MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA
POLICY NUMBER	MP 9.043

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**1/1/2025**

I. POLICY

Autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** in individuals with primary refractory or relapsed Hodgkin lymphoma.

Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered **medically necessary** in individuals with primary refractory or relapsed Hodgkin lymphoma.

Tandem autologous HCT may be considered **medically necessary**:

- In individuals with primary refractory Hodgkin lymphoma; **or**
- In individuals with relapsed disease with poor risk features who do not attain a complete remission to cytoreductive chemotherapy prior to transplantation (see Policy Guidelines section).

Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Other uses of HCT in patients with Hodgkin lymphoma are considered **investigational**, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

POLICY GUIDELINES

In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous hematopoietic stem-cell transplantation (HCT) for first relapse or refractory Hodgkin lymphoma (HL), poor-risk relapsed HL was 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 disease was 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 first-line treatment.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced intensity conditioning allogeneic HCT. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically >55 or >60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen-identical matched siblings. Related donors mismatched at a single locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Program is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Cross-references:

MP 9.042 Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
MP 9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

III. DESCRIPTION/BACKGROUND

TOP

HODGKIN LYMPHOMA

Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2022, the estimated number of new cases in the United States was approximately 8540, with 920 estimated deaths. The disease has a bimodal distribution, with most patients diagnosed between the ages of 20 and 39 years, with a second peak in adults aged 65 years and older.

The 2008 World Health Organization classification divides HL into 2 main types; these classifications did not change in the 2022 update:

1. “Classical” HL

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte depleted
- Lymphocyte rich

2. Nodular lymphocyte-predominant HL.

In Western countries, “classical” HL accounts for 95% of cases of HL and, for nodular lymphocyte-predominant HL, only 5 %. “Classical” HL is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. Nodular lymphocyte-predominant HL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells termed “popcorn cells”.

Staging

The Ann Arbor staging system for HL recognizes that the disease is thought typically to arise in a single lymph node and spread to contiguous lymph nodes with eventual involvement of extranodal sites. The staging system attempts to distinguish patients with localized HL who can be treated with extended field radiation from those who require systemic chemotherapy.

Each stage is subdivided into A and B categories. “A” indicates no systemic symptoms are present and “B” indicates the presence of systemic symptoms, which include unexplained weight loss of more than 10% of body weight, unexplained fevers greater than 38°, or drenching night sweats (see Table 1).

Table 1. Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Area of Concern
I	Single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE)
II	2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved should be indicated by a subscript (eg, II_2).
III	Involvement of lymph node regions or structures on both sides of the diaphragm. which may involve an extralymphatic organ or site (IIIE), spleen (IIIS), or both (IIIE+S)
IV	Disseminated (multifocal) involvement of 1 or more extralymphatic organs, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement

Patients with HL are generally classified into 3 groups: early-stage favorable (stage I-II with no B symptoms, large mediastinal lymphadenopathy, or other unfavorable factors), early-stage unfavorable (stage I-II with large mediastinal mass, multiple involved nodal regions, B symptoms, extranodal involvement, or elevated erythrocyte sedimentation rate ≥50), and advanced-stage disease (stage III-IV).

Treatment

Patients with nonbulky stage IA or IIA disease are considered to have the clinically early-stage disease. These patients are candidates for chemotherapy, combined modality therapy, or radiotherapy alone. Patients with obvious stage III or IV disease, bulky disease (defined as a 10-cm mass or mediastinal disease with a transverse diameter >33% of the transthoracic diameter), or the presence of B symptoms will require combination chemotherapy with or without additional radiotherapy.

HL is highly responsive to conventional chemotherapy, and up to 80% of newly diagnosed patients can be cured with chemotherapy and/or radiotherapy. Patients who prove refractory or who relapse after first-line therapy have a significantly worse prognosis. Primary refractory HL is defined as disease regression of less than 50% after 4 to 6 cycles of anthracycline-containing chemotherapy, disease progression during induction therapy, or progression within 90 days after the completion of first-line treatment.

In patients with relapse, the results of salvage therapy vary depending on a number of prognostic factors, as follows: the length of the initial remission, stage at recurrence, and the severity of anemia at the time of relapse. Early and late relapse are defined as less or more than 12 months from the time of remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous hematopoietic cell transplantation (HCT) but not more than 40% with early first relapse.

Only 25% to 35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within 1 to 2 years, and once relapse occurs posttransplant, median survival is less than 12 months.

