When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

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

Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) in patients with primary refractory or relapsed Hodgkin lymphoma (HL) to be eligible for coverage.

Based on review of available data, the Company may consider allogenic hematopoietic cell transplantation, using either myeloablative or reduced-intensity conditioning regimens in patients with primary refractory or relapsed Hodgkin lymphoma to be eligible for coverage.

Based on review of available data, the Company may consider tandem autologous hematopoietic cell transplantation (HCT) to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility for tandem autologous hematopoietic cell transplantation (HCT) will be considered when any of the following criteria are met:

- Primary refractory Hodgkin lymphoma (HL); or
- Relapsed disease with poor risk features who do not attain a complete remission (CR) to cytoreductive chemotherapy prior to transplantation.

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers tandem autologous hematopoietic cell transplantation (HCT) to be investigational* when patient selection criteria are not met.

Based on review of available data, the Company considers a second autologous cell transplantation for relapsed lymphoma after a prior autologous hematopoietic stem cell transplantation (HCT) to be investigational.*

Other uses of hematopoietic cell transplantation (HCT) in patients with Hodgkin lymphoma (HL), including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission (CR) to be investigational.*
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Policy Guidelines
In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous HCT for first relapse or refractory Hodgkin lymphoma, poor-risk relapsed Hodgkin lymphoma was defined as 2 or more of the following risk factors at first relapse: time to relapse less than 12 months, stage III or IV at relapse, and relapse within previously irradiated sites. 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 HCT (allo-HCT). They 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 score) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen–identical matched siblings. Related donors mismatched at 1 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.

Background/Overview
Hematopoietic Cell Transplantation
Hematopoietic cell transplantation refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow 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 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 “naïve” 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 a critical factor for achieving a good outcome with allo-HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. Human leukocyte antigens refer to the tissue type expressed at the Class I and Class II loci on 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).
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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 GVHD, which also increase susceptibility of the patient 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. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

Reduced-Intensity Conditioning (RIC) for Allo-HCT
Reduced-intensity conditioning refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional 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 non-relapse 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. Reduced-intensity conditioning 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 allogeneic 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 the purposes of this policy, the term RIC will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) 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
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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 World Health Organization (WHO) classification divides HL into two main types:

1. “Classical” HL (CHL)
   a. Nodular sclerosis
   b. Mixed cellularity
   c. Lymphocyte depleted
   d. Lymphocyte rich

2. Nodular Lymphocyte-Predominant (NLPHL)

In Western countries, CHL accounts for 95% of cases of HL and NLPHL only 5%. Classic HL is characterized by the presence of neoplastic Reed-Sternberg cells in a background of numerous non-neoplastic inflammatory cells. Nodular Lymphocyte-Predominant 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 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 Stating 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 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 (IIE). The number of lymph node regions involved should be indicated by a subscript (eg, II_2).</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: periatic 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 HL are generally classified into three groups: early-stage favorable (stage I–II with no B symptoms or large mediastinal lymphadenopathy), early-stage unfavorable (stages 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 clinical 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 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 combination 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 4–6 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 upon 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 CT, but not more than 40% with early first relapse.

Only approximately 25%-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 1–2 years and once relapse occurs post-transplant, median survival is <12 months.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**
The FDA regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation (CFR) title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Centers for Medicare and Medicaid Services (CMS)
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.

**Rationale/Source**
This policy has been updated regularly with reviews of the MEDLINE database. The most recent literature review was performed through November 9, 2016.
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Autologous HCT for HL
Initial Therapy for HL
A study published by Federico and colleagues concluded that high-dose chemotherapy (HDC) with autologous HCT offered no benefit in outcomes over conventional chemotherapy in front-line therapy for advanced HL patients.

Carella and colleagues 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, CR was achieved in 92% of patients in the autologous HSCT arm and 89% in the standard chemotherapy arm (p=0.6). Five-year overall survival (OS) was 88% (95% confidence interval [CI]: 80–96%) in the autologous HSCT arm and 88% (95% CI: 79–96%) in the CT arm (p=0.99). Ten-year OS was 85% (95% CI: 78–90%) versus 84% (95% CI: 77–89%) 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 or Refractory HL
A systematic review and meta-analysis of available randomized controlled trials (RCTs) was published by Rancea et al in 2014. This study 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 HSCT treatment, with a hazard ratio of 0.55 (95% CI, 0.35 to 0.86).

