

8.01.29 Hematopoietic Cell Transplantation for Hodgkin Lymphoma			
Original Policy Date:	January 7, 2011	Effective Date:	April 1, 2024
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Policy Statement

- I. Autologous hematopoietic cell transplantation (HCT) may be considered **medically necessary** in individuals with primary refractory or relapsed Hodgkin lymphoma.
- II. Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered **medically necessary** in individuals with primary refractory or relapsed Hodgkin lymphoma.
- III. Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered **investigational**.
- IV. Tandem autologous HCT is considered **investigational** in individuals with Hodgkin lymphoma.
- V. Other uses of HCT in individuals with Hodgkin lymphoma are considered **investigational**, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

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 hematopoietic cell transplantation. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically >55 or >60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status score) preclude 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.

Coding

CPT centralized codes describing allogeneic and autologous hematopoietic cell support services to the hematology section (CPT 38204-38242). Not all codes are applicable for each high-dose

chemotherapy with stem cell support procedure. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207–38215):

The following CPT code describes cryopreservation and storage:

- **38207:** Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage

The following CPT codes describe thawing and washing of cryopreserved cells:

- **38208:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
- **38209:** Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor

The following CPT codes describe certain cell types being depleted:

- **38210:** Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
- **38211:** Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
- **38212:** Transplant preparation of hematopoietic progenitor cells; red blood cell removal
- **38213:** Transplant preparation of hematopoietic progenitor cells; platelet depletion
- **38214:** Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion

The following CPT codes describes plasma cell concentration:

- **38215:** Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer.

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.

Related Policies

- Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibit plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 1 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 1. 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	<ul style="list-style-type: none"> Classical HL at high risk of relapse or progression as post-autologous HCT consolidation Classical HL after failure of autologous 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

Background

Hodgkin Lymphoma

Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2023, the estimated number of new cases in the United States was approximately 8830, with 900 estimated deaths related to HL.¹ 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 types²; these classifications did not change in the 2022 update³:

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%.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 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 2).⁴

Table 2. 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

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).⁴

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.⁵ 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.⁶

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.⁷ 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.⁸

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 cancer patients 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 (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 allogeneic stem cell transplantation, 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 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 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 1.

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% 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).¹⁰ In addition, 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 (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.

Literature Review

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

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

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities

[Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma First-Line Therapy for Hodgkin Lymphoma

Clinical Context and Therapy Purpose

The purpose of autologous hematopoietic cell transplantation (HCT) as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with Hodgkin lymphoma (HL).

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

Populations

The relevant population of interest is individuals with HL.

Interventions

The therapy being considered is autologous HCT as first-line therapy.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Randomized Controlled Trials

Federico et al (2003) published results from an RCT of 163 patients with unfavorable HL who had received autologous HCT or additional standard chemotherapy for consolidation after initial conventional chemotherapy.¹³ Patients were randomized to high-dose chemotherapy (HDC) followed by autologous HCT (n=83) or to 4 additional courses of the same standard chemotherapy used in the induction phase (n=80). After treatment, complete remission (CR) was achieved in 92% of patients in the autologous HCT arm and 89% in the standard chemotherapy arm (p=.6). Five-year survival rates (overall, failure-free, and relapse-free) did not differ between the treatment groups, and the authors concluded that HDC with autologous HCT offered no benefit in outcomes over conventional chemotherapy as first-line therapy for patients with advanced HL.

Carella et al (2009) published 10-year follow-up results for the Federico study.¹⁴ Ten-year OS rates were 85% (95% confidence interval [CI], 78% to 90%) for the HDC autologous HCT group and 84%

(95% CI, 77% to 89%; $p=.7$) for the standard chemotherapy group. Ten-year failure-free survival rates were 79% (95% CI, 72% to 85%) for the HDC autologous HCT group and 75% (95% CI, 67% to 82%; $p=.8$) for the standard chemotherapy group. The authors concluded that, after a median follow-up of 107 months, their data suggested patients who respond to induction therapy with conventional chemotherapy do not achieve superior outcomes with consolidation with HDC and autologous HCT.

