

MEDICAL POLICY – 8.01.29

Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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RELATED MEDICAL POLICIES:

8.01.529 Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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Introduction

Hodgkin lymphoma is cancer of the lymphatic system, which is part of the immune system. Hodgkin lymphoma affects a certain type of white blood cell called a lymphocyte. Lymphocytes are formed in the bone marrow from certain blood-forming cells called “hematopoietic” cells. When a person has Hodgkin lymphoma, they make too many lymphocytes. Different types of treatment have been used against Hodgkin lymphoma, including chemotherapy and radiation. Another common type of treatment is a hematopoietic cell transplant. In a hematopoietic cell transplant, hematopoietic cells are taken from a donor’s bone marrow and are given to the person who has Hodgkin lymphoma, just like in a transfusion. It is hoped that these new cells will then settle into the bone marrow and start producing normal lymphocytes, and the person will no longer have Hodgkin lymphoma.

When the hematopoietic cells are harvested from another person, it is called an allogeneic transplant. When the cells come from the patient himself, it is called an autologous cell transplant. This policy discusses when different types of hematopoietic cell transplants might be medically necessary to treat Hodgkin lymphoma.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a

service may be covered.

Policy Coverage Criteria

Transplant	Medical Necessity
Autologous hematopoietic cell transplantation (HCT)	Autologous hematopoietic cell transplantation (HCT) may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma (HL).
Allogeneic HCT (allo-HCT)	Allogeneic HCT (allo-HCT), using either myeloablative or reduced-intensity conditioning regimens, may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma.

Transplant	Investigational
Second autologous HCT	Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered investigational.
Tandem autologous HCT	Tandem autologous HCT is considered investigational in individuals with Hodgkin lymphoma.
Other uses of HCT	Other uses of HCT in individuals with HL are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.

Additional Information

- In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous hematopoietic cell transplantation (HCT) 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. The 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. They include those with malignancies that are effectively treated with myeloablative allogeneic



Additional Information

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 the use of a standard myeloablative conditioning regimen.

- The ideal allogeneic donors are human leukocyte antigen (HLA)-identical matched siblings. Related donors mismatched at one 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.

Documentation Requirements

The individual's medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Prior treatment (if any) individual has received
- Any poor risk features

Coding

Code	Description
CPT	
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2142	Cord blood-derived stem-cell transplantation, allogeneic



Code	Description
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for individuals participating in NIH-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

Evidence Review

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.

Background

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 related to HL.¹ The disease has a bimodal distribution, with most individuals 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 types²; these classifications did not change in the 2022 update:³

1. "Classical" HL
 - a. Nodular sclerosis
 - b. Mixed cellularity
 - c. Lymphocyte depleted
 - d. 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%.⁴ "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 individuals 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°C, or drenching night sweats (see [Table 1](#)).⁴

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 (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 (III _E), spleen (III _S), or both (III _{E+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

Individuals with HL are generally classified into three groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal lymphadenopathy, or other unfavorable factors), early-stage unfavorable (stage I-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-IV).⁴

Treatment

Individuals with nonbulky stage IA or IIA disease are considered to have clinically early-stage disease. These individuals are candidates for chemotherapy, combined modality therapy, or radiotherapy alone.⁵ Individuals 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 individuals can be cured with chemotherapy and/or radiotherapy. Individuals 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.⁶

In individuals 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.⁷ Early and late relapse are defined as less or more than 12 months from the time of remission, respectively. Approximately 70% of individuals with late first relapse can be salvaged by autologous HCT but not more than 40% with early first relapse.⁸

Only 25% to 35% of individuals 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 intravenously infused to restore bone marrow and immune function in individuals 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 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.

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. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. 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 (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pre-transplant conditioning. Intense conditioning regimens are limited to individuals 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 after a relapse or primary refractory disease. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced Intensity Conditioning for Allogeneic Hematopoietic Cell Transplantation

Reduced Intensity Conditioning (RIC) refers to the pre-transplant 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 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. Individuals 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 policy, 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 HL treatment landscape is the emergence of several novel agents that are now being used as alternatives to stem cell transplantation in individuals 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 or pembrolizumab which are two programmed death receptor-1 (PD-1) blocking antibodies. The US 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),⁹ 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], 0.40-0.81). 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).¹⁰ A study by Smith et al (2018)¹¹ 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.¹² 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 (OS) (85.6 versus 17.1 months; $P < .001$). The availability of safe and effective targeted systemic therapy represents an improvement to the use of a second autologous transplant or planned tandem autologous HCT for HL consolidation treatment or relapse/refractory disease treatment.



