Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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Section: Transplants
Place(s) of Service: Outpatient, Inpatient

Precertification is required for this service.

I. Description

Hodgkin lymphoma 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 Hodgkin lymphoma, particularly in the setting of relapse or refractory disease.

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

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

For individuals who have relapsed Hodgkin lymphoma after an autologous HCT who receive a second autologous HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs or nonrandomized comparative studies were identified. In 1 case series,
treatment-related mortality at 100 days was 11%; at a median follow-up of 72 months, the mortality rate was 73%. The evidence is insufficient to determine the effects of the technology on health outcomes.

**Allo-HCT**

For individuals who have Hodgkin lymphoma who receive allo-HCT as initial therapy, the evidence includes no published studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for Hodgkin lymphoma were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have relapsed Hodgkin lymphoma after autologous HCT who receive allo-HCT, the evidence includes case series and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT was significantly associated with higher 1- and 2-year overall survival 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 Hodgkin lymphoma who receive reduced-intensity conditioning (RIC) with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after RIC allo-HCT in patients with relapsed or refractory Hodgkin lymphoma. 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 who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT may be higher than that for single autologous HCT. This study is not definitive due to potential selection bias, and 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.

Clinical input obtained in 2009 supported the use of tandem autologous HCT in specific situations, including primary refractory HL and relapsed disease with poor risk features, not in remission. Tandem autologous HCT may be considered medically necessary for these situations.

Background

HEMATOPOIETIC CELL TRANSPLANTATION

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT [allo-HCT]). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

CONDITIONING FOR HCT

Conventional Conditioning

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include preengraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which also increase susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal
hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**Reduced-Intensity Conditioning for Allo-HCT**
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally 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, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For this evidence review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**HODGKIN LYMPHOMA**
Hodgkin lymphoma is a relatively uncommon B-cell lymphoma. In 2011, the estimated number of cases in the United States was approximately 8830 new diagnoses and 1300 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 divides Hodgkin lymphoma into 2 main types:

1. **“Classical” Hodgkin lymphoma (CHL)**
   - Nodular sclerosis
   - Mixed cellularity
   - Lymphocyte depleted
   - Lymphocyte rich
2. **Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)**

In Western countries, CHL accounts for 95% of cases of Hodgkin lymphoma and, for NLPHL, only 5%.3 CHL is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. NLPHL lacks Reed-Sternberg cells but is characterized by the presence of lymphocytic and histiocytic cells termed “popcorn cells.”

**Staging for Hodgkin Lymphoma**
The Ann Arbor staging system for Hodgkin lymphoma 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 Hodgkin lymphoma 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>
<thead>
<tr>
<th>Stage</th>
<th>Area of Concern</th>
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<tbody>
<tr>
<td>I</td>
<td>Single lymph node region (I) or localized involvement of a single extralymphatic 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 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). The number of lymph node regions involved should be indicated by a subscript (e.g., II&lt;sub&gt;2&lt;/sub&gt;).</td>
</tr>
</tbody>
</table>
| III   | 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: paraaortic or pelvic node involvement |
| 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 Hodgkin lymphoma are generally classified into 3 groups: early-stage favorable (stage I-II with no B symptoms or large mediastinal lymphadenopathy), early-stage unfavorable (stage I-II with large mediastinal mass, with or without B symptoms; stage IB-IIB with bulky disease), and advanced-stage disease (stage III-IV).

Patients with nonbulky stage IA or IIA disease are considered to have clinically early-stage disease. These patients are candidates for chemotherapy, combined modality therapy, or radiotherapy alone.1 Patients with obvious stage III or IV disease, bulky disease (defined as a 10-cm mass or mediastinal disease with a transverse diameter exceeding 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 Hodgkin lymphoma is defined as disease regression of less than 50% after 4 to 6 cycles of anthracycline-containing chemotherapy, disease progression during induction therapy, or progression within 90 days after the completion of first-line treatment.

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 HCT but not more than 40% with early first relapse.

Only approximately 25% to 35% of patients with primary progressive or poor-risk recurrent Hodgkin lymphoma 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.

II. Criteria

A. Autologous hematopoietic cell transplantation (HCT) is covered (subject to Limitation and Administrative Guidelines) in patients with primary refractory or relapsed Hodgkin lymphoma (HL).

B. Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens are covered (subject to Limitation and Administrative Guidelines) in patients with primary refractory or relapsed Hodgkin lymphoma.