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Cord blood is discussed in detail in MP 9.001 Placental/Umbilical Cord Blood as a Source of Stem Cells.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for HCT

Conventional Conditioning

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to

destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse events that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increase susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiotherapy to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity Conditioning for Allo-HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor-cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Targeted Chemotherapy and Autologous Hematopoietic Cell Transplantation for the Treatment of Hodgkin Lymphoma

A recent important development in the Hodgkin lymphoma treatment landscape is the emergence of several novel agents that are now being used as alternatives to stem cell transplantation in patients at high-risk for relapse after chemotherapy or relapse following autologous HCT. These agents include brentuximab vedotin, a CD30-directed antibody-drug conjugate, and nivolumab and pembrolizumab which are 2 programmed death receptor-1 (PD-1) blocking antibodies. The U.S. Food and Drug Administration (FDA) regulatory status of these agents for the treatment of HL is summarized in Table 2.

Brentuximab vedotin was evaluated in a large, phase 3, multinational, double-blind randomized controlled trial known as the AETHERA trial (abbreviation definition unknown). Moskowitz et al

(2015)10, reported on the outcomes for 329 individuals with HL with risk factors for post-transplantation relapse or progression (e.g., primary refractory HL, relapse <12 months after initial therapy, and/or relapse with extranodal disease). Results showed that early consolidation with brentuximab vedotin after autologous HCT significantly improved 2-year progression-free survival (PFS) versus placebo (63% versus 51%, hazard ratio [HR] 0.57; 95% confidence interval [CI], 0.40 to 0.81). At 5-year follow-up, the significant PFS benefit for brentuximab vedotin persisted (59% versus 41%; HR 0.52; 95% CI, 0.38 to 0.72).11, In addition, a study by Smith et al (2018)12, of tandem autologous HCT observed that the 2-year PFS of 63% for brentuximab vedotin demonstrated in the AETHERA RCT "matches" the 2-year PFS rates for tandem autologous HCT.

A survival benefit with novel agents has been found in the setting of relapse post-autologous HCT. Bair et al (2017) reported a retrospective comparative analysis that evaluated the outcomes of 87 individuals with relapsed/refractory HL who had relapsed post-autologous HCT. Compared to individuals who did not receive any novel agents, those that received novel agents, including brentuximab vedotin or nivolumab, experienced a significant improvement in median overall survival (85.6 versus 17.1 months; P<.001). The availability of safe and effective targeted systemic therapy represents an alternative to the use of a second autologous transplant or planned tandem autologous HCT for HL consolidation treatment or relapse/refractory disease treatment.

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 Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Table 2. Novel agents Approved by the U.S. Food and Drug Administration

Drug	BLA	Type of agent	Manu-facturer	FDA-approved indications for post-autologous HCT use	Date FDA approved
Brentuximab vedotin	125388	CD30-directed antibody-drug conjugate	Seattle Genetics	• Classical HL at high-risk of relapse or progression as post-autologous HCT consolidation • Classical HL after failure of autologous hematopoietic stem cell transplantation	Aug 2015

Nivolumab	125554	Programmed death receptor-1 (PD-1) blocking antibody	Bristol Myers Squibb	Classical HL that has relapsed or progressed after autologous HCT and post-transplantation brentuximab vedotin	May 2016
Pembro-lizumab	125514	Programmed death receptor-1 (PD-1) blocking antibody	Merck Sharp Dohme	Adult and pediatric patients with refractory classical HL, or who relapsed after 3 or more prior lines of therapy*	Mar 2017

BLA: Biologic License Application; FDA: U.S. Food and Drug Administration; HL: Hodgkin Lymphoma; HCT: Hematopoietic Cell Transplantation
* In the pivotal trial, a multicenter, nonrandomized, open-label study, prior lines of therapy included prior autologous HCT (61%) and brentuximab (83%)

IV. RATIONALE

TOP

SUMMARY OF EVIDENCE

Autologous HCT
For individuals who have HL who receive autologous HCT as first-line therapy, the evidence includes randomized control trials (RCTs). The relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality and morbidity. RCTs of autologous HCT as first-line treatment have reported that this therapy does not provide additional benefit compared with conventional chemotherapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory HL who receive autologous HCT, the evidence includes RCTs, a meta-analysis, nonrandomized comparative studies, and case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Two RCTs in patients with relapsed or refractory disease have reported a benefit in progression-free survival (PFS) and a trend toward a benefit in OS. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed HL after an autologous HCT who receive a second autologous HCT, the evidence includes case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs or nonrandomized comparative studies were identified. In a case series, treatment-related mortality at 100 days was 11%; at a median follow-up of 72 months, the mortality rate was 73%. The evidence is insufficient to determine the effects of the technology on health outcomes.

