Hematopoietic Cell Transplantation for Hodgkin Lymphoma

**Policy**

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

Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered medically necessary in patients 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 patients with Hodgkin lymphoma.

Other uses of HCT in patients with Hodgkin lymphoma are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission.

**Policy Guidelines**

In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous hematopoietic cell transplantation for first relapse or refractory Hodgkin lymphoma, poor-risk relapsed Hodgkin lymphoma was defined as 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites. 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 patients for whom a conventional myeloablative allotransplant could be curative may be
considered candidates for reduced-intensity conditioning allogeneic hematopoietic cell transplantation. They 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 patient, with whom usually there is sharing of only 3 of the 6 major histocompatibility antigens. Most patients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Coding
Please see the Codes table for details.

BENEFIT APPLICATION

BlueCard/National Account Issues
The following considerations may supersede this policy:

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

BACKGROUND

Hodgkin Lymphoma
Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2017, the estimated number of new cases in the United States was approximately 8260 and 1070 estimated deaths. The disease has a bimodal distribution, with most patients diagnosed between the ages of 15 and 30 years, with a second peak in adults aged 55 years and older.

The 2008 World Health Organization classification divided HL into 2 main types; these classifications did not change in the 2016 update:

1. "Classical" HL
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte depleted
   - Lymphocyte-rich
2. Nodular lymphocyte-predominant HL.

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

**Staging**

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

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

**Table 1. Ann Arbor Staging System for Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node region (I) or localized involvement of a single extra lymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extra lymphatic organ or site and its regional lymph node(s) with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of lymph node regions involved should be indicated by a subscript (e.g., II₂).</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions or structures on both sides of the diaphragm. These patients are further subdivided as follows:· · III-1: disease limited to spleen or upper abdomen· · III-2: periaortic or pelvic node involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Disseminated (multifocal) involvement of 1 or more extra lymphatic organs, with or without associated lymph node involvement, or isolated extra lymphatic organ involvement with distant (nonregional) nodal involvement</td>
</tr>
</tbody>
</table>

Patients with HL are generally classified into three groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal lymphadenopathy), early-stage unfavorable (stage I-II with a large mediastinal mass, with or without B symptoms; stage IB-IIB with the bulky disease), and advanced-stage disease (stage III-IV).

**Treatment**

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

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

In patients with relapse, the results of salvage therapy vary depending on a number of prognostic factors, as follows: the length of the initial remission, stage at recurrence, and the severity of anemia at the time of relapse. Early and late relapse are defined as less or more than 12 months from the time of
remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous hematopoietic cell transplantation (HCT) but not more than 40% with early first relapse. Only 25% to 35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within 1 to 2 years, and once relapse occurs posttransplant, median survival is less than 12 months.

**Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation (HCT) 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]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in evidence review 7.01.50.

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. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome six. An acceptable donor will match the patient at all or most of the HLA loci.

**Conditioning for Hematopoietic Cell Transplantation**

**Conventional Conditioning**

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of 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, 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 GVH disease.

**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 GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

**Targeted Chemotherapy and Autologous HCT 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 two programmed death receptor-1 (PD-1) blocking antibodies. The FDA regulatory status of these agents for the treatment of Hodgkin lymphoma is summarized in Table 2.

Brentuximab vedotin was evaluated in a large, phase 3, multinational, double-blind randomized controlled trial known as the AETHERA trial (abbreviation definition unknown). Moskowitz et al (2015) 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 extra nodal disease). Results showed that early consolidation with brentuximab vedotin after autologous HCT significantly improved 2-year progression-free survival (PFS) versus placebo (63% versus 51%, hazard ratio [HR] 0.57; 95% confidence interval [CI], 0.40-0.81). At 5-year follow-up, the significant PFS benefit for brentuximab vedotin persisted (59% versus 41%; HR 0.52; 95% CI, 0.38 to 0.72). In addition, a recent study by Smith et al (2018) of tandem autologous HCT observed that the 2-year PFS of 63% for brentuximab vedotin demonstrated in the AETHERA RCT "matches" the 2-year PFS rates for tandem autologous HCT.