C. Tandem autologous HCT is covered (subject to Limitations and Administrative Guidelines):
   1. In patients with primary refractory HL; or
   2. In patients with relapsed disease with poor risk features who do not attain a complete remission to cytoreductive chemotherapy prior to transplantation (see Guidelines).

III. 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 (HL), poor-risk relapsed HL was defined as 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites. Primary refractory disease was defined as disease regression less than 50% after 4 to 6 cycles of doxorubicin-containing chemotherapy or disease progression during induction or within 90 days after the end of first-line treatment.

Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HCT. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically >55 or >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen (HLA)-identical matched siblings. Related donors mismatched at 1 locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry 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. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.
IV. Limitations

A. A second autologous cell transplantation for relapsed lymphoma after a prior autologous HCT is not covered as it is not known to be effective in improving health outcomes.

B. Other uses of HCT in patients with HL, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission, are not covered as they are not known to be effective in improving health outcomes.

V. Administrative Guidelines

Precertification is required for a transplant evaluation and for the transplant itself and should be submitted by the proposed treating facility. To precertify, please complete HMSA's Precertification Request and mail or fax the form, or iExchange as indicated along with the required documentation.

CODING

In 2003, 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. For example, Plans should determine if cryopreservation is performed. A range of codes describes services associated with cryopreservation, storage, and thawing of cells (38207-38215).

CPT 38208 and 38209 describe thawing and washing of cryopreserved cells
CPT 38210-38214 describe certain cell types being depleted
CPT 38215 describes plasma cell concentration.

<table>
<thead>
<tr>
<th>CPT Codes</th>
<th>Description</th>
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<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38207</td>
<td>Transplant preparation of hematopoietic progenitor cells; cryopreservation and storage</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
</tr>
<tr>
<td>38209</td>
<td>Thawing of previously frozen harvest, with washing, per donor</td>
</tr>
<tr>
<td>38210</td>
<td>Specific cell depletion with harvest, T cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>Tumor cell depletion</td>
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<tr>
<td>HCPCS Code</td>
<td>Description</td>
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<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>Q0083 - Q0085</td>
<td>Chemotherapy, administration code range</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</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 post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)</td>
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**ICD-10-PCS**

<table>
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<tr>
<th>Description</th>
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<td>ICD-10-PCS codes are only used for inpatient services.</td>
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<table>
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<tr>
<th>Code List</th>
<th>Description</th>
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<tbody>
<tr>
<td>30243G0, 30243X0, 30243Y0</td>
<td>Administration, circulatory, transfusion, central vein, percutaneous, 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>07DQ0ZZ, 07DQ3ZZ, 07DR0ZZ, 07DR3ZZ,</td>
<td>Surgical, lymphatic and hemic systems, extraction, bone marrow, code list</td>
</tr>
</tbody>
</table>
VI. Rationale

This policy has been updated regularly with searches of the MEDLINE database. The most recent literature review was performed for the period through November 9, 2016.

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR HODGKIN LYMPHOMA

Initial Therapy for Hodgkin Lymphoma

A study published by Federico et al (2003) concluded that high-dose chemotherapy (HDC) with autologous hematopoietic cell transplantation (HCT) offered no benefit in outcomes over conventional chemotherapy in front-line therapy for advanced Hodgkin lymphoma (HL).

Carella et al (2009) reported the long-term results of 163 patients with unfavorable HL who had received either an autologous HCT or additional standard chemotherapy for consolidation after initial conventional chemotherapy. Patients were randomly assigned to receive HDC followed by an autologous HCT (n=83) or 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 overall survival (OS) was 88% (95% confidence interval [CI], 80 to 96%) in the autologous HCT arm and 88% (95% CI, 79 to 96%) in the CT arm (p=0.99). Ten-year OS was 85% (95% CI, 78 to 90%) versus 84% (95% CI, 77 to 89%) for the autologous HCT versus the standard chemotherapy group, respectively. The authors concluded that, after a median follow-up of 107 months, their data supported that patients who respond to induction therapy with conventional chemotherapy do not achieve superior outcomes with consolidation with HDC and autologous HCT.

Subsection Summary: Autologous HCT as Initial Therapy for Hodgkin Lymphoma

There are a small number of RCTs that use autologous HCT as first-line treatment, and these trials have reported no benefit above that of conventional chemotherapy.

