

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

Note: Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas is addressed separately in medical policy 00062.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) for Hodgkin lymphoma to be **eligible for coverage**** when **EITHER** of the following criteria are met:

- For treatment of primary refractory Hodgkin lymphoma; **OR**
- For treatment of relapsed Hodgkin lymphoma.

Based on review of available data, the Company may consider allogenic hematopoietic cell transplantation (HCT) for Hodgkin lymphoma using either myeloablative or reduced-intensity conditioning (RIC) regimens to be **eligible for coverage**** when **EITHER** of the following criteria are met:

- For treatment of primary refractory Hodgkin lymphoma; **OR**
- For treatment of relapsed Hodgkin lymphoma.

Note: The primary refractory disease was defined in a study 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.

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers a second autologous hematopoietic cell transplantation (HCT) for relapsed lymphoma after a prior autologous HCT to be **not medically necessary**.**

Based on review of available data, the Company considers tandem autologous hematopoietic cell transplantation (HCT) in individuals with Hodgkin lymphoma to be **not medically necessary**.**

Based on review of available data, the Company considers other uses of hematopoietic cell transplantation (HCT) in individuals with Hodgkin lymphoma including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission to be **not medically necessary**.**

Policy Guidelines

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

Some individuals for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning allogeneic hematopoietic cell transplantation. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically greater than 55 or greater than 60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude the 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 individual, with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens. Most individuals 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.

Background/Overview

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2025, the estimated number of new cases in the United States was approximately 8720, with 1150 estimated deaths

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

related to HL. 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 divided 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 $>38^{\circ}\text{C}$, or drenching night sweats (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 (I _E)
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 (II _E). 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 (III _E), spleen (III _S), or both (III _{E+S})

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

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 to II with no B symptoms, large mediastinal lymphadenopathy, or other unfavorable factors), early-stage unfavorable (stage I to II with a large mediastinal mass, multiple involved nodal regions, B symptoms, extranodal involvement, or elevated erythrocyte sedimentation rate ≥ 50), and advanced-stage disease (stage III to 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.

Hodgkin lymphoma 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 the 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

Hematopoietic cell transplantation is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in patients with cancer who receive bone marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

(allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allo-HCT, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigen 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 Hematopoietic Cell Transplantation

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 cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional 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 graft-versus-malignancy effect of allogeneic transplantation develops. Reduced-intensity conditioning regimens range from nearly total myeloablative to minimally myeloablative with

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

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 RIC 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 HL 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 (RCT) known as the AETHERA trial (abbreviation definition unknown). Moskowitz et al (2015) reported on the outcomes for 329 individuals with HL with risk factors for post-transplantation relapse or progression (eg, 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% vs. 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% vs. 41%; HR 0.52; 95% CI, 0.38 to 0.72). In addition, a study by Smith et al (2018) 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 vs. 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

The FDA 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.

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

Table 2 describes several novel agents that have been approved by the FDA for use as alternatives to tandem autologous HCT or a second autologous HCT in individuals at high-risk for, or with, respectively, refractory or relapsed HL following autologous HCT.

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

Drug	BLA	Type of agent	Manufacturer	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 HCT	Aug 2015
Nivolumab	125554	PD-1 blocking antibody	Bristol Myers Squibb	Classical HL that has relapsed or progressed after autologous HCT and posttransplantation brentuximab vedotin	May 2016
Pembrolizumab	125514	PD-1 blocking antibody	Merck Sharp Dohme	Adult and pediatric patients with refractory classical HL, or who have relapsed after 3 or more prior lines of therapy ^a	Mar 2017

BLA: Biologic License Application; FDA: U.S. Food and Drug Administration; HCT: hematopoietic cell transplantation; HL: Hodgkin lymphoma; PD-1: programmed death receptor-1.

^a In the pivotal, multicenter, nonrandomized, open-label study, prior lines of therapy included prior autologous HCT (61%) and brentuximab (83%)

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

Description

Hodgkin lymphoma (HL) results from a clonal expansion of a B-cell lineage, characterized by the presence of Reed-Sternberg cells on pathology. Standard treatment is based on the stage at presentation and may involve chemotherapy with or without radiotherapy. Hematopoietic cell transplantation (HCT) has been used for HL, particularly in the setting of relapse or refractory disease.