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

**Regulatory Status**

The U.S. Food and Drug Administration (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 2 describes several novel agents that have been approved by the FDA for use as alternatives to tandem autologous HCT or a second autologous HCT in individuals at high-risk for, or with, respectively, refractory or relapsed HL following autologous HCT.
Table 2. Novel agents Approved by the U.S. Food and Drug Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>BLA</th>
<th>Type of agent</th>
<th>Manufacturer</th>
<th>FDA-approved indications for post-autologous HCT use</th>
<th>Date FDA approved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>125388</td>
<td>CD30-directed antibody-drug conjugate</td>
<td>Seattle Genetics</td>
<td>• Classical HL at high risk of relapse or progression as post-autologous HCT consolidation</td>
<td>Aug 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Classical HL after failure of autologous hematopoietic stem cell transplantation</td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>125554</td>
<td>Programmed death receptor-1 (PD-1) blocking antibody</td>
<td>Bristol Myers Squibb</td>
<td>Classical HL that has relapsed or progressed after autologous HCT and post transplantation brentuximab vedotin</td>
<td>May 2016</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>125514</td>
<td>Programmed death receptor-1 (PD-1) blocking antibody</td>
<td>Merck Sharp Dohme</td>
<td>Adult and pediatric patients with refractory classical HL, or who have relapsed after 3 or more prior lines of therapy^</td>
<td>Mar 2017</td>
</tr>
</tbody>
</table>

BLA: Biologic License Application; FDA: U.S. Food and Drug Administration; HL: Hodgkin Lymphoma; HCT: Hematopoietic Cell Transplantation

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

**Rationale**

This evidence review was created in December 1999 and has been updated regularly with searches of the PubMed database. The most recent literature review was performed through April 30, 2020.

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, two domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

**Autologous Hematopoietic Cell Transplantation for Hodgkin Lymphoma**

**First-Line Therapy for Hodgkin Lymphoma**

**Clinical Context and Therapy Purpose**

The purpose of autologous HCT as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with HL.

The question addressed in this evidence review is: does the use of autologous HCT as first-line therapy improve the net health outcomes of patients with HL?

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

**Patients**

The relevant population of interest is individuals with HL.

**Interventions**

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

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

**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 (TRM), 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**

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. 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=0.6). 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. 13

Carella et al (2009) published 10-year follow-up results for the Federico study. 13 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=0.7) 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=0.8) 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 HCT 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 patients with relapsed or refractory HL.

The question addressed in this evidence review is: does the use of autologous HCT improve the net health outcomes of patients with relapsed or refractory HL?

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

**Patients**

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

**Interventions**

The therapy being considered is autologous HCT.

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

**Comparators**

Comparators of interest include standard of care.

**Outcomes**

The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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

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).\textsuperscript{15} Reviewers included 3 RCTs, 2 (1993, 2002) of which compared HDC plus autologous HCT with conventional treatment.\textsuperscript{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).

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.\textsuperscript{18} Forty patients with relapsed or refractory HL were given chemotherapy without a transplant (n=20) or autologous HCT after HDC (n=20).\textsuperscript{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.\textsuperscript{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 vs 34% in the non-transplanted 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.\textsuperscript{19}

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.\textsuperscript{6}

Section Summary: Autologous HCT for Relapsed or Refractory Hodgkin Lymphoma

RCTs and a meta-analysis have evaluated the use of auto-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 HCT for Relapsed Hodgkin Lymphoma After Prior Autologous HCT

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 patients with relapsed HL after an autologous HCT.

The question addressed in this evidence review is: does the use of a second autologous HCT improve the net health outcomes of patients with relapsed HL after an autologous HCT?

The following PICO was used to select literature to inform this review.
Patients
The relevant population of interest is individuals with relapsed HL after an autologous HCT.

Interventions
The therapy being considered is a second autologous HCT.

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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
Few treatment options exist for patients who relapse following an autologous HCT; they 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 one year.\(^{20}\)

There is limited experience with second autologous HCT, and TRM is high (25%-40%).\(^{16}\) Smith et al (2008) reported on the outcomes of 40 patients (21 with HL, 19 with non-Hodgkin lymphoma) who underwent a second autologous HCT for relapsed lymphoma.\(^{21}\) Reported results were combined for the two populations, but the authors stated the outcomes for both patient groups were similar. Median age at second HCT was 38 years (range, 16-61 years). In 82% of patients, the second HCT was performed more than 1 year after the first. The TRM at day 100 posttransplant was 11% (95% CI, 3% to 22%). At a median follow-up of 72 months (range, 12-124 months) after the second HCT, 73% of patients had died\(^{22}\) 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 HCT for Relapsed Hodgkin Lymphoma After Prior Autologous HCT

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

Allogeneic HCT for Hodgkin Lymphoma
First-Line Therapy for Hodgkin Lymphoma
Clinical Context and Therapy Purpose
The purpose of allo-HCT as first-line therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with HL.