Allo-HCT
For individuals who have HL who receive allo-HCT as first-line therapy, the evidence includes no published studies. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. No studies specifically addressing allo-HCT as first-line treatment for HL were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have relapsed or refractory HL who receive allo-HCT, the evidence includes a number of case series and a meta-analysis. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis identified 38 case series evaluating allo-HCT for relapsed or refractory HL. The pooled analysis found a 6-month OS rate of 83% and a 3-year OS rate of 50%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed HL after autologous HCT who receive allo-HCT, the evidence includes case series and a meta-analysis. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT followed by allo-HCT was significantly associated with higher 1- and 2-year OS rates and significantly higher recurrence-free survival rates at one year compared with no previous autologous HCT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive RIC with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after RIC with allo-HCT in patients with relapsed or refractory HL. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Tandem Autologous HCT
For individuals who have HL who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT might be higher than that for single autologous HCT. This study was not definitive due to potential selection bias; further studies and RCTs are needed to determine the impact of tandem autologous HCT on health outcomes in this population. However, at this time, the evidence is sufficient to determine that this technology results in the meaningful improvement of the net health outcome.

V. DEFINITIONS

TOP

ALLOGENIC refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor; after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA). Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor effect. Their disadvantage is the risk of graft-versus host disease (GVHD), which increases with great HLA disparity and recipient age.

AUTOLOGOUS refers to originating within an individual, i.e., self-donation. These stem cells are harvested from patients prior to myeloablative therapy.

REDUCED-INTENSITY ALLOGENIC STEM CELL TRANSPLANTATION uses lower doses of chemotherapy than standard allogenic transplant, it does not completely inactivate the patient's immune system or treat the ALL as aggressively. Older, sicker patients may be helped with this type of treatment.

RELAPSED refers to patients who have achieved remission but later have decreased numbers of normal blood cells and a return of leukemia in their bone marrow.

REFRACTORY refers to patients who have residual leukemia cells in their bone marrow even after they receive intensive treatment.

VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits, and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

TOP

Capital Blue Cross' medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

TOP

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes								
S2150	38204	38205	38206	38208	38209	38210	38211	38212
38213	38214	38215	38230	38232	38240	38241		

ICD-10-CM Diagnosis Codes	Description
C81.0A	Nodular lymphocyte predominant Hodgkin lymphoma, in remission
C81.01	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.02	Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes
C81.03	Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes
C81.04	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.05	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.06	Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes
C81.07	Nodular lymphocyte predominant Hodgkin lymphoma, spleen
C81.08	Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites
C81.09	Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites
C81.1A	Nodular sclerosis Hodgkin lymphoma, in remission
C81.11	Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.12	Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes
C81.13	Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes
C81.14	Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.15	Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.16	Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes
C81.17	Nodular sclerosis Hodgkin lymphoma, spleen
C81.18	Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites
C81.19	Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites
C81.2A	Mixed cellularity Hodgkin lymphoma, in remission

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA
POLICY NUMBER	MP 9.043

ICD-10-CM Diagnosis Codes	Description
C81.21	Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.22	Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes
C81.23	Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes
C81.24	Mixed cellularity Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.25	Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.26	Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes
C81.27	Mixed cellularity Hodgkin lymphoma, spleen
C81.28	Mixed cellularity Hodgkin lymphoma, lymph nodes of multiple sites
C81.29	Mixed cellularity Hodgkin lymphoma, extranodal and solid organ sites
C81.3A	Lymphocyte depleted Hodgkin lymphoma, in remission
C81.31	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.32	Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes
C81.33	Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes
C81.34	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.35	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.36	Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes
C81.37	Lymphocyte depleted Hodgkin lymphoma, spleen
C81.38	Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites
C81.39	Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites
C81.4A	Lymphocyte-rich Hodgkin lymphoma, in remission
C81.41	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.42	Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes
C81.43	Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes
C81.44	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb
C81.45	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.46	Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes
C81.47	Lymphocyte-rich Hodgkin lymphoma, spleen
C81.48	Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites
C81.49	Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites
C81.7A	Other Hodgkin lymphoma, in remission
C81.71	Other Hodgkin lymphoma, lymph nodes of head, face, and neck
C81.72	Other Hodgkin lymphoma, intrathoracic lymph nodes
C81.73	Other Hodgkin lymphoma, intra-abdominal lymph nodes
C81.74	Other Hodgkin lymphoma, lymph nodes of axilla and upper limb

