Autologous or myeloablative allogeneic hematopoietic stem-cell transplantation (HSCT) may be considered medically necessary in patients with primary refractory or relapsed Hodgkin lymphoma (HL).

Tandem autologous HSCT may be considered medically necessary:

- in patients with primary refractory HL or
- in patients with relapsed disease with poor risk features who do not attain a complete remission to cytoreductive chemotherapy prior to transplantation (see Policy Guidelines section).

Reduced-intensity allogeneic HSCT may be considered medically necessary to treat HL in patients:

- who have failed a prior autologous HSCT used to treat primary refractory or relapsed disease or
- in patients who would otherwise qualify for a myeloablative allogeneic transplant, but would be unable to tolerate a standard myeloablative conditioning regimen (see Policy Guidelines section) or
- when insufficient stem cells are collected for an autologous HSCT.

Second autologous HSCT for relapsed lymphoma after a prior autologous HSCT is considered investigational. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.

Other uses of HSCT in patients with HL are considered investigational, including, but not limited to, initial therapy for newly diagnosed disease to consolidate a first complete remission. There is insufficient evidence to support a conclusion concerning the health outcomes or benefits associated with this procedure.
Policy Guidelines

In the Morschhauser et al (2008) study of risk-adapted salvage treatment with single or tandem autologous hematopoietic stem-cell transplantation (HSCT) for first relapse or refractory Hodgkin lymphoma (HL), (1) 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 HSCT. These include those with malignancies that are effectively treated with myeloablative allogeneic transplantation, but whose age (typically older than 55 years) or comorbidities (e.g., 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.

Cross-references:

- **MP-9.038** Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
- **MP-9.039** Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia
- **MP-9.040** Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
- **MP-9.041** Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia
- **MP-9.042** Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphoma
- **MP-9.044** Hematopoietic Stem-Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- **MP-9.045** Hematopoietic Stem-Cell Transplantation for Primary Amyloidosis
- **MP-9.046** Hematopoietic Stem-Cell Transplantation for Waldenstrom Macroglobulinemia
- **MP-9.047** Hematopoietic Stem-Cell Transplantation for Epithelial Ovarian Cancer
- **MP-9.048** Hematopoietic Stem-Cell Transplantation Miscellaneous Solid Tumors in Adults
II. PRODUCT VARIATIONS

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) 110.23, Stem Cell Transplantation.

**The Federal Employee Program (FEP) may include specific conditions in which autologous and nonmyeloablative (reduced-intensity conditioning or RIC) allogeneic blood or marrow stem cell transplants may be considered eligible for coverage. Refer to the Service Plan Benefit Brochure for covered indications.

III. DESCRIPTION/BACKGROUND

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) 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 HSCT) or from a donor (allogeneic HSCT [allo-HSCT]). 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). Cord blood is discussed in greater

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an
issue in autologous HSCT. However, immunologic compatibility between donor and patient is a
critical factor for achieving a good outcome with allo-HSCT. 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).

**Conventional Preparative Conditioning for HSCT**
The conventional (“classical”) practice of allo-HSCT 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-HSCT, immunosuppressant drugs are required to minimize graft
rejection and GVHD, which also increase susceptibility of the patient to opportunistic infections.

The success of autologous HSCT 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 HSCT is typically performed as consolidation therapy when the
patient’s disease is in complete remission. Patients who undergo autologous HSCT are
susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment,
but not GVHD.

**Reduced-Intensity Conditioning for Allo-HSCT**
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-HSCT 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 evidence review, the term RIC 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%. Classic Hodgkin lymphoma 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.”

The following staging system for Hodgkin lymphoma recognizes that the disease is thought to typically 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.

**Staging for Hodgkin Lymphoma**

Staging for Hodgkin lymphoma is based on the Ann Arbor staging system. 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.
**Stage I**
Involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).

**Stage II**
Involvement of 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 (e.g., II₂).

**Stage 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: periaortic or pelvic node involvement

**Stage 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 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 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 HSCT 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 HSCT, 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.

**Regulatory Status**

The U.S. Food and Drug Administration 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.