The question addressed in this evidence review is: does the use of allo-HCT as first-line therapy improve the net health outcomes of patients with HL?

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

Patients
The relevant population of interest is individuals with HL.

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

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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
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.22,23

Section Summary: Allo-HCT 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 patients with relapsed or refractory HL.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcomes of patients with relapsed or refractory HL?

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

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

Interventions
The therapy being considered is allo-HCT.

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

Comparators
Comparators of interest include standard of care.

Outcomes
The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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
Rashidi et al (2016) published a systematic review and meta-analysis of studies evaluating allo-HCT in HL.22 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 (total 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**

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

Adapted from Rashidi et al (2016).{sup}

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: Allo-HCT 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%.

**Allo-HCT for Relapsed Hodgkin lymphoma After Prior Autologous HCT**

**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 patients with relapsed HL after an autologous HCT.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcomes of patients with relapsed HL after an autologous HCT?

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

**Patients**

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

**Interventions**

The therapy being considered is allo-HCT.

Patients are actively managed by hematologists/oncologists in an outpatient clinical setting.

**Comparators**

Comparators of interest include standard of care.

**Outcomes**

The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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**

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. 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=0.012) and 2-year (p=0.040) OS rates and significantly higher relapse-free survival at 1 year (p=0.005) compared with no previous autologous HCT.

**Section Summary: Allo-HCT for Relapsed Hodgkin Lymphoma After Prior Autologous HCT**

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 Allo-HCT**

**Clinical Context and Therapy Purpose**

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

The question addressed in this evidence review is: does the use of RIC with allo-HCT improve the net health outcomes of patients with relapsed or refractory HL?

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

**Patients**

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

**Interventions**

The therapy being considered is RIC with allo-HCT.

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

**Comparators**

Comparators of interest include standard of care.

**Outcomes**

The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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**

Perales et al (2015) conducted an evidence review as part of the development of clinical guidelines on HCT for HL. Reviewers evaluated a number of studies that showed better outcomes with RIC and 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 a RIC with allo-HCT and were compared with 79 patients who received myeloablative conditioning (i.e., conventional group). Sixty-two percent of the RIC group had undergone a previous autologous HCT vs 41% of the myeloablative group. Although the incidence of relapse was nearly double in the RIC group (57% vs 30%), after a median follow-up for surviving patients of 75 months (range, 12-120 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, 1.59; 95% CI, 1.07 to 2.35; \( p = 0.02 \)), the use of myeloablative conditioning (relative risk=1.62; 95% CI, 1.27 to 3.29; \( p = 0.04 \)), and the presence of refractory disease (relative risk=1.51; 95% CI, 1.03 to 2.21; \( p = 0.003 \)). 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 TRM [treatment-related mortality] including in patients who have had a prior ASCT [autologous stem cell transplant].”

Sureda et al (2012) published a phase II study (HDR-ALLO) of allogeneic stem cell transplantation (allo-SCT) after RIC for patients with relapsed or refractory Hodgkin’s lymphoma. Ninety-two patients were included, of which 90% had received more than two lines of therapy, 87% prior radiotherapy, and 86% had failed a previous auto-SCT. 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-SCT, 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 Allo-HCT**

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 allogeneic stem cell transplantation.

**Tandem Autologous HCT 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 patients with HL.
The question addressed in this evidence review is: does the use of tandem autologous HCT improve the net health outcomes of patients with HL?

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

**Patients**

The relevant population of interest is individuals with HL.

**Interventions**

The therapy being considered is tandem autologous HCT.

Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

**Comparators**

Comparators of interest include standard of care.

**Outcomes**

The general outcomes of interest are OS, DSS, change in disease status, morbid events, TRM, 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**

No RCTs have compared tandem autologous HCT with other standard of care therapies. One prospective, nonrandomized study has compared tandem to single autologous HCL for HL. Morschhäuser 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.26,27 Median follow-up time in the initial publication by Morschhäuser et al (2008) was 51 months (range, 20-110 months). Sibon et al (2016) reported on the 10-year follow-up. Patients categorized as poor-risk (n=150) had the 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 or CR), whereas 55 patients had the chemotherapy-resistant disease. A total of 137 patients (including the 94 patients with chemotherapy-sensitive disease and 43 of 55 with the chemotherapy-resistant disease) received the
first autologous HCT. Among 121 patients who were fully restaged, 64 patients had achieved a complete response, 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 complete response, 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 complete response), and 17 achieved a complete response 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),21 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.25 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.25 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 vs 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.25 The study involved patients with primary progressive and 18 with recurrent HL who were enrolled in the study between 1998 and 2000. Patients had at least one of the following poor prognostic factors: first CR less than 12 months, extra nodal 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, 1.6-8.1 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 initial response of ≤ 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%–64%) and 84% (95% CI: 74%–90%).