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA
POLICY NUMBER	MP 9.043

ICD-10-CM Diagnosis Codes	Description
C81.75	Other Hodgkin lymphoma, lymph nodes of inguinal region and lower limb
C81.76	Other Hodgkin lymphoma, intrapelvic lymph nodes
C81.77	Other Hodgkin lymphoma, spleen
C81.78	Other Hodgkin lymphoma, lymph nodes of multiple sites
C81.79	Other Hodgkin lymphoma, extranodal and solid organ sites
C81.9A	Hodgkin lymphoma, unspecified, in remission
C82.0A	Follicular lymphoma grade I, in remission
C82.1A	Follicular lymphoma grade II, in remission
C82.2A	Follicular lymphoma grade III, unspecified, in remission
C82.3A	Follicular lymphoma grade IIIa, in remission
C82.4A	Follicular lymphoma grade IIIb, in remission
C82.5A	Diffuse follicle center lymphoma, in remission
C82.6A	Cutaneous follicle center lymphoma, in remission
C82.8A	Other types of follicular lymphoma, in remission
C82.9A	Follicular lymphoma, unspecified, in remission
C83.0A	Small cell B-cell lymphoma, in remission
C83.1A	Mantle cell lymphoma, in remission
C83.390	Primary central nervous system lymphoma
C83.398	Diffuse large B-cell lymphoma of other extranodal and solid organ sites
C83.3A	Diffuse large B-cell lymphoma, in remission
C83.5A	Lymphoblastic (diffuse) lymphoma, in remission
C83.7A	Burkitt lymphoma, in remission
C83.8A	Other non-follicular lymphoma, in remission
C83.9A	Non-follicular (diffuse) lymphoma, unspecified, in remission
C84.0A	Mycosis fungoides, in remission
C841.A	Sezary disease, in remission
C84.4A	Peripheral T-cell lymphoma, not elsewhere classified, in remission
C84.6A	Anaplastic large cell lymphoma, ALK-positive, in remission
C84.7B	Anaplastic large cell lymphoma, ALK-negative, in remission
C84.9A	Mature T/NK-cell lymphomas, unspecified, in remission
C84.AA	Cutaneous T-cell lymphoma, unspecified, in remission
C84.ZA	Other mature T/NK-cell lymphomas, in remission
C85.1A	Unspecified B-cell lymphoma, in remission
C85.2A	Mediastinal (thymic) large B-cell lymphoma, in remission
C85.8A	Other specified types of non-Hodgkin lymphoma, in remission
C85.9A	Non-Hodgkin lymphoma, unspecified, in remission
C86.00	Extranodal NK/T-cell lymphoma, nasal type not having achieved remission
C86.01	Extranodal NK/T-cell lymphoma, nasal type, in remission
C86.10	Hepatosplenic T-cell lymphoma not having achieved remission
C86.11	Hepatosplenic T-cell lymphoma, in remission

ICD-10-CM Diagnosis Codes	Description
C86.20	Enteropathy-type (intestinal) T-cell lymphoma not having achieved remission
C86.21	Enteropathy-type (intestinal) T-cell lymphoma, in remission
C86.30	Subcutaneous panniculitis-like T-cell lymphoma not having achieved remission
C86.31	Subcutaneous panniculitis-like T-cell lymphoma, in remission
C86.40	Blastic NK-cell lymphoma not having achieved remission
C86.41	Blastic NK-cell lymphoma, in remission
C86.50	Angioimmunoblastic T-cell lymphoma not having achieved remission
C86.51	Angioimmunoblastic T-cell lymphoma, in remission
C86.60	Primary cutaneous CD30-positive T-cell proliferations not having achieved remission
C86.61	Primary cutaneous CD30-positive T-cell proliferations, in remission