Relapsed/Refractory HL

Autologous HCT is widely considered the therapy of choice for relapsed and refractory HL. Two randomized, controlled trials showed benefit in using autologous HCT in these patients:

A systematic review and meta-analysis of available RCTs on HCT for patients with relapsed or refractory HL was published by Rancea et al in 2014. Reviewers included 3 RCTs, 2 of which compared HDC followed by autologous HCT to conventional treatment. Both trials were judged to be at moderate risk of bias using the Cochrane Collaboration risk of bias tool. 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 (BNLI) study (1993) was the first to show a progression-free survival (PFS) benefit with autologous HCT over conventional chemotherapy in relapsed or refractory HL patients. Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20). A significantly better event-free survival (EFS) at 3 years of 53% versus 10% was reported in the patients who underwent transplant versus the group that did not.

Subsequently, these findings were confirmed in a larger trial by the German Hodgkin Study Group (GHSG) and European Group for Blood and Marrow Transplantation (EBMT). Patients relapsing after initial chemotherapy were randomly assigned to chemotherapy without 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 subgroup analysis, regardless of early or late relapse, and the results were confirmed in follow-up data at 7 years.

In addition to the RCTs, several large retrospective studies identified in 1 systematic review have reported EFS 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.

**Subsection Summary: Autologous HCT for Relapsed or Refractory HL**

At least RCTs evaluating auto-HCT for relapsed or refractory HL have been completed, along with meta-analyses of the 2 trials. The studies report no difference in OS, but a significant improvement in PFS, for patients treated with autologous HCT.

**Second Autologous HCT for Relapsed HL After Prior Autologous HCT**

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

There is limited experience with second autologous HCT, and treatment-related mortality is high (25 to 40%). Smith et al. reported the outcomes of 40 patients (21 with HL and 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HCT for relapsed lymphoma. Results reported were combined for the two populations, but the authors state that the outcomes of patients with HL and NHL were similar. Median age at second HCT was 38 years (range, 16 to 61). The second HCT was performed more than 1 year after the first in 82%. Treatment-related mortality at day 100 post-transplant 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% of these due to relapsed lymphoma. One-, 3-, and 5-year PFS probabilities were 50% (95% CI, 34 to 66%), 36% (95% CI, 21 to 52%), and 30% (95% CI, 16 to 46%), respectively. Corresponding OS probabilities were 65% (95% CI, 50 to 79%), 36% (95% CI, 22 to 52%), and 30% (95% CI, 17 to 46%), respectively. The authors stated that limitations to their study included the absence of an appropriate comparison group and that it was not known 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, they stated that the heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

**Subsection Summary: Second Autologous HCT for Relapsed HL After Prior Autologous HCT**

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 HCT FOR HL**

**Initial Therapy for HL**

The application of allogeneic HCT to the treatment of patients with HL initially appeared limited, due to a 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.

**Subsection Summary: Allogeneic HCT as Initial Therapy for HL**

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

**Relapsed or Refractory HL**

In 2016, Rashidi et al published a systematic review and meta-analysis of studies evaluating allo-HCT in HL. A total of 38 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 2.

**Table 2: Findings of the Rashidi et al (2016) Meta-Analysis**

<table>
<thead>
<tr>
<th>Follow-Up</th>
<th>Relapse-Free Survival (95% CI)</th>
<th>Overall Survival (95% CI)</th>
</tr>
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<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>
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</table>

CI: confidence interval.

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

**Subsection Summary: Allogeneic HCT as for Relapsed or Refractory HL**

A 2016 meta-analysis identified 38 case series evaluating allo-HCT for relapsed or refractory HL. Pooled analysis found a 6-month OS rate of 83% and a 3-year OS rate of 50%.
Allo-HCT for Relapsed HL After Prior Autologous HCT
The Rashidi 2016 meta-analysis (described above) included a number of studies with 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- and 2-year survival rates than no previous autologous HCT.

Section Summary: Allo-HCT for Relapsed HL After Prior Autologous HCT
A 2016 meta-analysis of 38 case series 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 RFS at 1 year (p=0.005) compared with no previous autologous HCT.