Section Summary: Autologous Hematopoietic Cell Transplantation as First-Line Therapy for Hodgkin Lymphoma

A small number of RCTs have evaluated the use of autologous HCT as first-line treatment for HL, and these trials have reported no benefit above that of conventional chemotherapy.

Relapsed or Refractory Hodgkin Lymphoma

Clinical Context and Therapy Purpose

The purpose of autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory HL.

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

Populations

The relevant population of interest is individuals with relapsed or refractory HL.

Interventions

The therapy being considered is autologous HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

A systematic review and meta-analysis of the available RCTs on HCT for patients with relapsed or refractory HL were published by Rancea et al (2014).¹⁵ Reviewers included 3 RCTs, 2 (1993, 2002) of which compared HDC plus autologous HCT with conventional treatment.^{16,17} Both trials (described below) were judged to be at moderate risk of bias using the Cochrane criteria. Combined analysis for the outcome of OS demonstrated a hazard ratio of 0.67 for patients treated with autologous HCT, which was not statistically significant (95% CI, 0.41 to 1.07). For the outcome of progression-free survival (PFS), there was a significant improvement for autologous HCT treatment, with a hazard ratio of 0.55 (95% CI, 0.35 to 0.86).

Randomized Controlled Trials

The British National Lymphoma Investigation study (1993) was the first to show that autologous HCT offered patients with relapsed or refractory HL a PFS benefit over conventional chemotherapy.¹⁸ Forty patients with relapsed or refractory HL were given chemotherapy without a transplant (n=20) or autologous HCT after HDC (n=20).¹⁶ A significantly better event-free survival rate at 3 years (53%) was reported for patients who underwent HCT than for those who did not (10%).

Subsequently, these findings were confirmed in a larger 2002 trial by the German Hodgkin Study Group and European Group for Blood and Marrow Transplantation.¹⁷ Patients relapsing after initial chemotherapy were randomized to chemotherapy without a transplant or to autologous HCT. In the final analysis of 144 patients, freedom from treatment failure at 3 years was 55% in the transplanted group versus 34% in the nontransplanted group. This benefit was maintained in a 2007 subgroup analysis, regardless of early or late relapse, and the results were confirmed in follow-up data at 7 years.¹⁹

Nonrandomized Studies

In addition to the RCTs, several large retrospective studies identified in a systematic review have reported event-free survival rates ranging from 25% to 60%, with OS rates from 35% to 66%, showing that disease status before autologous HCT was the most important prognostic factor for the final outcome.⁶

A retrospective observational cohort study by Merryman et al (2021) evaluated autologous HCT after anti-programmed death-1 (PD-1) therapy for patients with relapsed or refractory HL.²⁰ Seventy-eight patients were identified who underwent autologous HCT as a third-line (or later) treatment; 74% of patients underwent autologous HCT after anti-PD-1 treatment and 26% of patients received anti-PD-1 treatment along with additional therapy prior to autologous HCT. The 18-month PFS and OS after autologous HCT were 81% (95% CI, 69 to 89) and 96% (95% CI, 87 to 99), respectively.

Favorable outcomes were reported for patients who had received greater than 4 systemic therapies before autologous HCT (18-month PFS, 73%), who were refractory to 2 consecutive therapies immediately prior to anti-PD-1 treatment (18-month PFS, 78%), and who had positive pre-HCT positron emission tomography (PET) (18-month PFS, 75%); patients who were non-responders to anti-PD-1 treatment had inferior outcomes (18-month PFS, 51%).

Section Summary: Autologous Hematopoietic Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma

Randomized controlled trials and a meta-analysis have evaluated the use of autologous HCT for relapsed or refractory HL. The studies reported no difference in OS, but a significant improvement in PFS, for patients treated with autologous HCT.

Second Autologous Hematopoietic Cell Transplantation for Relapsed Hodgkin Lymphoma After Prior Autologous Hematopoietic Cell Transplantation

Clinical Context and Therapy Purpose

The purpose of a second autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed HL after an autologous HCT.

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

Populations

The relevant population of interest is individuals with relapsed HL after an autologous HCT.