Summary of Evidence

Autologous Hematopoietic Cell Transplantation

For individuals who have Hodgkin lymphoma (HL) who receive autologous hematopoietic cell transplantation (HCT) as first-line therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality and morbidity. Randomized controlled trials 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 that the technology results in an improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive autologous HCT, the evidence includes RCTs, a meta-analysis, nonrandomized studies, and case series. 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 an 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. 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 that the technology results in an improvement in the net health outcome.

Allogeneic Hematopoietic Cell Transplantation

For individuals who have HL who receive allogeneic HCT (allo-HCT) as first-line therapy, the evidence includes no published studies. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for HL were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive allo-HCT, the evidence includes a number of case series and a meta-analysis. Relevant outcomes are OS, DSS, change in disease status,

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

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 of 50%. The evidence is sufficient to determine that the technology results in an 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. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality 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 1 year compared with no previous autologous HCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have relapsed or refractory HL who receive reduced-intensity conditioning (RIC) with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. 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 an improvement in the net health outcome.

Tandem Autologous Hematopoietic Cell Transplantation

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.

Supplemental Information

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2020 Input

Clinical input was sought to help determine whether the use of either second autologous hematopoietic cell transplantation (HCT) for relapsed Hodgkin lymphoma (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,

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

clinical input was received from 4 respondents, including 3 complete responses with 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 a 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.

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 College of Radiology

In 2016, the American College of Radiology issued an Appropriateness Criteria on recurrent HL. The criteria stated that while salvage therapy followed by autologous HCT is standard of care for relapsed HL, alternative therapies may be considered in select patients. For example, there is evidence that in patients with small isolated relapses occurring more than 3 years after initial presentation, a course of radiotherapy or combined modality therapy without autologous HCT may be considered. Also, radiotherapy may be considered as part of combined modality therapy for patients with local relapse after treatment with chemotherapy alone or for relapses outside of the original site of disease.

American Society for Transplantation and Cellular Therapy

In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation (now referred to as the American Society for Transplantation and Cellular Therapy) on indications for autologous and allogeneic HCT. These guidelines were updated in 2020. Recommendations described the current consensus on the use of HCT in and out of the clinical trial setting. The 2015 and 2020 Society recommendations on HL are provided in Table 3.

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

Table 3. Recommendations for Use of HCT to Treat Hodgkin Lymphoma

Indication	Allogeneic HCT (2015 recommendation)	Allogeneic HCT (2020 recommendation)	Autologous HCT (2015 recommendation)	Autologous HCT (2020 recommendation)
<i>Adult</i>				
First complete response (PET negative)	Not generally recommended	Not generally recommended	Not generally recommended	Not generally recommended
First complete response (PET positive)	Not generally recommended	Subsection removed ^a	Standard of care, clinical evidence available	Subsection removed ^a
Primary refractory, sensitive	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care	Standard of care
Primary refractory, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
First relapse, sensitive	Standard of care	Standard of care	Standard of care	Standard of care
First relapse, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
Second or greater relapse	Standard of care, clinical evidence available	Standard of care	Standard of care	Standard of care
Relapse after autologous transplant	Standard of care, clinical evidence available	Standard of care	Not generally recommended	Not generally recommended
<i>Pediatric</i>				
First complete response	Not generally recommended	Not generally recommended	Not generally recommended	Not generally recommended
Primary refractory, sensitive	Standard of care, clinical evidence available	Not generally recommended	Standard of care, clinical evidence available	Standard of care, clinical evidence available
Primary refractory, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

First relapse, sensitive	Standard of care, clinical evidence available	Not generally recommended	Standard of care, clinical evidence available	Standard of care
First relapse, resistant	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Not generally recommended	Not generally recommended
Second or greater relapse	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care, clinical evidence available	Standard of care, clinical evidence available

HCT: hematopoietic cell transplantation; PET: positron emission tomography.

^aSubsection on positron emission tomography positive complete remission was removed because updated response criteria for these lymphoma essentially require normalization of [¹⁸F]2-fluoro-2-deoxy-D-glucose positron emission tomography to be assessed as a first complete remission.

In 2015, the Society also published guidelines on the role of cytotoxic therapy with HCT in patients with HL. Select recommendations are shown in Table 4.