IX. REFERENCES

TOP

1. *Morschhauser F, Brice P, Ferme C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: results of the prospective multicenter H96 trial by the GELA/SFGM study group. J Clin Oncol. Dec 20 2008; 26(36): 5980-7. PMID 19018090*
2. *National Cancer Institute (NCI). Adult Hodgkin Lymphoma Treatment (PDQ) - Health Professional Version. Updated January 18, 202;*
3. *Swerdlow S, Campo E, Harris N, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4 ed. Lyon France: IARC; 2008.*
4. *Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. May 19 2016; 127(20): 2375-90. PMID 26980727*
5. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hodgkin disease/lymphoma. Version 2.2024.*
6. *American Cancer Society (ACS). Hodgkin Lymphoma Stages. Updated May 1, 2018.*
7. *Brice P. Managing relapsed and refractory Hodgkin lymphoma. Br J Haematol. Apr 2008; 141(1): 3-13. PMID 18279457*
8. *Schmitz N, Sureda A, Robinson S. Allogeneic transplantation of hematopoietic stem cells after nonmyeloablative conditioning for Hodgkin's disease: indications and results. Semin Oncol. Feb 2004; 31(1): 27-32. PMID 14970934*
9. *Schmitz N, Dreger P, Glass B, et al. Allogeneic transplantation in lymphoma: current status. Haematologica. Nov 2007; 92(11): 1533-48. PMID 18024402*
10. *Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. May 09 2015; 385(9980): 1853-62. PMID 25796459*
11. *Moskowitz CH, Walewski J, Nademanee A, et al. Five-year PFS from the AETHERA trial of brentuximab vedotin for Hodgkin lymphoma at high risk of progression or relapse. Blood. Dec 20 2018; 132(25): 2639-2642. PMID 30266774*

12. *Smith EP, Li H, Friedberg JW, et al. Tandem Autologous Hematopoietic Cell Transplantation for Patients with Primary Progressive or Recurrent Hodgkin Lymphoma: A SWOG and Blood and Marrow Transplant Clinical Trials Network Phase II Trial (SWOG S0410/BMT CTN 0703). Biol Blood Marrow Transplant. Apr 2018; 24(4): 700-707. PMID 29289757*
13. *Bair SM, Strelec L, Nagle SJ, et al. Outcomes of patients with relapsed/refractory Hodgkin lymphoma progressing after autologous stem cell transplant in the current era of novel therapeutics: A retrospective analysis. Am J Hematol. Sep 2017; 92(9): 879-884. PMID 28512788*
14. *Federico M, Bellei M, Brice P, et al. High-dose therapy and autologous stem-cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy. J Clin Oncol. Jun 15 2003; 21(12): 2320-5. PMID 12805333*
15. *Carella AM, Bellei M, Brice P, et al. High-dose therapy and autologous stem cell transplantation versus conventional therapy for patients with advanced Hodgkin's lymphoma responding to front-line therapy: long-term results. Haematologica. Jan 2009; 94(1): 146-8. PMID 19001284*
16. *Rancea M, von Tresckow B, Monsef I, et al. High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed or refractory Hodgkin lymphoma: a systematic review with meta-analysis. Crit Rev Oncol Hematol. Oct 2014; 92(1): 1-10. PMID 24855908*
17. *Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: results of a BNLI randomised trial. Lancet. Apr 24 1993; 341(8852): 1051-4. PMID 8096958*
18. *Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. Lancet. Jun 15 2002; 359(9323): 2065-71. PMID 12086759*
19. *Seftel M, Rubinger M. The role of hematopoietic stem cell transplantation in advanced Hodgkin Lymphoma. Transfus Apher Sci. Aug 2007; 37(1): 49-56. PMID 17716946*
20. *Murphy F, Sirohi B, Cunningham D. Stem cell transplantation in Hodgkin lymphoma. Expert Rev Anticancer Ther. Mar 2007; 7(3): 297-306. PMID 17338650*
21. *Todisco E, Castagna L, Sarina B, et al. Reduced-intensity allogeneic transplantation in patients with refractory or progressive Hodgkin's disease after high-dose chemotherapy and autologous stem cell infusion. Eur J Haematol. Apr 2007; 78(4): 322-9. PMID 17253967*
22. *Smith SM, van Besien K, Carreras J, et al. Second autologous stem cell transplantation for relapsed lymphoma after a prior autologous transplant. Biol Blood Marrow Transplant. Aug 2008; 14(8): 904-12. PMID 18640574*
23. *Perales MA, Ceberio I, Armand P, et al. Role of cytotoxic therapy with hematopoietic cell transplantation in the treatment of Hodgkin lymphoma: guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Jun 2015; 21(6): 971-83. PMID 25773017*