Interventions

The therapy being considered is a second autologous HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over the years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Few treatment options exist for patients who relapse following an autologous HCT. These include single-agent palliative chemotherapy or occasionally, localized radiotherapy.¹⁹ If further remission is attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than 1 year.²¹

Case Series

There is limited experience with second autologous HCT, and treatment-related mortality is high (25% to 40%).¹⁶ Smith et al (2008) reported on the outcomes of 40 patients (21 with HL, 19 with non-HL) who underwent a second autologous HCT for relapsed lymphoma.²² Reported results were combined for the 2 populations, but the authors stated the outcomes for both patient groups were similar. Median age at second HCT was 38 years (range, 16 to 61 years). In 82% of patients, the second HCT was performed more than 1 year after the first. The treatment-related mortality at day 100 posttransplant was 11% (95% CI, 3% to 22%). At a median follow-up of 72 months (range, 12 to 124 months) after the second HCT, 73% of patients had died, 62% due to relapsed lymphoma. One-, 3-, and 5-year PFS estimates were 50% (95% CI, 34% to 66%), 36% (95% CI, 21% to 52%), and 30% (95% CI, 16% to 46%), respectively. Corresponding OS estimates were 65% (95% CI, 50% to 79%), 36% (95% CI, 22% to 52%), and 30% (95% CI, 17% to 46%), respectively. Study limitations included the absence of an appropriate comparison group and lack of data on how many patients were considered for a second HCT but were unable to mobilize sufficient stem cells or were otherwise unable to proceed to the second transplant. Finally, heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

Section Summary: Second Autologous Hematopoietic Cell Transplantation for Relapsed Hodgkin Lymphoma After Prior Autologous Hematopoietic Cell Transplantation

The evidence is limited to case series; no RCTs or nonrandomized comparative studies were identified. In 1 series, treatment-related mortality at 100 days was 11%, and the mortality rate was 73% at a median follow-up of 72 months.

**Allogeneic Hematopoietic Cell Transplantation for Hodgkin Lymphoma
First-Line Therapy for Hodgkin Lymphoma****Clinical Context and Therapy Purpose**

The purpose of allogeneic (allo)-HCT as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with HL.

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

Populations

The relevant population of interest is individuals with HL.

Interventions

The therapy being considered is allo-HCT as first-line therapy.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over the years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

The application of allo-HCT to the treatment of patients with HL appears limited, due to high procedure-related mortality. No controlled trials evaluating allo-HCT as first-line treatment for HL were identified. In addition, 2015 and 2016 systematic reviews of HCT for HL did not discuss studies using allo-HCT as first-line therapy.^{23,24}

Section Summary: Allogeneic Hematopoietic Cell Transplantation as First-Line Therapy for Hodgkin Lymphoma

No studies specifically addressing allo-HCT as first-line treatment for HL were identified.

Relapsed or Refractory Hodgkin Lymphoma**Clinical Context and Therapy Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory HL.

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

Populations

The relevant population of interest is individuals with relapsed or refractory HL.

Interventions

The therapy being considered is allo-HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence**Systematic Reviews**

Rashidi et al (2016) published a systematic review and meta-analysis of studies evaluating allo-HCT in HL.²⁴ Thirty-eight studies were selected. Three studies included more than 1 series and were divided into more than 1 group; a total of 42 series were included in the meta-analysis. Sample sizes of included studies ranged from 5 to 285 patients (N=1850 patients). Twenty-eight studies were retrospective and 14 prospective. None was an RCT. Median follow-up in the studies ranged from 11 to 104 months. Results of the meta-analyses are shown in Table 3.

Table 3. Meta-Analytic Outcomes

Follow-Up	Relapse-Free Survival (95% CI), %	Overall Survival (95% CI), %
6 months	77 (59 to 91)	83 (75 to 91)
1 year	50 (42 to 57)	68 (62 to 74)
2 years	37 (31 to 43)	58 (52 to 64)
3 years	31 (25 to 37)	50 (41 to 58)

Adapted from Rashidi et al (2016).²⁴

CI: confidence interval.