Section Summary: Tandem Autologous HCT 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.
Summary of Evidence

Autologous HCT

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

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

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

Allogeneic HCT

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

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

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

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

**Tandem Autologous HCT**

For individuals who have Hodgkin lymphoma (HL) who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are OS, DSS, change in disease status, morbid events, and TRM and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT might be higher than for single autologous HCT. This study was not definitive due to potential selection bias; RCTs are needed to determine the impact of tandem autologous HCT on health outcomes in this population. The evidence is insufficient to determine the effects of the technology on health outcomes.

**SUPPLEMENTAL INFORMATION**

**Clinical Input from Physician Specialty Societies and Academic Medical Centers**

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

2020

Clinical input was 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. In response to requests, clinical input was received from 4 respondents, including 3 complete responses including 2 physician-level responses identified through specialty societies and 1 physician-level response identified through an academic medical center.

For individuals with relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation who receive second autologous hematopoietic cell transplantation, 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 Hodgkin lymphoma who receive tandem autologous hematopoietic cell transplantation, 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**

**National Comprehensive Cancer Network Guidelines**

Current National Comprehensive Cancer Network guidelines for Hodgkin lymphoma (HL; v.2.2020) 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 1-3 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 vedotin for 1 year is recommended for patients with high-risk of relapse.

**American Society for Blood and Marrow Transplantation**

In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation on indications for autologous and allogeneic HCT. Recommendations described the current consensus on the use of HCT in and out of the clinical trial setting. The Society recommendations on HL are provided in Table 4.

**Table 4. Recommendations for Use of HCT to Treat Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First complete response (PET negative)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>First complete response (PET positive)</td>
<td>N</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>C</td>
<td>S</td>
</tr>
<tr>
<td>Relapse after autologous transplant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td><strong>Pediatric</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First complete response</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Primary refractory, sensitive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Primary refractory, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>First relapse, sensitive</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>First relapse, resistant</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Second or greater relapse</td>
<td>C</td>
<td>C</td>
</tr>
</tbody>
</table>

C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; PET: positron emission tomography; S: standard of care.

The Society (2015) also published guidelines on the role of cytotoxic therapy with HCT in patients with Hodgkin Lymphoma. Select recommendations are shown in Table 5.

**Table 5. Recommendations on Use of Cytotoxic Therapy with HCT to Treat Hodgkin Lymphoma**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOR</th>
<th>Highest LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous HCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous HCT should not be offered as first-line therapy for advanced disease</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>Autologous HCT should be offered as first-line therapy for patients who fail to achieve CR</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>Autologous HCT should be offered as salvage therapy over nontransplantation (except localized disease or in patients with low-stage disease)</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>Autologous HCT should be offered to pediatric patients with primary refractory disease or high-risk relapse who respond to salvage therapy</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>Tandem autologous HCT is not routinely recommended in standard-risk patients</td>
<td>C</td>
<td>2+</td>
</tr>
<tr>
<td><strong>Allogeneic HCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allo-HCT should be used for relapse after ASCT instead of conventional therapy</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>RIC is the recommended regimen intensity</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>All donor sources can be considered</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>There are limited data for tandem autologous HCT/allo-HCT</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Allo-HCT is preferred over autologous HCT as second HCT (except in late relapse)</td>
<td>C</td>
<td>2+</td>
</tr>
</tbody>
</table>

allo: allogeneic; CR: Complete response; GOR: grade of recommendation; HCT: hematopoietic cell transplantation; LOE: level of evidence; RIC: reduced-intensity conditioning.
American College of Radiology

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

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 “advanced Hodgkin’s disease who have failed conventional therapy and have no HLA [human leukocyte antigen]-matched donor.”

