used internationally and approved by several groups performing aHSCT regularly. A patient NEED NOT fulfill ALL criteria, but the common theme is of uncontrolled disease based on repeated inflammatory events leading to irreversible early damage.
3	The American Academy of Neurology, the American Society for Blood and Marrow Transplantation and the European Committee on the Treatment and Research of MS (along with the EBMT) have similar positions.

Question 3:

Is there any key evidence missing from the attached reference list on pages 9-10 that demonstrates clinically meaningful improvement in net health outcome?

#	YES	NO
1	X	
2	X	
3	X	

If YES, please share any relevant scientific citations of missing evidence (including the PMID).

#	Citations
1	Boffa G et al. Mult Scler J 2025;31:1401-16 PMID: 40620225 Kalincik T et al. Brain 2026;149(3):951-962 PMID: 40755195 Kvistad CE et al. Mult Scler J 2024;30:751-4 PMID: 38345003 Moore JJ et al. J Neurol Neurosurg Psychiatr 2019;90:514-21 PMID: 30538138 Muraro PA et al. Nature Rev Neurol 2017;13:391-405 PMID: 28621766 Muraro P et al. Nature Rev Neurol 2025;21:140–58 PMID: 39814869 Orlewska K et al. Value Health Reg Issues 2021;25:104-7 PMID: 33865219 Sormani MP et al. Mult Scler J 2017;23:201-04 PMID: 27207454
2	I agree with the list provided by Dr. Cohen. In addition: - Kazmi M. et al. Br J Haematol. 2025;207:977–991. DOI: 10.1111/bjh.20199 - Noui Y. et al. J Neurol Neurosurg Psychiatry 2025;0:1–9. DOI:10.1136/jnnp-2024-335512 - Fan L. et al. Multiple Sclerosis and Related Disorders 92 (2024) 105944; DOI.org/10.1016/j.msard.2024.105944 - Mariottini A. et al. J Neurol Neurosurg Psychiatry 2025;0:1–9. doi:10.1136/jnnp-2025-336808 - Muraro PA, et al. J Neurol Neurosurg Psychiatry 2025;0:1–10. doi:10.1136/jnnp-2025-336755 - Mariottini A. et al. Multiple Sclerosis and Related Disorders 78 (2023) 104932;doi.org/10.1016/j.msard.2023.104932
3	Marrottini MA et al, J Neurol Neurosurg Psych 2026. PMID: 41115787 Pavlovic I et al. Ann Clin Transl Neurol 2026. PMID:41088777 Muraro PA et al. J Neurol Neurosurg Psych 2026. PMID: 40912910 Kalincik T et al. Brain 2026; PMID: 40755195 Emgren I et al. J Neuroinflamm 2025. PMID: 40676588 Boffa G et al. Mult Scler J 2025. PMID: 40620225 Kazmi M et al. Br J Haematol 2025.PMID: 40500866 Muraro PA et al. Ann Neurol 2025. PMID: 40251896 Desaga AM. Mult Scler 2025. PMID: 39957535 Muraro P et al. Nature Rev Neurol 2025. PMID: 39814869 Sormani MP et al. Mult Scler J 2017. PMID: 27207454 Volz T et al. Front Neurol 2024. PMID: 38751886 Entire issue of Handbook of Clinical Neurology, 2024, Volume 202.

2020 Clinical Input - Summary

Respondents

Clinical input was provided by the following physician members identified by a specialty society or clinical health system:

- Reid Merryman, MD, Lymphoma specialist in Hematology/Oncology, Dana-Farber Cancer Institute (DFCI)
- Mehdi Hamadani, MD, Professor of Medicine, Bone Marrow Transplant & Cellular Therapy specialist in Hematology/Oncology, CIBMTR & Medical College of Wisconsin, identified by American Society for Transplantation and Cellular Therapy (ASTCT)**

- Loretta Nastoupil, MD, Associate Professor, Lymphoma specialist in Hematology/Oncology, University of Texas MD Anderson Cancer Center, identified by American Society of Clinical Oncology (ASCO)

Note: A 4th clinical input response was received as outlined in the Appendix; however, this response is not included in this summary because it was considered incomplete, not providing supporting rationale.

* Indicates that no response was provided regarding conflicts of interest related to the topic where clinical input is being sought.

** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

Clinical input provided by the specialty society at an aggregate level is attributed to the specialty society. Clinical input provided by a physician member designated by a specialty society or health system is attributed to the individual physician and is not a statement from the specialty society or health system. Specialty society and physician respondents participating in the Evidence Street® clinical input process provide review, input, and feedback on topics being evaluated by Evidence Street. However, participation in the clinical input process by a specialty society and/or physician member designated by a specialty society or health system does not imply an endorsement or explicit agreement with the Evidence Opinion published by BCBSA or any Blue Plan.