IV. **RATIONALE**

**Autologous Hematopoietic Stem Cell Transplantation for Hodgkin Lymphoma**

**First-Line Therapy**

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

Carella et al reported the long-term results of 163 patients with unfavorable HL who had received either an autologous HSCT or additional standard chemotherapy for consolidation after initial conventional chemotherapy. Patients were randomly assigned to receive HDC followed by an autologous HSCT (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 HSCT 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 HSCT 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 HSCT 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 HSCT.

**Relapsed/Refractory HL**

Autologous HSCT is widely considered the therapy of choice for relapsed and refractory HL. Two randomized controlled trials (RCTs) showed benefit in using autologous HSCT in these patients.

A systematic review and meta-analysis of available RCTs was published by Rancea et al in 2014. This study included 3 RCTs, 2 of which compared HDC followed by autologous HSCT
to conventional treatment\textsuperscript{11,12} 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 HSCT, 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 benefit in PFS with autologous HSCT over conventional chemotherapy in relapsed or refractory HL patients.\textsuperscript{13} Forty patients with relapsed or refractory HL were given chemotherapy without transplant (n=20) or autologous transplant after HDC (n=20).\textsuperscript{11} A significantly better event-free survival (EFS) at 3 years of 53\% was reported in the patients who underwent transplant versus 10\% in the group that did not.

Subsequently, these findings were confirmed in a larger trial by the German Hodgkin Study Group and European Group for Blood and Marrow Transplantation (EBMT).\textsuperscript{12} 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.\textsuperscript{14}

Several large retrospective studies identified in 1 review have reported EFS rates ranging from 25\% to 60\%, with OS rates from 35\% to 66\%, showing that disease status before autologous HSCT was the most important prognostic factor for the final outcome.\textsuperscript{5}

Limited treatment options exist for patients who relapse following an autologous HSCT and include single-agent palliative chemotherapy or occasionally, localized radiotherapy.\textsuperscript{14} When a further remission may be attained with conventional-dose chemotherapy, it is rarely durable, with a median OS of less than 1 year.\textsuperscript{15} There is limited experience with second autologous HSCT, and treatment-related mortality is high (25\%-40\%).\textsuperscript{11} Smith et al reported the outcomes of 40 patients (21 with HL, 19 with non-Hodgkin lymphoma [NHL]) who underwent a second autologous HSCT for relapsed lymphoma.\textsuperscript{16} Results reported were combined for the 2 populations, but the authors state that the outcomes of patients with HL and NHL were similar. Median age at second HSCT was 38 years (range, 16-61 years). In 82\% of patients, the second HSCT was performed more than 1 year after the first. Treatment-related mortality at day 100 posttransplant was 11\% (95\% CI, 3\% to 22\%). At a median follow-up of 72 months (range, 12-124 months) after the second HSCT, 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 HSCT 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.

**Section Summary: Autologous HSCT for HL**

There are a small number of RCTs that use autologous HSCT as first-line treatment, and these trials report no benefit above that of conventional chemotherapy. For relapsed or refractory disease, 2 RCTs 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 HSCT. For relapse after first HSCT, there is limited evidence consisting of small case series, which do not permit conclusions on efficacy.

**Allogeneic HSCT for HL**

The application of allogeneic HSCT (allo-HSCT) to the treatment of patients with HL initially appeared limited, due to a high procedure-related mortality.

To date, most of the RIC allo-HSCTs have been performed in patients who have failed a previous autologous HSCT for primary relapsed/refractory HL, and most of the studies are characterized by small numbers of patients, disparate preparative and graft-versus-host disease (GVHD) prophylaxis regimens, and varying lengths of follow-up. Nonetheless, they have demonstrated reduced nonrelapse mortality (NRM), and some suggest a graft-versus-HL effect with favorable disease control in these poor-prognosis patients.

