

MEDICAL POLICY

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

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input checked="" type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	5/1/2026

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.

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.

Tandem autologous HCT is considered **investigational** in individuals with Hodgkin lymphoma. 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 individuals 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

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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.

PRODUCT VARIATIONS

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

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

DESCRIPTION/BACKGROUND

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

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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 (e.g., 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

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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

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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.

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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	Type of agent	FDA-approved indications for post-autologous HCT use
Brentuximab vedotin BLA: 125388 <i>Seattle Genetics</i>	CD30-directed antibody-drug conjugate	<ul style="list-style-type: none"> Classical HL at high-risk of relapse or progression as post-autologous HCT consolidation Classical HL after failure of autologous hematopoietic stem cell transplantation
Nivolumab BLA: 125554 <i>Bristol Myers Squibb</i>	Programmed death receptor-1 (PD-1) blocking antibody	Classical HL that has relapsed or progressed after autologous HCT and post-transplantation brentuximab vedotin
Pembrolizumab BLA: 125514 <i>Merck Sharp Dohme</i>	Programmed death receptor-1 (PD-1) blocking antibody	Adult and pediatric patients with refractory classical HL, or who relapsed after 3 or more prior lines of therapy*

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%)

RATIONALE

SUMMARY OF EVIDENCE

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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.

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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. 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 for single autologous HCT. This study was not definitive due to potential selection bias; RCTs are needed to determine the impact of tandem autologous HCT on health outcomes in this population. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

DEFINITIONS

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 allogeneic 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.

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DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

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		

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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 October 24, 2025.
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 3.2025*

POLICY HISTORY

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 10/01/2024.
	11/20/2024 Administrative Update. Removed NCCN statement.
	02/28/2025 Minor Review. Tandem auto HCT now investigational.
	06/11/2025 Administrative Update. Removing the Benefit Variations Section and updating the Disclaimer.
	01/27/2026 Consensus review. No change to policy stance, updated reference.

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