Respondent Profile

	Physician				
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by Dana-Farber Cancer Institute					
1	Reid Merryman	MD	Dana-Farber Cancer Institute (DFCI)	Lymphoma specialist in Hematology/Oncology	Internal Medicine, Hematology/Oncology
Identified by American Society for Transplantation and Cellular Therapy					
2	Mehdi Hamadani	MD	Professor of Medicine, CIBMTR & Medical College of Wisconsin	Bone Marrow Transplant & Cellular Therapy specialist in Hematology/Oncology	Hematology, Medical Oncology
Identified by American Society of Clinical Oncology					
3	Loretta Nastoupil	MD	Associate Professor, University of Texas MD Anderson Cancer Center	Lymphoma specialist in Hematology/Oncology	Internal Medicine, Hematology, Medical Oncology
4	Anonymous	MD	Anonymous clinical practice	Hematology/Oncology	Hematology/Oncology

Respondent Conflict of Interest Disclosure

#	1) Research support related to the topic where clinical input is being sought		2) Positions, paid or unpaid, related to the topic where clinical input is being sought		3) Reportable, more than \$1,000, health care–related assets or sources of income for myself, my spouse, or my dependent children related to the topic where clinical input is being sought		4) Reportable, more than \$350, gifts or travel reimbursements for myself, my spouse, or my dependent children related to the topic where clinical input is being sought	
	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation	YES/NO	Explanation
1	No		No		No		No	
2	No		Yes	Direct a BMT & Cellular Therapy Program that provides care for Hodgkin lymphoma patients in both transplant and non transplant settings.	No		No	
3	No		No		No		No	
4	No		No		No		No	

Individual physician respondents answered at individual level. Specialty Society respondents provided aggregate information that may be relevant to the group of clinicians who provided input to the Society-level response. NR = not reported

Clinical Input Responses

			Confidence Level That Clinical Use Expected to Provide Clinically Meaningful Improvement in Net Health Outcome										Confidence Level that Clinical Use is Consistent with Generally Accepted Medical Practice											
			NO					YES					NO					YES						
			High	Intermediate	Low	Low	Intermediate	High	High	Intermediate	Low	Low	Intermediate	High	High	Intermediate	Low	Low	Intermediate	High				
Clinical Indication	Respondent	Identified by	Yes or No	5	4	3	2	1	1	2	3	4	5	Yes or No	5	4	3	2	1	1	2	3	4	5
Use of second autologous hematopoietic cell transplantation for individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation	Dr. Merryman	DFCI	No											No										
	Dr. Hamadani**	ASTCT	No											No										
	Dr. Nastoupil	ASCO	No											No										
Use of tandem autologous hematopoietic cell transplantation for individuals with Hodgkin lymphoma	Dr. Merryman	DFCI	No											No										
	Dr. Hamadani**	ASTCT	No											No										
	Dr. Nastoupil	ASCO	No											No										

DFCI: Dana-Farber Cancer Institute; ASTCT: American Society for Transplantation and Cellular Therapy; ASCO: American Society of Clinical Oncology
 ** Indicates that conflicts of interest related to the topic where clinical input is being sought were identified by this respondent (see Appendix).

The following PICO applies to the clinical input.

Populations	Interventions	Comparators	Outcomes
Individuals: With relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation	Interventions of interest are: Second autologous hematopoietic cell transplantation	Comparators of interest are: Standard of care	Relevant outcomes include: - Overall survival - Disease-specific survival - Change in disease status - Morbid events - Treatment-related mortality - Treatment-related morbidity
Individuals: With Hodgkin lymphoma	Interventions of interest are: Tandem autologous hematopoietic cell transplantation	Comparators of interest are: Standard of care	Relevant outcomes include: - Overall survival - Disease-specific survival - Change in disease status - Morbid events - Treatment-related mortality - Treatment-related morbidity

Clinical input is sought to help determine whether the use of either second autologous hematopoietic cell transplantation for relapsed Hodgkin lymphoma or tandem autologous hematopoietic cell transplantation for Hodgkin lymphoma would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice

Detailed Responses

Question 1.