The British National Lymphoma Investigation (BNLI) study was the first to show a PFS benefit with autologous HSCT 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 HSCT. 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.
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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
Few treatment options exist for patients who relapse following an autologous HCT; they include single-agent palliative chemotherapy or occasionally, localized radiotherapy. 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%-40%). Smith et al (2008) reported the outcomes of 40 patients (21 with HL, 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HCT for relapsed lymphoma. Reported results were combined for the 2 populations, but authors stated that 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. Treatment-related mortality at day 100 post-transplant was 11% (95% CI, 3% to 22%). At a median follow-up of 72 months (range, 12-124 months) after the second HCT, 73% of patients had died-62% due to relapsed lymphoma. One-, 3-, and 5-year PFS estimates were 50% (95% CI, 34% to 66%), 36% (95% CI, 21% to 52%), and 30% (95% CI, 16% to 46%), respectively. Corresponding OS estimates were 65% (95% CI, 50% to 79%), 36% (95% CI, 22% to 52%), and 30% (95% CI, 17% to 46%), respectively. Study limitations included the absence of an appropriate comparison group and lack of data on how many patients were considered for a second HCT but were unable to mobilize sufficient stem cells or were otherwise unable to proceed to the second transplant. Finally, heterogeneity of the preparative regimens used in this population precluded comparison of efficacy.

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 (allo-HCT) to the treatment of patients with HL appears 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>
</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>

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.

RIC 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. Reviewers cited a number of studies that showed better outcomes with RIC and with myeloablative conditioning regimens. For example, reviewers cited a 2008 study by the 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). 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
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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: RIC 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 and colleagues 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: 40–69%) and 49% (95% CI: 34–63%), respectively.

Morschhauser and colleagues 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 HSCT, 5-year OS rates were 86% and 37% for complete and partial responders, respectively. 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 HCT for HL
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 2.

Table 2. 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>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.

Clinical Input Received 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 HCT after a prior autologous HCT, which both thought would be medically necessary in
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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.

Summary of Evidence
Autologous HCT
For individuals who have Hodgkin lymphoma who receive autologous HCT as initial therapy, the evidence includes 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
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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 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.

References

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Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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Policy History
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Current Effective Date: 05/17/2017

12/06/2001 Medical Policy Committee review
03/25/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy.
05/07/2004 Medical Director review
05/18/2004 Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem Cell Support for Hodgkin’s Disease policy developed separately from current HDC with Hematopoietic Stem Cell Support policy.
06/28/2004 Managed Care Advisory Council approval
05/03/2005 Medical Director review
05/17/2005 Medical Policy Committee review. Coverage eligibility unchanged.
05/23/2005 Managed Care Advisory Council approval
05/03/2006 Medical Director review
05/17/2006 Medical Policy Committee approval. Format revision, including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
04/04/2007 Medical Director review
04/18/2007 Medical Policy Committee approval. No change in coverage eligibility.

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04/02/2008 Medical Director review
04/02/2008 Medical Policy Committee approval. No change to coverage eligibility.
04/04/2008 Medical Director review
04/15/2008 Medical Policy Committee approval. Title changed to match BCBSA. No change to coverage.
04/08/2010 Medical Policy Committee approval
04/21/2010 Medical Policy Implementation Committee approval. Added tandem autologous HSCT to be eligible for coverage with criteria. Added reduced-intensity allogeneic HSCT to treat Hodgkin Lymphoma to be eligible for coverage with criteria. Added that a second autologous stem-cell transplantation for relapsed lymphoma after a prior autologous HSCT to be investigational. Updated background/overview, rationale and references.
04/07/2011 Medical Policy Committee review
04/12/2012 Medical Policy Implementation Committee approval
04/25/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/02/2013 Medical Policy Committee review
05/22/2013 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/01/2014 Medical Policy Committee review
05/21/2014 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2015 Medical Policy Committee review
05/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017 Medical Policy Committee review
05/17/2017 Medical Policy Implementation Committee approval. “Stem” removed from title and policy. Removed statement on reduced intensity allogenic HCT, added coverage statement for allogenic HCT, using either myeloablative or reduced-intensity conditioning regimens in patients with primary refractory or relapsed Hodgkin lymphoma. Added a policy guidelines section.

Next Scheduled Review Date: 05/2018

Coding
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<tr>
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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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   2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
   3. Reference to federal regulations.

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A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and

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

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

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