In multivariate analysis, more recent studies (i.e., those that started to accrue patients in 2000 or later) had significantly higher 6-month and 1-year survival rates than older studies.

Section Summary: Allogeneic Hematopoietic Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma

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%.

Allogeneic Hematopoietic Cell Transplantation for Relapsed Hodgkin lymphoma After Prior Autologous Hematopoietic Cell Transplantation**Clinical Context and Therapy Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed HL after an autologous HCT.

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

Populations

The relevant population of interest is individuals with relapsed HL after an autologous HCT.

Interventions

The therapy being considered is allo-HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over the years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

The Rashidi et al (2016) meta-analysis (described above) included 38 case series assessing patients who underwent allo-HCT after a prior failed autologous HCT.²⁴ In a multivariate analysis of factors associated with survival outcomes, reviewers found that a previous autologous HCT was significantly associated with higher 1-year ($p=.012$) and 2-year ($p=.040$) OS rates and significantly higher relapse-free survival at 1 year ($p=.005$) compared with no previous autologous HCT.

Section Summary: Allogeneic Hematopoietic Cell Transplantation for Relapsed Hodgkin Lymphoma After Prior Autologous Hematopoietic Cell Transplantation

A 2016 meta-analysis found that a previous autologous HCT was significantly associated with higher OS rates and significantly higher relapse-free survival rates compared with no previous autologous HCT.

**Reduced-Intensity Conditioning with Allogeneic Hematopoietic Cell Transplantation
Clinical Context and Therapy Purpose**

The purpose of reduced-intensity conditioning (RIC) with allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with relapsed or refractory HL.

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

Populations

The relevant population of interest is individuals with relapsed or refractory HL.

Interventions

The therapy being considered is RIC with allo-HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over the years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Reviews

Perales et al (2015) conducted an evidence review as part of the development of clinical guidelines on HCT for HL.²³ Reviewers evaluated a number of studies that showed better outcomes with RIC than with myeloablative conditioning regimens. For example, reviewers cited a 2008 study by the European Group for Blood and Marrow Transplantation reporting outcomes in 89 HL patients with relapsed or refractory disease who received an RIC with allo-HCT and were compared with 79 patients who received myeloablative conditioning (i.e., conventional group).²⁵ Sixty-two percent of the RIC group had undergone a previous autologous HCT versus 41% of the myeloablative group.

Although the incidence of relapse was nearly double in the RIC group (57% v.s 30%), after a median follow-up for surviving patients of 75 months (range, 12 to 120 months), 24 in the RIC group (26.9%) and 18 in the conventional group (22.8%) were alive. Five-year OS rates were 28% (95% CI, 18% to 38%) for the RIC group and 22% (95% CI, 13% to 31%) for the conventional group. Independent adverse prognostic factors for OS were a previously failed autologous HCT (relative risk [RR], 1.59; 95% CI, 1.07 to 2.35; $p=.02$), the use of myeloablative conditioning (RR, 1.62; 95% CI, 1.27 to 3.29; $p=.04$), and the presence of refractory disease (RR, 1.51; 95% CI, 1.03 to 2.21; $p=.003$). Perales et al (2015) concluded: "As a result, the preferred conditioning intensity in adult patients with relapsed/refractory HL is RIC, which results in acceptable treatment-related mortality including in patients who have had a prior ASCT [autologous stem cell transplant]."

Nonrandomized Study

Sureda et al (2012) published a phase II study (HDR-ALLO) of allo-HCT after RIC for patients with relapsed or refractory HL.²⁶ Ninety-two patients were included, of which 90% had received more than 2 lines of therapy, 87% prior radiotherapy, and 86% had failed a previous autologous HCT.

Fourteen individuals (15%) progressed under salvage therapy and were excluded from further study treatment. The remaining 78 patients proceeded to allograft (50 were in complete or partial remission and 29 in stable disease). Non-relapse mortality was 8% at 100 days and 15% at 1 year; OS was 71% at 1 year and 43% at 4 years from trial entry. For those who received allo-HCT, PFS was 48% at 1 year and 24% at 4 years. The study was limited by its small sample size and by the non-relapse mortality being adversely influenced by older age, poor performance score, and by the presence of refractory disease.