For use of second autologous hematopoietic cell transplantation for individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation:

- We are seeking your opinion on whether this use provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience and address these points in your response:
 - Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
 - Specific outcomes that are clinically meaningful;
 - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
 - Supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	There are no clinical scenarios where I would recommend a second autologous hematopoietic stem cell transplant. In the last 5 years, several new treatments (brentuximab vedotin, nivolumab, pembrolizumab) have been approved for patients who are ineligible for or who relapse after ASCT, and outcomes in this patient population have improved significantly (PMID 28512788). For patients who relapse after ASCT, we would favor treatment with allogeneic stem cell transplantation for eligible patients.
2	No randomized or prospective trials have evaluated safety and feasibility of second autologous transplantation in HL patients. A CIBMTR analysis (PMID: 18640574), reported outcomes of lymphoma patient undergoing a second autologous HCT, including 21 HL subject. The treatment related mortality was high (15% at day 100 and 18% at 1 year), with only a subset of patients with disease control at 3 years (36%). This analysis was conducted before active salvage agents in HL were available (including brentuximab vedotin, check point inhibitors, alternative donor transplantation using modern platforms or cell therapies on genetically modified immune effector cells). Considering the availability of several approved and investigational agents in the management of HL, and quality of evidence available to date, the practice of second autologous transplant cannot be consider standard-of-care.
3	There is insufficient evidence to support a second autologous hematopoietic cell transplantation for relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation.
4	NR

NR = not reported

- Based on the evidence and your clinical experience for the use of second autologous hematopoietic cell transplantation for individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation:
- Respond YES or NO whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
		1	2	3	4	5
1	No				X	
2	No			X		
3	No					X
4	No			X		

NR = not reported

- Based on the evidence and your clinical experience for the use of second autologous hematopoietic cell transplantation for individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation:
- Respond YES or NO whether this intervention is consistent with generally accepted medical practice; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
		1	2	3	4	5
1	No				X	
2	No				X	
3	No				X	
4	No			X		

NR = not reported

Question 2.

For use of tandem autologous hematopoietic cell transplantation for individuals with Hodgkin lymphoma:

- We are seeking your opinion on whether this use provides a clinically meaningful improvement in net health outcome. Please respond based on the evidence and your clinical experience and address these points in your response:
 - Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
 - Specific outcomes that are clinically meaningful;
 - Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
 - Supporting evidence from the authoritative scientific literature (please include PMID).

#	Rationale
1	We do not treat with tandem autologous transplants. While there is phase 2 data, it has not been clearly shown to be superior to our standard approach. We favor allogeneic transplant over tandem autologous transplantation for patients with chemorefractory disease.
2	No randomized trials have evaluated efficacy of tandem autologous transplantation in HL patients. While the question of tandem HCT has been evaluated in prospective single arm studies several years ago, only a single SWOG/BMT CTN trial has assessed this question in the modern era (PMID: 29289757). This study enrolled 89 subjects, including 64 patients high-risk disease (primary refractory disease or early relapse). There were no treatment-related deaths in the first year after transplantation. With a median follow-up of 6.2 years (range, 2 to 7.7) for eligible patients who remained alive, the 2-year and 5-year PFS were 63% (95% CI, 52% to 72%) and 55% (95% CI, 44% to 64%) respectively; the 2-year and 5-year overall survival were 91% (95% CI, 83% to 95%) and 84% (95% CI, 74% to 90%), respectively. While these results are encouraging and acknowledging hazards of cross trial comparison, in patients with high risk HL, similar (or better) results can be expected with single autologous transplant followed by brentuximab vedotin maintenance. The latter is supported by randomized, prospective data from AETHERA trial (Moskowitz et al. Lancet 2015) and is the current standard-of-care
3	There is insufficient evidence for tandem autologous hematopoietic cell transplantation in individuals with Hodgkin lymphoma.
4	NR

NR = not reported

- Based on the evidence and your clinical experience for the use of tandem autologous hematopoietic cell transplantation for individuals with Hodgkin lymphoma:
- Respond YES or NO whether the intervention would be expected to provide a clinically meaningful improvement in net health outcome; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
		1	2	3	4	5
1	No				X	
2	No				X	
3	No					X
4	No			X		

NR = not reported

- Based on the evidence and your clinical experience for the use of tandem autologous hematopoietic cell transplantation for individuals with Hodgkin lymphoma:
- Respond YES or NO whether this intervention is consistent with generally accepted medical practice; AND Rate your level of confidence in your YES or NO response using the 1 to 5 scale outlined below.

#	YES / NO	Low Confidence		Intermediate Confidence		High Confidence
		1	2	3	4	5
1	No				X	
2	No					X
3	No					X
4	No			X		

NR = not reported

New information or technology that would be relevant for Wellmark to consider when this policy is next reviewed may be submitted to:

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 Medical Policy Analyst
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