Table 4. Recommendations on Use of Cytotoxic Therapy with HCT to Treat Hodgkin Lymphoma

Recommendation	GOR	Highest LOE
<i>Autologous HCT</i>		
Autologous HCT should not be offered as first-line therapy for advanced disease	A	1+
Autologous HCT should be offered as first-line therapy for patients who fail to achieve CR	B	2++
Autologous HCT should be offered as salvage therapy over nontransplantation (except localized disease or in patients with low-stage disease)	A	1+
Autologous HCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy	B	2++
Tandem autologous HCT is not routinely recommended in standard-risk patients	C	2+
<i>Allogeneic HCT</i>		
Allo-HCT should be used for relapse after ASCT instead of conventional therapy	B	2++
RIC is the recommended regimen intensity	B	2++

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

All donor sources can be considered	A	1+
There are limited data for tandem autologous HCT/allo-HCT	D	4
Allo-HCT is preferred over autologous HCT as second HCT (except in late relapse)	C	2+

allo: allogeneic; ASCT: autologous stem cell transplantation; CR: complete response; GOR: grade of recommendation; HCT: hematopoietic cell transplantation; LOE: level of evidence; RIC: reduced-intensity conditioning.

National Comprehensive Cancer Network Guidelines

Current National Comprehensive Cancer Network (NCCN) guidelines for HL (v.1.2026) include a recommendation for autologous or allogeneic HCT in patients with biopsy-proven refractory disease who have undergone second-line systemic therapy and are Deauville stage 5 according to restaging based on findings from positron emission tomography or computed tomography. Additionally, in patients with biopsy-proven refractory disease who have undergone second-line systemic therapy and are Deauville stage 1 to 3 according to restaging based on findings from positron emission tomography or computed tomography, high-dose therapy and autologous stem cell rescue plus either observation or brentuximab vendotin for 1 year is recommended for patients with high-risk of relapse.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

Autologous HCT is considered reasonable and necessary and is covered under Medicare (NCD 110.23 [formerly 110.8.1]) for patients with “[a]dvanced Hodgkin’s disease who have failed conventional therapy and have no HLA [human leukocyte antigen]-matched donor.”

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
<i>Unpublished</i>			
NCT00574496	An Intention-to-Treat Study of Salvage Chemotherapy Followed by Allogeneic Hematopoietic Stem Cell Transplant for the	25	Aug 2022

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

	Treatment of High-Risk or Relapsed Hodgkin Lymphoma		
NCT01203020	Once Daily Intravenous Busulfex as Part of Reduced-toxicity Conditioning for Patients With Relapsed/Refractory Hodgkin's and Non-Hodgkin's Lymphomas Undergoing Allogeneic Hematopoietic Progenitor Cell Transplantation - A Multicenter Phase II Study	22	Sep 2021
NCT03200977 ^a	Observational Cohort Study to Characterize the Safety of Allogeneic Hematopoietic Cell Transplantation (HCT) For Patients With Classical Hodgkin Lymphoma (CHL) Treated With Nivolumab	95	Dec 2022

NCT: national clinical trial.

^a Denotes an industry sponsored or cosponsored study

References

1. National Cancer Institute (NCI). Adult Hodgkin Lymphoma Treatment (PDQ) - Health Professional Version. Updated February 12, 2025; <http://www.cancer.gov/cancertopics/pdq/treatment/adulthodgkins/healthprofessional>.
2. Swerdlow S, Campo E, Harris N, et al. WHO classification of tumours of haematopoietic and lymphoid tissues. 4 ed. Lyon France: IARC; 2008.
3. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. *Leukemia*. Jul 2022; 36(7): 1720-1748. PMID 35732829
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Hodgkin lymphoma. Version 1.2026. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf.
5. American Cancer Society (ACS). Hodgkin Lymphoma Stages. Updated October 6, 2025. <https://www.cancer.org/cancer/hodgkin-lymphoma/detection-diagnosis-staging/staging.html>.
6. Brice P. Managing relapsed and refractory Hodgkin lymphoma. *Br J Haematol*. Apr 2008; 141(1): 3-13. PMID 18279457
7. 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
8. Schmitz N, Dreger P, Glass B, et al. Allogeneic transplantation in lymphoma: current status. *Haematologica*. Nov 2007; 92(11): 1533-48. PMID 18024402
9. 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