Ongoing and Unpublished Clinical Trials

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

Table 6. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00574496</td>
<td>An Intention-to-Treat Study of Salvage Chemotherapy Followed by Allogeneic</td>
<td>30</td>
<td>Nov 2021</td>
</tr>
<tr>
<td></td>
<td>Hematopoietic Stem Cell Transplant for the Treatment of High-Risk or Relapsed</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hodgkin Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01203020</td>
<td>Once Daily Targeted Intravenous (IV) Busulfex as Part of Reduced-toxicity</td>
<td>32</td>
<td>Jun 2020</td>
</tr>
<tr>
<td></td>
<td>Conditioning for Patients with Refractory Lymphomas Undergoing Allogeneic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transplantation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

ESSENTIAL HEALTH BENEFITS

The Affordable Care Act (ACA) requires fully insured non-grandfathered individual and small group benefit plans to provide coverage for ten categories of Essential Health Benefits ("EHBs"), whether the benefit plans are offered through an Exchange or not. States can define EHBs for their respective state. States vary on how they define the term small group. In Idaho, a small group employer is defined as an employer with at least two but no more than fifty eligible employees on the first day of the plan or contract year, the majority of whom are employed in Idaho. Large group employers, whether they are self-funded or fully insured, are not required to offer EHBs, but may voluntarily offer them.

The Affordable Care Act requires any benefit plan offering EHBs to remove all dollar limits for EHBs.

REFERENCES

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


**CODES**

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td></td>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td></td>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td></td>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td></td>
<td>38208</td>
<td>; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td></td>
<td>38209</td>
<td>; thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td></td>
<td>38210</td>
<td>; specific cell depletion within harvest, T cell depletion</td>
</tr>
<tr>
<td></td>
<td>38211</td>
<td>; tumor cell depletion</td>
</tr>
<tr>
<td></td>
<td>38212</td>
<td>; red blood cell removal</td>
</tr>
<tr>
<td></td>
<td>38213</td>
<td>; platelet depletion</td>
</tr>
<tr>
<td></td>
<td>38214</td>
<td>; plasma (volume) depletion</td>
</tr>
<tr>
<td></td>
<td>38215</td>
<td>; cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td></td>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td></td>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td></td>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td></td>
<td>38241</td>
<td>; autologous</td>
</tr>
<tr>
<td></td>
<td>86812, 86813, 86816, 86817, 86821, 86825, 86826</td>
<td>Histocompatibility studies code range (e.g., for allogeneic transplant)</td>
</tr>
<tr>
<td>HCPCS</td>
<td>Q0083, Q0084, Q0085</td>
<td>Chemotherapy, administration code range</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
<td></td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
<td></td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of posttransplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)</td>
<td></td>
</tr>
<tr>
<td>ICD-10-CM</td>
<td>C81.00-C81.99</td>
<td>Hodgkin lymphoma code range</td>
</tr>
<tr>
<td>ICD-10-PCS</td>
<td>30243G0, 30243X0,</td>
<td>ICD-10-PCS codes are only used for inpatient services.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Administration, circulatory, transfusion, central vein, percutaneous,</td>
</tr>
</tbody>
</table>
### Hematopoietic Cell Transplantation for Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30243Y0</td>
<td>autologous, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>30243G2, 30243X2, 30243Y2</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, allogeneic related, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>30243G3, 30243X3, 30243Y3</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, allogeneic unrelated, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>30243G4, 30243X4, 30243Y4</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, allogeneic unspecified, code by substance (bone marrow, cord blood or stem cells, hematopoietic) code list</td>
</tr>
<tr>
<td>07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ, 07DS0ZZ, 07DS3ZZ</td>
<td>Surgical, lymphatic, and hemic systems, extraction, bone marrow, code list</td>
</tr>
</tbody>
</table>

**Type of service:** Therapy  
**Place of service:** Inpatient/Outpatient

### Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/14/16</td>
<td>Replace policy</td>
<td>Policy updated with literature review through October 27, 2015; reference 10 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/27/17</td>
<td>Replace policy</td>
<td>Policy updated with literature review through November 9, 2016; references 16-17 and 22-24 added. “Stem” removed from title and Policy. HSCT changed to HCT in Policy and Policy Guidelines. First policy statement divided into 2, 1 on allogeneic HCT and 1 on autologous HCT. The statement on allogeneic HCT was changed to state that either myeloablative or reduced-intensity conditioning can be used. Policy statement on reduced-intensity conditioning removed.</td>
</tr>
<tr>
<td>01/30/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho annual review, no change to policy.</td>
</tr>
<tr>
<td>02/26/18</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through November 7, 2017; reference 24 added; note 26 updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/24/19</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 01/24/2019. Policy updated with literature review through November 15, 2018; reference 3 added; reference 4 updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/23/20</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted changes as noted, effective 01/23/2020. Policy updated with literature review through November 15, 2018; reference 3 added; reference 4 updated. Policy statements unchanged.</td>
</tr>
<tr>
<td>06/25/20</td>
<td>Replace policy</td>
<td>Blue Cross of Idaho adopted change as noted, effective 09/22/2020. Policy updated with literature review through April 30, 2020; references added. Policy updated with clinical input and change to policy statement to Investigational for tandem</td>
</tr>
</tbody>
</table>