Section Summary: Reduced-Intensity Conditioning with Allogeneic Hematopoietic Cell Transplantation

A 2015 systematic review assessed a number of studies, including some with comparison groups, showing acceptable outcomes after RIC with allo-HCT in patients with relapsed or refractory HL. A phase II study found slightly improved results for patients receiving RIC and allo-HCT.

Tandem Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma**Clinical Context and Therapy Purpose**

The purpose of tandem autologous HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in individuals with HL.

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

Populations

The relevant population of interest is individuals with HL.

Interventions

The therapy being considered is tandem autologous HCT.

Comparators

Comparators of interest include standard of care.

Outcomes

The general outcomes of interest are OS, DSS, change in disease status, morbid events, treatment-related mortality, and treatment-related morbidity.

Follow-up over the years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence**Nonrandomized Studies**

No RCTs have compared tandem autologous HCT with other standard of care therapies. One prospective, nonrandomized study has compared tandem to single autologous HCT for HL.

Morschhauser et al (2008) and Sibon et al (2016) reported on the results of a prospective multicenter trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HCT in 245 patients with relapsed or refractory HL.^{27,28} Median follow-up time in the initial publication by Morschhauser et al (2008) was 51 months (range, 20 to 110 months). Sibon et al (2016) reported on the 10-year follow-up. Patients categorized as poor-risk (n=150), had primary refractory disease (n=77), or 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV disease at the time of relapse, or relapse in previously irradiated sites (n=73). In this trial, these poor-risk patients were eligible for tandem autologous transplants. Intermediate-risk (n=95) patients, defined as 1 risk factor at relapse, were eligible for a single transplant. Overall, 70% of the poor-risk patients received tandem transplants, and 97% of the intermediate-risk patients received a single transplant.

Ninety-four poor-risk patients responded to cytoreductive chemotherapy (partial response or CR), whereas 55 patients had chemotherapy-resistant disease. A total of 137 patients (including the 94 patients with chemotherapy-sensitive disease and 43 of 55 with chemotherapy-resistant disease) received the first autologous HCT. Among 121 patients who were fully restaged, 64 patients had achieved a CR, 37 a partial response, and 4 had stable disease. These 105 patients then underwent a second autologous HCT after a median of 65 days. Among them, 80 patients achieved a CR, including 17 patients who had achieved partial response and 3 patients with stable disease after the first transplant. Among the 55 patients who had cytoreduction failure, 30 responded to the first transplant (9 with CR), and 17 achieved a CR after the second transplant. Outcome analysis based on the intention-to-treat sample revealed the 5-year freedom from the second failure and OS estimates were 73% and 85% for the intermediate-risk group and 46% and 57% for the poor-risk group, all respectively. At the 10-year follow-up reported by Sibon et al (2016),²⁸ freedom from second failure and OS rates were 64% (95% CI, 54% to 74%) and 70% (95% CI, 61% to 80%) for the intermediate-risk group, and 41% (95% CI, 33% to 49%) and 47% (95% CI, 39% to 55%) for the poor-risk group.

In the poor-risk group, patients who underwent tandem transplant and had a CR to cytoreduction chemotherapy did not have superior outcomes compared with complete responders receiving a single transplant in previous studies by the same group.²⁹ However, in this 2002 study, poor-risk patients who were partial responders and underwent tandem transplants did better compared with partial responders who received a single transplant in previous studies. In this study, 5-year OS rates for poor-risk patients who completed the tandem transplant were 79% and 73% for complete and partial responders, whereas, in a previous trial of single autologous HCT, 5-year OS rates were 86% and 37% for complete and partial responders, all respectively.²⁹ The findings suggested that a single autologous HCT would be appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy, but that tandem autologous HCT showed a benefit in patients with chemotherapy-resistant disease and in partial responders to cytoreductive conditioning. The authors concluded that a trial, randomizing patients to single versus tandem autologous HCT was unrealistic, given the low yearly incidence of poor-risk patients. In their estimation, the best possible comparisons would be with data from previous findings with single transplants.