Reduced-Intensity Conditioning With Allo-HCT
In 2015, Perales et al conducted an evidence review as part of the process for developing a clinical guideline on HCT for HL.16 Reviewers cited a number of studies that showed better outcomes with reduced-intensity conditioning (RIC) and with myeloablative conditioning regimens. For example, reviewers cited a 2008 study by the European Group for Blood and Marrow Transplantation (EBMT) reporting outcomes in 89 HL patients with relapsed or refractory disease who received an RIC allo-HCT and were compared with 79 patients who received myeloablative conditioning (ie, conventional group).18 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% 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 [RR], 1.59; 95% CI, 1.07 to 2.35; p=0.02), the use of myeloablative conditioning (RR=1.62; 95% CI, 1.27 to 3.29; p=0.04), and the presence of refractory disease (RR=1.51; 95% CI, 1.03 to 2.21; p=0.003). Perales et al 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].”

Section Summary: Reduced-Intensity Conditioning With Allo-HCT
A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after RIC in patients with relapsed or refractory HL.

TANDEM AUTOLOGOUS HCT FOR HL
Fung et al (2007) reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HCT in patients with primary refractory or poor risk recurrent HL. The study involved 28 patients with primary progressive and 18 with recurrent HL who were enrolled in the study between April 1998 and March 2000. Patients had at least one of the following poor prognostic factors: first CR less than 12 months, extranodal disease, or B symptoms at relapse. Forty-one patients (89%) received the second transplant. With a median follow-up of 5.3 years (range, 1.6-8.1), the 5-year OS and PFS were 54% (95% CI, 40 to 69%) and 49% (95% CI, 34 to 63%), respectively.
Morschhauser et al. reported on the results of a multicenter prospective trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HCT in 245 patients with relapsed/refractory HL. Median follow-up time was 51 months (range, 20–110 months). Patients who were 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 occurring within previously irradiated sites (n=73). In this study, these poor-risk patients were eligible for tandem autologous transplants. Intermediate-risk patients (n=95), 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.

Overall, 94 poor-risk patients responded to cytoreductive chemotherapy (partial response [PR] 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 PR, and 4 had stable disease. These 105 patients then underwent the second autologous HCT after a median of 65 days. Among them, 80 patients achieved a CR, including 17 patients who had achieved PR, 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 CR after the second transplant.

Outcome analysis based on the intent-to-treat sample showed 5-year freedom from second failure and OS were 73% and 85% for the intermediate-risk group and 46% and 57% for the poor-risk group, all respectively.

In the poor-risk group, patients who underwent tandem transplant and had a complete response to cytoreduction chemotherapy did not have superior outcomes compared to complete responders receiving a single transplant in previous studies. However, in this study, poor-risk patients who were partial responders who underwent tandem transplants did better when compared to 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. (24) The authors concluded that a single autologous HCT is 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 stated that a trial of random assignment of single versus tandem autologous HCT was unrealistic, given the low yearly incidence of poor-risk patients, and that the best possible comparisons are with data from previous findings with single transplants.

**Section Summary: Tandem (Autologous-Autologous) HCT**

There are no RCTs comparing tandem autologous HCT to alternatives. One prospective, nonrandomized study reported that patients who had not achieved a CR to conventional chemotherapy had better outcomes with tandem HCT compared with single HCT. However, the results of this trial are not definitive and RCTs are needed to determine the efficacy of tandem transplants.
ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 3.

Table 3. 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>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00574496</td>
<td>Combination Chemotherapy Followed by Donor Stem Cell Transplant in Treating Patients With Relapsed or High-Risk Primary Refractory Hodgkin Lymphoma</td>
<td>30</td>
<td>Nov 2017</td>
</tr>
<tr>
<td>NCT01203020</td>
<td>Once Daily Targeted Intravenous (IV) Busulfex as Part of Reduced-toxicity Conditioning for Patients With Refractory Lymphomas Undergoing Allogeneic Transplantation</td>
<td>32</td>
<td>Dec 2018</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

SUMMARY OF EVIDENCE

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

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

For individuals who have relapsed Hodgkin lymphoma after an autologous HCT who receive a second autologous HCT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs or nonrandomized comparative studies were identified. In 1 case series, treatment-related mortality at 100 days was 11%; at a median follow-up of 72 months, the mortality rate was 73%. The evidence is insufficient to determine the effects of the technology on health outcomes.
**Allo-HCT**

For individuals who have Hodgkin lymphoma who receive allo-HCT as initial therapy, the evidence includes no published studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for Hodgkin lymphoma were identified. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