Sarina et al reported a retrospective study of 185 patients with HL who had failed an autologous HSCT. One hundred twenty-two had donors available for a salvage reduced-intensity conditioning (RIC) allo-HSCT; of these, 104 (85%) were transplanted. Sixty-three patients did not have a suitable donor and were treated with salvage chemotherapy or radiotherapy. Clinical characteristics between the 2 groups did not differ. After a median follow-up of 48 months, PFS and OS were better in the donor group that underwent the salvage allo-HSCT (39.3% vs 14.2% and 66% vs 42%, respectively; p<0.001), showing a survival benefit of an RIC allo-HSCT versus conventional treatment after a failed autologous HSCT for HL.

Peggs et al investigated outcomes with RIC allo-HSCT, and T-cell depletion in multiply relapsed patients. Forty-nine patients were enrolled, 90% of whom had failed a previous autologous transplant. Primary study end points were engraftment, toxicity, NRM, and GVHD incidence. All patients achieved engraftment. Thirty-one patients had a human leukocyte antigen (HLA)–matched donor and 18 had an unrelated donor. The cumulative incidence of NRM was 4.1% at 100 days posttransplant and 16.3% at 730 days posttransplant. Patients with unrelated donors had a significantly higher NRM (34% vs 7%) at 730 days. Projected 4-year OS and PFS were 56% and 39%, respectively.

Alvarez et al reported the results of a Spanish prospective cooperative protocol using RIC allo-HSCT in 40 patients with relapsed or refractory HL. Seventy-three percent of patients had failed a previous autologous HSCT. Thirty-eight patients received hematopoietic cells from an HLA-identical sibling. One-year treatment-related mortality was 25%. OS and PFS were 48% and 32%, respectively, at 2 years. For patients who had failed a previous autologous HSCT, 2-
year OS and PFS were 75% and 70%, respectively, in the subset that relapsed more than 12 months after autologous HSCT.

Todisco et al evaluated the efficacy of RIC allo-HSCT in 14 patients with refractory or progressive HL after HDC and autologous HSCT. All patients had received at least 1 prior course of HDC, and 50% had undergone 2 previous courses. The median time from the first and second courses of HDC and the RIC allo-HSCT was 15 and 8 months, respectively (range, 2-34 and 2-31 months, respectively). With a median follow-up of 21 months post-RIC allo-HSCT (range, 3-74 months), 10 of the 14 patients were alive. Estimated OS at 1 and 2 years was 93% and 73%, respectively, for the entire population; 83% and 44%, respectively, for patients with chemotherapy-resistant disease; and 100% at both 1 and 2 years for those with chemotherapy-sensitive disease.

A review of the role of allo-HSCT in HL by Laport summarizes the results of the most recent and largest studies of the use of RIC allo-HSCT for HL as follows: most patients have failed a prior autologous HSCT and are therefore heavily pretreated going into the RIC allo-HSCT; chemotherapy sensitivity is a reliable predictor of outcome; a matched versus an unmatched related donor did not affect survival in most reports; and approximately one-third to one-half of these patients may be cured with RIC allo-HSCT.

EBMT published results of the outcomes of 89 HL patients with relapsed or refractory disease who received an RIC allo-HSCT 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 HSCT versus 41% of the patients in 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 was 22% (95% CI, 13% to 31%) for the conventional group and 28% (95% CI, 18% to 38%) for the RIC group. Independent adverse prognostic factors for OS were a previously failed autologous HSCT (risk ratio [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).

Anderlini et al published the results of 58 patients from 1 institution with relapsed/refractory HL who received uniform conditioning regimens for RIC allogeneic HSCT. Fifty-seven percent of patients received their allograft from an unrelated donor. Eighty-three percent of patients had failed a prior autologous HSCT. Projected 2-year OS and PFS rates were 64% (range, 49%-76%) and 32% (range, 20%-45%), with 2-year disease progression/relapse at 55% (range, 43%-70%). There were no statistically significant differences in OS, PFS, or disease progression/relapse between matched related and unrelated donor transplants.