Summary of Evidence

Autologous Hematopoietic Cell Transplantation

For individuals who have Hodgkin lymphoma (HL) who receive autologous HCT as first-line therapy, the evidence includes randomized controlled trials (RCTs). The relevant outcomes are OS, disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality (TRM) and morbidity. RCTs of autologous HCT as first-line treatment have reported that this therapy does not provide additional benefit compared to 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 comparative studies, and case series. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. Two RCTs in individuals 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. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. No RCTs or nonrandomized comparative studies were identified. In a case series, TRM 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 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 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. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM 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 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. 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 1 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 TRM 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 individuals 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. The relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. One prospective, nonrandomized study reported that, in individuals with poor prognostic markers, response to tandem autologous HCT may be higher than that 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. The evidence is insufficient to determine that the effects of the technology results in an improvement in the health outcome.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in [Table 2](#).



Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT00574496	An Intention-to-Treat Study of Salvage Chemotherapy Followed by Allogeneic Hematopoietic Stem Cell Transplant for the Treatment of High-Risk or Relapsed Hodgkin Lymphoma	25	Aug 2022
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	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.

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



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

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

Practice Guidelines and Position Statements

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

Guidelines or position statements will be considered for inclusion 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.³¹ 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 individuals. For example, there is evidence that in individuals with small isolated relapses occurring more than three 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.³² These guidelines were updated in 2020.³³ Recommendations described the current consensus on use of HCT in and out of the



clinical trial setting. The 2015 and 2020 Society recommendations on HL are provided in [Table 3](#).

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
Adult				
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
Pediatric				
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



Indication	Allogeneic HCT - 2015 recommendation	Allogeneic HCT -2020 recommendation	Autologous HCT -2015 recommendation	Autologous HCT - 2020 recommendation
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, 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 individuals with HL.²³ 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
Autologous HCT		
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+



Recommendation	GOR	Highest LOE
Allogeneic HCT		
Allo-HCT should be used for relapse after ASCT instead of conventional therapy	B	2++
RIC is the recommended regimen intensity	B	2++
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 (NCC) guidelines for HL (v.1.2026)⁴ include a recommendation for autologous or allogeneic HCT in individuals 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 individuals with biopsy-proven refractory disease who have undergone second-line systemic therapy and are Deauville stage 1-3 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 individuals with high-risk of relapse.

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.”³⁴

Regulatory Status

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.



Table 5 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 5. Novel Agents Approved by the US Food and Drug Administration

Drug	BLA	Type of agent	Manufacturer	FDA-approved Indications for Post-Autologous HCT Use	Date FDA Approved
Brentuximab vedotin (Adcetris)	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 (Opdivo)	125554	Programmed death receptor-1 (PD-1) blocking antibody	Bristol Myers Squibb	Classical HL that has relapsed or progressed after autologous HCT and posttransplantation brentuximab vedotin	May 2016
Pembrolizumab (Keytruda)	125514	Programmed death receptor-1 (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: US Food and Drug Administration; HL: Hodgkin Lymphoma; HCT: Hematopoietic Cell Transplantation; PD-1: programmed death receptor-1.

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

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History

Date	Comments
06/25/98	Add to Therapy Section - New Policy
10/06/98	Replace policy - Incorporate recommended changes from Oncology Advisory Panel
04/04/00	Replace policy - Policy revised and renumbered to PR.8.01.110 (previously P7.03.107) to address specific malignancies.
12/21/00	Replace policy - Previous policy PR.8.01.110 replaced by policy BC.8.01.29.
06/17/03	Replace policy - Update CPT codes only
08/12/03	Replace policy - Policy revised; policy statement revised to indicate that auto-HDC may be considered medically necessary in any patient with relapsed disease.
05/10/05	Replace policy - Policy updated with literature search; no change to policy statement
05/09/06	Replace policy - Policy updated with literature search; no change to policy statement.
06/02/06	Disclaimer and Scope update - No other changes
06/12/07	Replace policy - Policy updated with literature review; no change in policy statement. Reviewed by OAP on May 24, 2007.
10/09/07	Cross References Updated - No other changes.
11/12/07	Code updated - CPT code 86817 removed as directed by RPIW.
05/13/08	Cross Reference Update - No other changes
12/16/08	Replace policy - Policy extensively updated with literature review. Policy statement updated to include "Hodgkin lymphoma relapsing after an autologous stem cell transplant used to treat primary refractory or relapse disease" under the first investigational statement. Title and body of the policy updated to delete "HDC" and add "SCT". References added.
01/12/10	Replace policy - Policy updated with literature search and revised extensively. New policy statements added that tandem autologous SCT and reduced-intensity conditioning (RIC) allogeneic SCT may be considered medically necessary in specific situations and that a second autologous stem-cell transplantation for relapsed lymphoma after a prior autologous hematopoietic stem cell transplant is considered Investigational. References added.
02/09/10	Code Update - New 2010 codes added.
01/11/11	Replace policy - Policy updated with literature review; policy statements unchanged. Reference 15 added; reference 1 updated.