For individuals who have relapsed Hodgkin lymphoma after autologous HCT who receive allo-HCT, the evidence includes case series and a meta-analysis. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2016 meta-analysis of 38 case series found that a previous autologous HCT was significantly associated with higher 1- and 2-year overall survival 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 Hodgkin lymphoma who receive reduced-intensity conditioning (RIC) with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2015 systematic review cited a number of studies, including some with comparison groups, showing acceptable outcomes after RIC allo-HCT in patients with relapsed or refractory Hodgkin lymphoma. 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 who receive tandem autologous HCT, the evidence includes nonrandomized comparative studies and case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. One prospective, nonrandomized study reported that, in patients with poor prognostic markers, response to tandem autologous HCT may be higher than that for single autologous HCT. This study is not definitive due to potential selection bias, and 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.

In response to requests, input was received from 2 academic medical centers while this policy was under review in 2009. The 2 reviewers agreed with the policy statements, with the exception of the use of a second autologous hematopoietic cell transplantation (HCT) after a prior autologous HCT, which both thought would be medically necessary in certain circumstances. Data to support the use of a second autologous HCT are extremely limited, and the policy statement for this use of HCT remains investigational.

Practice Guidelines and Position Statements

Comprehensive Cancer Network (NCCN) Guidelines
Current National Comprehensive Cancer Network guidelines for Hodgkin lymphoma (v.3.2016) include a recommendation for autologous hematopoietic cell transplantation (HCT) in patients with biopsy-proven refractory disease who have undergone second-line systemic therapy and Deauville stages 1 to 4 according to restaging based on findings from positron emission tomography or computed tomography.

American Society for Blood and Marrow Transplantation
In 2015, guidelines were published by the American Society for Blood and Marrow Transplantation (ASBMT) on indications for autologous and allogeneic HCT.22 Recommendations described the current consensus on use of HCT within and outside of the clinical trial setting. ASBMT recommendations on Hodgkin lymphoma are provided in Table 3.

Medicare National Coverage
Autologous HCT is considered reasonable and necessary and is covered under Medicare (NCD 110.8.1 effective 08/04/2010) for patients with advanced Hodgkin disease who have failed conventional therapy and have no human leukocyte antigen–matched donor.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First complete response (PET-)</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>First complete response (PET+)</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></td>
<td>C</td>
</tr>
</tbody>
</table>
In 2015, ASBMT published guidelines on the role of cytotoxic therapy with HCT in patients with Hodgkin Lymphoma. Select recommendations are shown in Table 4.

### Table 4: ASBMT Recommendations on Cytotoxic Therapy With HCT for Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Grade</th>
<th>Highest LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autologous HCT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCT should not be offered as first-line therapy for advanced disease</td>
<td>A</td>
<td>1+</td>
</tr>
<tr>
<td>ASCT should be offered as first-line therapy for patients who fail to achieve CR</td>
<td>B</td>
<td>2++</td>
</tr>
<tr>
<td>ASCT 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>ASCT 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 ASCT 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 ASCT/Allo-HCT</td>
<td>D</td>
<td>4</td>
</tr>
<tr>
<td>Allo-HCT is preferred over ASCT as second HCT (except in late relapse)</td>
<td>C</td>
<td>2+</td>
</tr>
</tbody>
</table>

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; PET: positron emission tomography; S: standard of care.

### European Society for Medical Oncology

In 2014, the European Society for Medical Oncology published guidelines on the diagnosis and treatment of Hodgkin lymphoma. The guidelines stated: “The standard of care for most patients with disease recurrence after first-line treatment consists of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT).”

### MEDICARE NATIONAL COVERAGE

Autologous HCT is considered reasonable and necessary and is covered under Medicare (NCD 110.8.1 effective 08/04/2010) for patients with advanced Hodgkin disease who have failed conventional therapy and have no human leukocyte antigen–matched donor.

### VII. Important Reminder

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.
Benefit determinations are subject to applicable member contract language. To the extent there
are any conflicts between these guidelines and the contract language, the contract language will
control.

This Medical Policy has been developed through consideration of the medical necessity criteria
under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4),
generally accepted standards of medical practice and review of medical literature and government
approval status. HMSA has determined that services not covered under this Medical Policy will not
be medically necessary under Hawaii law in most cases. If a treating physician disagrees with
HMSA’s determination as to medical necessity in a given case, the physician may request that
HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any
supporting documentation.

VIII. References

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