Tandem autologous HCT for HL has also been evaluated in single-arm studies. Fung et al (2007) reported results from a pilot study on HL that evaluated the toxicities and efficacy of tandem autologous HCT in patients with primary refractory or poor-risk recurrent HL.³⁰ The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled in the study between 1998 and 2000. Patients had at least 1 of the following poor prognostic factors: first CR less than 12 months, extranodal disease, or B symptoms (presence of systemic symptoms) at relapse. Forty-one (89%) patients received the second transplant. With a median follow-up of 5.3 years (range, 1.6 to 8.1 years), the 5-year OS and PFS rates were 54% (95% CI, 40% to 69%) and 49% (95% CI, 34% to 63%), respectively. Additionally, Smith et al (2018) reported results from a more recent Phase II trial of 89 patients with primary progressive or recurrent HL conducted by the Southwest Oncology Group (SWOG) Clinical Trials Network.¹¹ This single-arm trial was conducted at 10 centers and enrolled patients between 2006 and 2009. Key patient characteristics included that 53% had induction failure, 18% had an initial response \leq 12 months, 83% were stage III or IV at the time of trial enrollment, and 48% previously irradiated patients relapsed in an irradiated site. Eighty-two patients (92%) received the second transplant. With a median follow-up of 6.2 years, the 5-year PFS and OS rates were 55% (95% CI, 44% to 64%) and 84% (95% CI, 74% to 90%).

Section Summary: Tandem Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma

There are no RCTs comparing tandem autologous HCT with alternatives for treating HL. One prospective, nonrandomized study reported that patients who had not achieved a CR after conventional chemotherapy had better outcomes with tandem HCT than with single HCT. However,

the results of this trial were not definitive, and RCTs are needed to determine the efficacy of tandem transplants.

Supplemental Information

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

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, 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.

Further details from clinical input are included in the Appendix.

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.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 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.³² These guidelines were updated in 2020.³³ 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 4.

Table 4. 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
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 patients with HL.²³ Select recommendations are shown in Table 5.

Table 5. 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+
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 (NCCN) guidelines for HL (v.1.2024)⁴ 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."³⁴

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
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
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	22	Sep 2021

NCT No.	Trial Name	Planned Enrollment	Completion Date
	and Non-Hodgkin's Lymphomas Undergoing Allogeneic Hematopoietic Progenitor Cell Transplantation - A Multicenter Phase II Study		

NCT: national clinical trial.

^a Denotes an industry sponsored or cosponsored study.

Appendix 1

Clinical Input CI – Summary

Respondents

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

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

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

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

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

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

Respondent Profile

Physician					
#	Name	Degree	Institutional Affiliation	Clinical Specialty	Board Certification and Fellowship Training
Identified by Dana-Farber Cancer Institute					
1	Reid Merryman	MD	Dana-Farber Cancer Institute (DFCI)	Lymphoma specialist in Hematology/Oncology	Internal Medicine, Hematology/Oncology
Identified by American Society for Transplantation and Cellular Therapy					
2	Mehdi Hamadani	MD	Professor of Medicine, CIBMTR &	Bone Marrow Transplant & Cellular Therapy	Hematology, Medical Oncology

Physician					
			Medical College of Wisconsin	specialist in Hematology/Oncology	
Identified by American Society of Clinical Oncology					
3	Loretta Nastoupil MD		Associate Professor, University of Texas MD Anderson Cancer Center	Lymphoma specialist in Hematology/Oncology	Internal Medicine, Hematology, Medical Oncology
4	Anonymous MD		Anonymous clinical practice	Hematology/Oncology	Hematology/Oncology

Respondent Conflict of Interest Disclosure

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

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

Clinical Input Responses

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

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

The following PICO applies to the clinical input.

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> With relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation 	Interventions of interest are: <ul style="list-style-type: none"> Second autologous hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> With Hodgkin lymphoma 	Interventions of interest are: <ul style="list-style-type: none"> Tandem autologous hematopoietic cell transplantation 	Comparators of interest are: <ul style="list-style-type: none"> Standard of care 	Relevant outcomes include: <ul style="list-style-type: none"> Overall survival Disease-specific survival Change in disease status Morbid events Treatment-related mortality Treatment-related morbidity

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

Detailed Responses

Question 1.