24. *Rashidi A, Ebadi M, Cashen AF. Allogeneic hematopoietic stem cell transplantation in Hodgkin lymphoma: a systematic review and meta-analysis. Bone Marrow Transplant. Apr 2016; 51(4): 521-8. PMID 26726948*
25. *Sureda A, Robinson S, Canals C, et al. Reduced-intensity conditioning compared with conventional allogeneic stem-cell transplantation in relapsed or refractory Hodgkin's lymphoma: an analysis from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. J Clin Oncol. Jan 20 2008; 26(3): 455-62. PMID 18086796*
26. *Sureda A, Canals C, Arranz R, et al. Allogeneic stem cell transplantation after reduced intensity conditioning in patients with relapsed or refractory Hodgkin's lymphoma. Results of the HDR-ALLO study - a prospective clinical trial by the Grupo Espanol de Linfomas/Trasplante de Medula Osea (GEL/TAMO) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. Haematologica. Feb 2012; 97(2): 310-7. PMID 21993674*
27. *Sibon D, Morschhauser F, Resche-Rigon M, et al. Single or tandem autologous stem-cell transplantation for first-relapsed or refractory Hodgkin lymphoma: 10-year follow-up of the prospective H96 trial by the LYSA/SFGM-TC study group. Haematologica. Apr 2016; 101(4): 474-81. PMID 26721893*
28. *Ferme C, Mounier N, Divine M, et al. Intensive salvage therapy with high-dose chemotherapy for patients with advanced Hodgkin's disease in relapse or failure after initial chemotherapy: results of the Groupe d'Etudes des Lymphomes de l'Adulte H89 Trial. J Clin Oncol. Jan 15 2002; 20(2): 467-75. PMID 11786576*
29. *Fung HC, Stiff P, Schriber J, et al. Tandem autologous stem cell transplantation for patients with primary refractory or poor risk recurrent Hodgkin lymphoma. Biol Blood Marrow Transplant. May 2007; 13(5): 594-600. PMID 17448919*
30. *Majhail NS, Farnia SH, Carpenter PA, et al. Indications for Autologous and Allogeneic Hematopoietic Cell Transplantation: Guidelines from the American Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. Nov 2015; 21(11): 1863-1869. PMID 26256941*
31. *Winkfield KM, Advani RH, Ballas LK, et al. ACR Appropriateness Criteria(R) Recurrent Hodgkin Lymphoma. Oncology (Williston Park). Dec 15 2016; 30(12): 1099-103, 1106-8. PMID 27987203*
32. *Centers for Medicare & Medicaid Services. 110.23 - Stem Cell Transplantation (Formerly 110.8.1). 2016*
33. *Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. 2020;26(7):1247-1256. doi:10.1016/j.bbmt.2020.03.002 PMID 32165328*
34. *Kako S, Izutsu K, Kato K, et al. The role of hematopoietic stem cell transplantation for relapsed and refractory Hodgkin lymphoma. Am J Hematol. 2015;90(2):132-138. doi:10.1002/ajh.23897*
35. *Moskowitz MD, Craig, and Alencar MD, Alvaro J. Hematopoietic cell transplantation in classic Hodgkin lymphoma. [UpToDate] Updated March 17, 2022.*

36. *Ullah F, Dima D, Omar N, Ogbue O, Ahmed S. Advances in the treatment of Hodgkin lymphoma: Current and future approaches. Front Oncol. 2023;13:1067289. Published 2023 Mar 3. PMID: 39637412*
37. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hematopoietic Cell Transplantation (HCT). Version 3.2023*
38. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 8.01.29, Hematopoietic Cell Transplantation for Hodgkin Lymphoma. February 2024*

X. POLICY HISTORY

TOP

MP 9.043	**03/18/2020 Consensus Review**. No change to policy statement. References updated.
	03/18/2021 Consensus Review. No change to policy statement. References updated.
	02/25/2021 Consensus Review. No changes to policy statement. Summary of evidence updated to reflect statement. FEP references updated.
	03/02/2023 Consensus Review. No changes to policy statement. New definitions and references.
	03/12/2024 Consensus Review. No change to policy stance, NCCN statement added. New references.
	08/30/2024 Administrative Update. New ICD10 added, effective 10/1/2024.
	11/20/2024 Administrative Update. Removed NCCN statement.

Top