Sureda et al reported the results of a phase 2 study of 92 patients with relapsed HL and an HLA–identical sibling, a matched unrelated donor, or a 1-antigen mismatched, unrelated donor, who were treated with salvage chemotherapy followed by RIC allo-HSCT. Fourteen patients had refractory disease and died from progressive lymphoma with a median OS after trial entry of 10
months (range, 6-17 months). Seventy-eight patients proceeded to allograft (unrelated donors, n=23). Fifty were allografted in complete or partial remission and 28 in stable disease. NRM rate was 8% at 100 days and 15% at 1 year. Relapse was the major cause of failure. The PFS rate was 47% at 1 year and 15% at 4 years from trial entry. For the allografted population, the PFS rate was 48% at 1 year and 24% at 4 years. Chronic GVHD was associated with a lower incidence of relapse. Patients allografted in CR had a significantly better outcome. The OS rate was 71% at 1 year and 43% at 4 years.

Section Summary: Allo-HSCT for HL
There are no RCTs that compare allo-HSCT to alternatives (conventional chemotherapy, autologous HSCT). Case series have been published, most of which are in patients who have already failed autologous HSCT. Some series report response rates that are higher than expected with standard care, but definitive conclusions on treatment efficacy cannot be made due to the low quality of the published literature.

Tandem (Autologous-Autologous) HSCT
Fung et al reported results from a pilot study to evaluate the toxicities and efficacy of tandem autologous HSCT in patients with primary refractory or poor-risk recurrent HL. The study involved 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 1 of the following poor prognostic factors: first CR less than 12 months, extranodal disease, or B symptoms at relapse. Forty-one (89%) patients received the second transplant. With a median follow-up of 5.3 years (range, 1.6-8.1 years), the 5-year OS and PFS were 54% (95% CI, 40% to 69%) and 49% (95% CI, 34% to 63%), respectively.

Morschhauser et al reported on the results of a prospective multicenter trial that evaluated a risk-adapted salvage treatment with single or tandem autologous HSCT 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 (n=95) patients, defined as 1 risk factor at relapse, were eligible for a single transplant. Overall, 70% of the poor-risk patients received tandem transplants, and 97% of the intermediate-risk patients received a single transplant.

Overall, 94 poor-risk patients responded to cytoreductive chemotherapy (partial response [PR] or complete response [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 HSCT. 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 HSCT 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 intention-to-treat sample revealed that the 5-year freedom from second failure and OS estimates were 73% and 85%, respectively, for the intermediate-risk group and 46% and 57%, respectively, for the poor-risk group.

In the poor-risk group, patients who underwent tandem transplant and had a CR to cytoreduction chemotherapy did not have superior outcomes compared with complete responders receiving a single transplant in previous studies. However, in this study, poor-risk patients who were partial responders who underwent tandem transplants did better when compared with partial responders who received a single transplant in previous studies. In this study, 5-year OS rates for poor-risk patients who completed the tandem transplant were 79% and 73% for complete and partial responders, whereas in a previous trial of single autologous HSCT, 5-year OS rates were 86% and 37% for complete and partial responders, all respectively. The authors concluded that a single autologous HSCT is appropriate for intermediate-risk patients and for poor-risk patients who are complete responders to cytoreductive chemotherapy but that tandem autologous HSCT 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 HSCT 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) HSCT
There are no RCTs comparing tandem autologous HSCT to alternatives. One prospective, nonrandomized study reported that patients who had not achieved a CR to conventional chemotherapy had better outcomes with tandem HSCT compared with single HSCT. 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 1.

Table 1. Summary of Key Trials

<table>
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<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<td>810</td>
<td>May 2015</td>
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<td>NCT00920153</td>
<td>Study Characterizing the Impact of Different Therapeutic Strategies on Event Occurrence at 2 Years, 5 Years, 10 Years, and 15 Years, According to Prognostic Groups in Patients With Hodgkin Lymphoma</td>
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<td>May 2015</td>
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<td>NCT00025636</td>
<td>A Randomized Trial Of BEAM Plus PBSCT Versus Single Agent High-Dose Therapy Followed By BEAM Plus PBSCT In Patients With Relapsed Hodgkin’s Disease</td>
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<td>Unknown</td>
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</table>

NCT: national clinical trial.
Summary of Evidence

The evidence for autologous hematopoietic stem cell transplantation (HSCT) in individuals who have Hodgkin lymphoma includes randomized controlled trials (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. RCTs of autologous HSCT as first-line treatment have reported that autologous HSCT does not have additional benefit compared to conventional chemotherapy. 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. For patients with relapsed disease after first autologous HSCT, the evidence consists of small case series and no conclusions on efficacy can be drawn. This evidence permits the conclusion that treatment of relapsed or refractory Hodgkin lymphoma with autologous HSCT improves outcomes.