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

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

Rationale

- There are no clinical scenarios where I would recommend a second autologous hematopoietic stem cell transplant. In the last 5 years, several new treatments (brentuximab vedotin, nivolumab, pembrolizumab) have been approved for patients who are ineligible for or who relapse after ASCT, and outcomes in this patient population have improved significantly (PMID 28512788). For patients who relapse after ASCT, we would favor treatment with allogeneic stem cell transplantation for eligible patients.
- No randomized or prospective trials have evaluated safety and feasibility of second autologous transplantation in HL patients. A CIBMTR analysis (PMID: 18640574), reported outcomes of lymphoma patient undergoing a second

Rationale

autologous HCT, including 21 HL subject. The treatment related mortality was high (15% at day 100 and 18% at 1 year), with only a subset of patients with disease control at 3 years (36%).

This analysis was conducted before active salvage agents in HL were available (including brentuximab vedotin, checkpoint inhibitors, alternative donor transplantation using modern platforms or cell therapies on genetically modified immune effector cells). Considering the availability of several approved and investigational agents in the management of HL, and quality of evidence available to date, the practice of second autologous transplant cannot be considered standard-of-care.

3 There is insufficient evidence to support a second autologous hematopoietic cell transplantation for relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation.

4 NR

NR = not reported

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

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

NR = not reported

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

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

NR = not reported

Question 2.

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

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

Rationale

- We do not treat with tandem autologous transplants. While there is phase 2 data, it has not been clearly shown to be superior to our standard approach. We favor allogeneic transplant over tandem autologous transplantation for patients with chemorefractory disease.
- No randomized trials have evaluated efficacy of tandem autologous transplantation in HL patients. While the question of tandem HCT has been evaluated in prospective single arm studies several years ago, only a single SWOG/BMT CTN trial has assessed this question in the modern era (PMID: 29289757). This study enrolled 89 subjects, including 64 patients high-risk disease (primary refractory disease or early relapse). There were no treatment-related deaths in the first year after transplantation. With a median follow-up of 6.2 years (range, 2 to 7.7) for eligible patients who remained alive, the 2-year and 5-year PFS were 63% (95% CI, 52% to 72%) and 55% (95% CI, 44% to 64%) respectively; the 2-year and 5-year overall survival were 91% (95% CI, 83% to 95%) and 84% (95% CI, 74% to 90%), respectively.

While these results are encouraging and acknowledging hazards of cross trial comparison, in patients with high risk HL, similar (or better) results can be expected with single autologous transplant followed by brentuximab vedotin maintenance. The latter is supported by randomized, prospective data from ATHERA trial (Moskowitz et al. Lancet 2015) and is the current standard-of-care

- There is insufficient evidence for tandem autologous hematopoietic cell transplantation in individuals with Hodgkin lymphoma.

4 NR

NR = not reported

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

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

NR = not reported

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

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

NR = not reported

References

1. National Cancer Institute (NCI). Adult Hodgkin Lymphoma Treatment (PDQ) - Health Professional Version. Updated August 4, 2023; <http://www.cancer.gov/cancertopics/pdq/treatment/adulthodgkins/healthprofessional>. Accessed November 28, 2023.
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 disease/lymphoma. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. Accessed November 27, 2023.
5. American Cancer Society (ACS). Hodgkin Lymphoma Stages. Updated May 1, 2018. <https://www.cancer.org/cancer/hodgkin-lymphoma/detection-diagnosis-staging/staging.html>. Accessed November 28, 2023.
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
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 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). 2016; <https://www.cms.gov/medicare-coverage-database/view/ncd.aspx?ncdid=366>. Accessed November 28, 2023.