**Original Policy Date:** December 1999 **Page:** 25
autologous HCT in patients with Hodgkin lymphoma.

APPENDIX

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: 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

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Degree</th>
<th>Institutional Affiliation</th>
<th>Clinical Specialty</th>
<th>Board Certification and Fellowship Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Reid Merryman</td>
<td>MD</td>
<td>Dana-Farber Cancer Institute (DFCI)</td>
<td>Lymphoma specialist in Hematology/Oncology</td>
<td>Internal Medicine, Hematology/Oncology</td>
</tr>
<tr>
<td>2</td>
<td>Mehdi Hamadani</td>
<td>MD</td>
<td>Professor of Medicine, CIBMTR &amp; Medical College of Wisconsin</td>
<td>Bone Marrow Transplant &amp; Cellular Therapy specialist in Hematology/Oncology</td>
<td>Hematology, Medical Oncology</td>
</tr>
<tr>
<td>3</td>
<td>Loretta Nastoupil</td>
<td>MD</td>
<td>Associate Professor, University of Texas MD</td>
<td>Lymphoma specialist in Hematology/Oncology</td>
<td>Internal Medicine, Hematology, Medical Oncology</td>
</tr>
</tbody>
</table>
**Respondent Conflict of Interest Disclosure**

<table>
<thead>
<tr>
<th>#</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
<th>YES/NO</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td>Direct a BMT &amp; Cellular Therapy Program that provides care for Hodgkin lymphoma patients in both transplant and non-transplant settings.</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

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**

The following PICO applies to the clinical input.

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest</td>
<td>Comparators of interest</td>
<td>Relevant outcomes include:</td>
</tr>
</tbody>
</table>
**Hematopoietic Cell Transplantation for Hodgkin Lymphoma**

- With relapsed Hodgkin lymphoma after an autologous hematopoietic cell transplantation:
  - Second autologous hematopoietic cell transplantation

- Standard of care

- Overall survival
- Disease-specific survival
- Change in disease status
- Morbid events
- Treatment-related mortality
- Treatment-related morbidity

**Interventions of interest**
- Tandem autologous hematopoietic cell transplantation

**Comparators of interest**
- Standard of care

**Relevant outcomes include:**
- Overall survival
- Disease-specific survival
- Change in disease status
- Morbid events
- Treatment-related mortality
- Treatment-related morbidity

Individuals:
- With Hodgkin lymphoma

Interventions of interest
- Tandem autologous hematopoietic cell transplantation

Comparators of interest
- Standard of care

Relevant outcomes include:
- 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).

<table>
<thead>
<tr>
<th>#</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>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 autologous HCT, including 21 HL subject. The treatment related mortality was high (15% at day 100 and 18% at one 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, check point 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 consider standard-of-care.</td>
</tr>
<tr>
<td>3</td>
<td>There is insufficient evidence to support a second autologous hematopoietic cell transplantation for relapsed</td>
</tr>
</tbody>
</table>
Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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.

<table>
<thead>
<tr>
<th>#</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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:
  o Relevant clinical scenarios (e.g., a chain of evidence) where the technology is expected to provide a clinically meaningful improvement in net health outcome;
  o Specific outcomes that are clinically meaningful;
  o Any relevant patient inclusion/exclusion criteria or clinical context important to consider in identifying individuals for this indication;
  o Supporting evidence from the authoritative scientific literature (please include PMID).

<table>
<thead>
<tr>
<th>#</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>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 patents with chemo refractory disease.</td>
</tr>
</tbody>
</table>
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.

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.

<table>
<thead>
<tr>
<th>#</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>#</th>
<th>YES / NO</th>
<th>Low Confidence</th>
<th>Intermediate Confidence</th>
<th>High Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

NR = not reported