The evidence for allogeneic HSCT in individuals who have Hodgkin lymphoma consists of case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The case series report response rates for patients with refractory disease that are higher than expected with standard care. However, no definitive conclusions on the efficacy of allogeneic HSCT can be made due to the poor quality of the evidence base, and the impact on health outcomes is uncertain.

The evidence for tandem autologous HSCT in individuals who have Hodgkin lymphoma 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 HSCT may be higher than that for single autologous HSCT. This study is not definitive due to the possibility of selection bias, and RCTs are needed to determine the impact of tandem autologous HSCT on outcomes.

Clinical Input Received From Physician Specialty Societies and Academic Medical Centers

2009 Input

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. The 2 reviewers agreed with the policy statements, with the exception of the use of a second autologous HSCT after a prior autologous HSCT, which both reviewers thought would be medically necessary in certain circumstances. The data to support the use of a second autologous HSCT are extremely limited, and the policy statement for this use of HSCT remains investigational.
Practice Guidelines and Position Statements

**National Comprehensive Cancer Network Guidelines**
The National Comprehensive Cancer Network guidelines for Hodgkin lymphoma (v.2.2015) include a recommendation for autologous HSCT in patients with progressive and relapsed Hodgkin lymphoma. The guidelines state that allogeneic transplant is an option in select patients with progressive or relapsed disease as a category 3 recommendation and that allogeneic HSCT with RIC remains investigational. The guidelines do not specifically address tandem transplants.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
Autologous HSCT 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.

V. **DEFINITIONS**

NA

VI. **BENEFIT VARIATIONS**

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

VII. **DISCLAIMER**

Capital’s medical policies are developed to assist in administering a member’s benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this
medical policy and a member’s benefit information, the benefit information will govern. Capital considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