Documentation for Clinical Review

Please provide the following documentation:

- Referring provider history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
 - Diagnosis (including disease staging) and prognosis
 - Synopsis of alternative treatments performed and results
 - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
 - Clinical history including comorbidities
 - Specific issues identified during the transplant evaluation
 - Consultation reports/letters (when applicable)
 - Correspondence from referring providers (when applicable)
 - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
- Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient's ability to be an adequate candidate for transplant
- Radiology reports including:
 - Chest x-ray (CXR)
 - PET scan, CT scan and bone survey (as appropriate)
- Cardiology procedures and pulmonary function reports:
 - EKG
 - Echocardiogram
 - Pulmonary function tests (PFTs)
- Biopsy/Pathology reports including:
 - Bone marrow biopsy
 - Lymph node biopsy (as appropriate)
- Laboratory reports

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	38204	Management of recipient hematopoietic progenitor cell donor search and cell acquisition
	38205	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
	38206	Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous
	38207	Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage
	38208	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor
	38209	Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, with washing, per donor
	38210	Transplant preparation of hematopoietic progenitor cells; specific cell depletion within harvest, T-cell depletion
	38211	Transplant preparation of hematopoietic progenitor cells; tumor cell depletion
	38212	Transplant preparation of hematopoietic progenitor cells; red blood cell removal
	38213	Transplant preparation of hematopoietic progenitor cells; platelet depletion
	38214	Transplant preparation of hematopoietic progenitor cells; plasma (volume) depletion
	38215	Transplant preparation of hematopoietic progenitor cells; cell concentration in plasma, mononuclear, or buffy coat layer
	38220	Diagnostic bone marrow; aspiration(s)
	38221	Diagnostic bone marrow; biopsy(ies)
	38222	Diagnostic bone marrow; biopsy(ies) and aspiration(s)
	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
	86812	HLA typing; A, B, or C (e.g., A10, B7, B27), single antigen
	86813	HLA typing; A, B, or C, multiple antigens
	86816	HLA typing; DR/DQ, single antigen
	86817	HLA typing; DR/DQ, multiple antigens
	86821	HLA typing; lymphocyte culture, mixed (MLC)
HCPCS	Q0083	Chemotherapy administration by other than infusion technique only (e.g., subcutaneous, intramuscular, push), per visit

Type	Code	Description
	Q0084	Chemotherapy administration by infusion technique only, per visit
	Q0085	Chemotherapy administration by both infusion technique and other technique(s) (e.g. subcutaneous, intramuscular, push), per visit
	S2140	Cord blood harvesting for transplantation, allogeneic
	S2142	Cord blood-derived stem-cell transplantation, allogeneic
	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 posttransplant care in the global definition

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
01/07/2011	BCBSA Medical Policy adoption
07/31/2015	Coding Update
12/04/2015	Policy revision without position change
04/01/2016	Policy revision without position change
03/01/2017	Policy title change from Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma Policy revision without position change
01/01/2018	Coding update
04/01/2018	Policy revision without position change
04/01/2019	Policy revision without position change
11/01/2019	Policy revision without position change
05/01/2020	Annual review. No change to policy statement. Literature review updated.
09/01/2020	Policy statement and literature updated.
03/01/2021	Annual review. No change to policy statement. Literature review updated.
04/01/2022	Annual review. No change to policy statement. Literature review updated.
10/01/2022	Administrative update.
04/01/2023	Annual review. Policy statement, guidelines and literature review updated.
04/01/2024	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. 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 covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p>Hematopoietic Cell Transplantation for Hodgkin Lymphoma 8.01.29</p> <p>Policy Statement:</p> <ol style="list-style-type: none"> Autologous hematopoietic cell transplantation (HCT) may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma. Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma. Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered investigational. Tandem autologous HCT is considered investigational in individuals with Hodgkin lymphoma. Other uses of HCT in individuals with Hodgkin lymphoma are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission. 	<p>Hematopoietic Cell Transplantation for Hodgkin Lymphoma 8.01.29</p> <p>Policy Statement:</p> <ol style="list-style-type: none"> Autologous hematopoietic cell transplantation (HCT) may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma. Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered medically necessary in individuals with primary refractory or relapsed Hodgkin lymphoma. Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered investigational. Tandem autologous HCT is considered investigational in individuals with Hodgkin lymphoma. Other uses of HCT in individuals with Hodgkin lymphoma are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.