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

10. 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
11. 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
12. 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
13. 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
14. 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
15. 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
16. 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
17. 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
18. 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
19. Murphy F, Sirohi B, Cunningham D. Stem cell transplantation in Hodgkin lymphoma. *Expert Rev Anticancer Ther*. Mar 2007; 7(3): 297-306. PMID 17338650
20. Merryman RW, Redd RA, Nishihori T, et al. Autologous stem cell transplantation after anti-PD-1 therapy for multiply relapsed or refractory Hodgkin lymphoma. *Blood Adv*. Mar 23 2021; 5(6): 1648-1659. PMID 33710337
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

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

- 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 Español de Linfomas/Trasplante de Médula 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. Morschhauser F, Brice P, Fermé 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
 28. 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
 29. Fermé C, Mounier N, Diviné 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
 30. 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
 31. Winkfield KM, Advani RH, Ballas LK, et al. ACR Appropriateness Criteria® Recurrent Hodgkin Lymphoma. Oncology (Williston Park). Dec 15 2016; 30(12): 1099-103, 1106-8. PMID 27987203
 32. 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
 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. Jul 2020; 26(7): 1247-1256. PMID 32165328
 34. Centers for Medicare & Medicaid Services. 110.23 - Stem Cell Transplantation (Formerly 110.8.1). 2024; <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=366>.

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

Policy History

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

12/06/2001	Medical Policy Committee review
03/25/2002	Managed Care Advisory Council approval
06/24/2002	Format revision. No substance change to policy.
05/07/2004	Medical Director review
05/18/2004	Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Hodgkin's Disease policy developed separately from current HDC with Hematopoietic Stem Cell Support policy.
06/28/2004	Managed Care Advisory Council approval
05/03/2005	Medical Director review
05/17/2005	Medical Policy Committee review. Coverage eligibility unchanged.
05/23/2005	Managed Care Advisory Council approval
05/03/2006	Medical Director review
05/17/2006	Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007	Medical Director review
04/18/2007	Medical Policy Committee approval. No change in coverage eligibility.
04/02/2008	Medical Director review
04/16/2008	Medical Policy Committee approval. No change to coverage eligibility.
04/02/2009	Medical Director review
04/15/2009	Medical Policy Committee approval. Title changed. No change to coverage.
04/08/2010	Medical Policy Committee approval
04/21/2010	Medical Policy Implementation Committee approval. Added tandem autologous HSCT to be eligible for coverage with criteria. Added reduced-intensity allogeneic HSCT to treat Hodgkin Lymphoma to be eligible for coverage with criteria. Added that a second autologous stem-cell transplantation for relapsed lymphoma after a prior autologous HSCT to be investigational. Updated background/overview, rationale and references.
04/07/2011	Medical Policy Committee review
04/13/2011	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
04/12/2012	Medical Policy Committee review
04/25/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013	Medical Policy Committee review
05/22/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014	Medical Policy Committee review
05/21/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

05/07/2015	Medical Policy Committee review
05/20/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016	Medical Policy Committee review
05/18/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017	Medical Policy Committee review
05/17/2017	Medical Policy Implementation Committee approval. “Stem” removed from title and policy. Removed statement on reduced intensity allogeneic HCT, added coverage statement for allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens in patients with primary refractory or relapsed Hodgkin lymphoma. Added a policy guidelines section.
05/03/2018	Medical Policy Committee review
05/16/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2019	Medical Policy Committee review
05/15/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Tandem autologous hematopoietic cell transplantation changed from eligible for coverage to investigational.
05/05/2022	Medical Policy Committee review
05/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/04/2023	Medical Policy Committee review
05/10/2023	Medical Policy Implementation Committee approval. Replaced “patients” with “individuals” in the coverage section. Coverage eligibility unchanged.
05/02/2024	Medical Policy Committee review
05/08/2024	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2025	Medical Policy Committee review
05/13/2025	Medical Policy Implementation Committee approval Coverage eligibility unchanged.
05/07/2026	Medical Policy Committee review
05/13/2026	Medical Policy Implementation Committee approval. Changed all investigational statements to not medically necessary. Moved the definition for primary refractory

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

disease from the Policy Guidelines as a *Note* after the eligible for coverage statements. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2027

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38243 Delete code effective 06/01/2026: 38242
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All Related Diagnoses

****Medically Necessary** (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Policy # 00057

Original Effective Date: 01/28/2008

Current Effective Date: 06/01/2026

- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.