<table>
<thead>
<tr>
<th>CPT Codes®</th>
<th>38204</th>
<th>38205</th>
<th>38206</th>
<th>38208</th>
<th>38209</th>
<th>38210</th>
<th>38211</th>
<th>38212</th>
<th>38213</th>
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<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition</td>
</tr>
</tbody>
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*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Codes*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C81.01</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
</tr>
<tr>
<td>C81.02</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intrathoracic lymph nodes</td>
</tr>
<tr>
<td>C81.03</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>C81.04</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of axilla and upper limb</td>
</tr>
<tr>
<td>C81.05</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>C81.06</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, intrapelvic lymph nodes</td>
</tr>
<tr>
<td>C81.07</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, spleen</td>
</tr>
<tr>
<td>C81.08</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, lymph nodes of multiple sites</td>
</tr>
<tr>
<td>C81.09</td>
<td>Nodular lymphocyte predominant Hodgkin lymphoma, extranodal and solid organ sites</td>
</tr>
<tr>
<td>C81.11</td>
<td>Nodular sclerosis Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
</tr>
<tr>
<td>ICD-10-CM Diagnosis Codes*</td>
<td>Description</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------------------------------------------</td>
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<tr>
<td>C81.12</td>
<td>Nodular sclerosis Hodgkin lymphoma, intrathoracic lymph nodes</td>
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<tr>
<td>C81.13</td>
<td>Nodular sclerosis Hodgkin lymphoma, intra-abdominal lymph nodes</td>
</tr>
<tr>
<td>C81.14</td>
<td>Nodular sclerosis Hodgkin lymphoma, lymph nodes of axilla and upper limb</td>
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<tr>
<td>C81.15</td>
<td>Nodular sclerosis Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
</tr>
<tr>
<td>C81.16</td>
<td>Nodular sclerosis Hodgkin lymphoma, intrapelvic lymph nodes</td>
</tr>
<tr>
<td>C81.17</td>
<td>Nodular sclerosis Hodgkin lymphoma, spleen</td>
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<tr>
<td>C81.18</td>
<td>Nodular sclerosis Hodgkin lymphoma, lymph nodes of multiple sites</td>
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<tr>
<td>C81.19</td>
<td>Nodular sclerosis Hodgkin lymphoma, extranodal and solid organ sites</td>
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<tr>
<td>C81.21</td>
<td>Mixed cellularity Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
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<tr>
<td>C81.22</td>
<td>Mixed cellularity Hodgkin lymphoma, intrathoracic lymph nodes</td>
</tr>
<tr>
<td>C81.23</td>
<td>Mixed cellularity Hodgkin lymphoma, intra-abdominal lymph nodes</td>
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<td>C81.24</td>
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<td>C81.25</td>
<td>Mixed cellularity Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
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<td>C81.26</td>
<td>Mixed cellularity Hodgkin lymphoma, intrapelvic lymph nodes</td>
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<td>C81.27</td>
<td>Mixed cellularity Hodgkin lymphoma, spleen</td>
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<td>C81.29</td>
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<td>C81.31</td>
<td>Lymphocyte depleted Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
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<td>C81.32</td>
<td>Lymphocyte depleted Hodgkin lymphoma, intrathoracic lymph nodes</td>
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<td>Lymphocyte depleted Hodgkin lymphoma, intra-abdominal lymph nodes</td>
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<td>Lymphocyte depleted Hodgkin lymphoma, lymph nodes of axilla and upper limb</td>
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<td>Lymphocyte depleted Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
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<td>C81.36</td>
<td>Lymphocyte depleted Hodgkin lymphoma, intrapelvic lymph nodes</td>
</tr>
<tr>
<td>C81.37</td>
<td>Lymphocyte depleted Hodgkin lymphoma, spleen</td>
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<tr>
<td>C81.38</td>
<td>Lymphocyte depleted Hodgkin lymphoma, lymph nodes of multiple sites</td>
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<tr>
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<td>Lymphocyte depleted Hodgkin lymphoma, extranodal and solid organ sites</td>
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<tr>
<td>C81.41</td>
<td>Lymphocyte-rich Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
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<tr>
<td>C81.42</td>
<td>Lymphocyte-rich Hodgkin lymphoma, intrathoracic lymph nodes</td>
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<td>C81.43</td>
<td>Lymphocyte-rich Hodgkin lymphoma, intra-abdominal lymph nodes</td>
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<td>C81.44</td>
<td>Lymphocyte-rich Hodgkin lymphoma, lymph nodes of axilla and upper limb</td>
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<td>Lymphocyte-rich Hodgkin lymphoma, lymph nodes of inguinal region and lower limb</td>
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<td>C81.46</td>
<td>Lymphocyte-rich Hodgkin lymphoma, intrapelvic lymph nodes</td>
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<td>C81.47</td>
<td>Lymphocyte-rich Hodgkin lymphoma, spleen</td>
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<tr>
<td>C81.48</td>
<td>Lymphocyte-rich Hodgkin lymphoma, lymph nodes of multiple sites</td>
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<tr>
<td>C81.49</td>
<td>Lymphocyte-rich Hodgkin lymphoma, extranodal and solid organ sites</td>
</tr>
<tr>
<td>C81.71</td>
<td>Other Hodgkin lymphoma, lymph nodes of head, face, and neck</td>
</tr>
</tbody>
</table>
IX. REFERENCES


Other Sources

X. POLICY HISTORY

<p>| MP 9.043 | CAC 5/20/14 Minor. Information on HSCT for Hodgkin Lymphoma extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Policy guidelines and rationale section added. |
| CAC 6/2/15 Consensus. No change to policy statements. References and rationale reviewed. Codes reviewed. |
| CAC 5/31/16 Consensus. No change to policy statements. References and rationale updated. Coding reviewed. |
| Admin update 1/1/17: Product variation section reformatted. Revised diagnosis code definitions updated effective 10/1/16 |</p>
<table>
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<tr>
<th><strong>Policy Title</strong></th>
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<tbody>
<tr>
<td><strong>Policy Number</strong></td>
<td>MP-9.043</td>
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