Date	Comments
10/19/11	Codes 38220 and 38221 removed from policy.
01/06/12	Replace policy – Policy updated with literature search; no new references added; policy statements unchanged. ICD-10 codes added.
01/24/12	Code 38232 added.
02/10/12	The CPT code 38204 was removed from the policy.
06/20/12	Minor update: Related Policies updated; 8.01.17 replaced 8.01.507 effective June 12, 2012.
07/30/12	Updated titles in Related Policies for: 8.01.17, 8.01.22, 8.01.30, 8.01.31, 8.01.35, and 8.01.520.
10/01/12	Update Coding Section – ICD-10 codes are now effective 10/01/2014.
01/29/13	Replace policy. Policy rationale updated based on a literature review through September 2012. Reference 22 added; others renumbered. HCPCS codes G0265-G0267 related to cryopreservation added. Policy statements unchanged. Change title to Related Policy 8.01.21.
03/20/13	The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083-Q0085.
09/30/13	Update Related Policies. Change title to policy 8.01.31.
10/18/13	Update Related Policies. Change title to policy 8.01.17.
12/06/13	Update Related Policies. Remove 8.01.31 as it was archived.
02/24/14	Replace policy. Policy Guidelines reformatted & reworded for usability. Policy updated with literature search through October 15, 2013. Reference 3, 26 added, others renumbered/removed. Policy statements unchanged.
03/21/14	Update Related Policies. Remove 8.01.514 as it was deleted.
04/18/14	Update Related Policies. Remove 8.01.20 and add 8.01.529.
06/24/14	Update Related Policies. Remove 8.01.35, 8.01.42 and 8.01.54, then add 8.01.530, 8.01.531 and 8.01.532.
12/03/14	Update Related Policies. Remove 8.01.17 and 8.01.26.
02/25/15	Annual Review. Policy updated with literature review through September 30, 2014. No new references added. Policy statements unchanged. Remove related policies 8.01.23, 8.01.28, 8.01.30, and 8.01.520.
05/01/16	Annual Update, approved April 12, 2016. Policy updated with literature review through October 27, 2015; reference 10 added. Policy statements unchanged.
09/01/16	Update Related Policies. Remove 8.01.27 as it was archived.
11/04/16	Coding update. Removed codes that are transplant benefit related.



Date	Comments
04/01/17	Annual Review, approved March 14, 2017. Policy updated with literature review through November 9, 2016; references 16-17 and 22-24 added. "Stem" removed from title and Policy. HSCT changed to HCT in Policy and Policy Guidelines. First policy statement divided into 2, 1 on allogeneic HCT and 1 on autologous HCT. The statement on allogeneic HCT was changed to state that either myeloablative or reduced-intensity conditioning can be used. Policy statement on reduced-intensity conditioning removed.
06/09/17	Coding update; updated description for CPT codes 38230, 38240, 38241, and 38242.
08/01/17	Updated title of Related Policy 8.01.511.
11/10/17	Policy moved to new format, no changes to policy statement.
06/01/18	Annual Review, approved May 3, 2018. Policy updated with literature review through November 2017; reference 24 added; note 26 updated. Policy statements unchanged.
04/01/19	Minor update, added Documentation Requirements section.
05/01/19	Annual Review, approved April 2, 2019. Policy updated with literature review through November 2018; reference 3 added; reference 4 updated. Policy statements unchanged.
04/01/20	Delete policy, approved March 10, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020. Removed CPT code 38242 effective April 1, 2020; code does not match criteria.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.
09/01/20	Annual Review, approved August 11, 2020. Removed CPT's 38230, 38232 and HCPCS S2140, S2142, S2150. The following changes are effective Dec. 3, 2020, following 90-day provider notification. Policy updated with literature review through April, 2020; references added. Policy updated with clinical input and change to policy statement to Investigational for tandem autologous HCT in patients with Hodgkin lymphoma.
04/01/21	Annual Review, approved March 2, 2021. Policy updated with literature review through December 8, 2020; no references added. Policy statements unchanged. Added CPT's 38230, 38232 and HCPCS S2140, S2142, S2150 back to policy. Update Related Policies, removed reference to 8.01.22 and replaced with 8.01.538.
05/01/21	Update Related Policies. Removed policy 7.01.50 as it was archived.
04/01/22	Annual Review, approved March 21, 2022. Policy updated with literature review through December 6, 2021; references added. Policy statements unchanged.
10/01/22	Coding update. Removed HCPCS code S2140.
04/01/23	Annual Review, approved March 20, 2023. Policy updated with literature review through December 5, 2022; reference added. Minor editorial refinements to policy



Date	Comments
	statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization.
04/01/24	Annual Review, approved March 25, 2024. Policy updated with literature review through November 28, 2023; no references added. Policy statements unchanged.
04/01/25	Annual Review, approved March 10, 2025. Policy updated with literature review through December 10, 2024; no references added. Policy statements unchanged.
04/01/26	Annual Review, approved March 23, 2026. Policy updated with literature review through December 9, 2025; no references added. Policy statements unchanged.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2026 Premera All Rights Reserved.

Scope: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

