Medical Policy
Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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Policy Number: 207
BCBSA Reference Number: 8.01.29

Related Policies
- Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphomas, #143
- Placental/Umbilical Cord Blood as a Source of Stem Cells, #285

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

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

Allogeneic HCT, using either myeloablative or reduced-intensity conditioning regimens, may be considered **MEDICALLY NECESSARY** in patients with primary refractory or relapsed Hodgkin lymphoma.

Tandem autologous HCT is considered **INVESTIGATIONAL** in patients with Hodgkin lymphoma.

Second autologous HCT for relapsed lymphoma after a prior autologous HCT is considered **INVESTIGATIONAL**.

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

Prior Authorization Information

Inpatient
- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient
- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.
Outpatient

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>Prior authorization is required.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>Prior authorization is required.</td>
</tr>
</tbody>
</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

**CPT Codes**

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
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**HCPCS Codes**

<table>
<thead>
<tr>
<th>HCPCS codes</th>
<th>Code Description</th>
</tr>
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<tbody>
<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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</table>

**ICD-10 Procedure Codes**

<table>
<thead>
<tr>
<th>ICD-10-PCS procedure codes</th>
<th>Code Description</th>
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</thead>
<tbody>
<tr>
<td>30233G0</td>
<td>Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243X0</td>
<td>Transfusion of Autologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>3E03305</td>
<td>Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>3E04305</td>
<td>Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>3E05305</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach</td>
</tr>
<tr>
<td>3E06305</td>
<td>Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach</td>
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Description
Hodgkin Lymphoma
Hodgkin lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2020, the estimated number of new cases in the United States was approximately 8,480 and 970 estimated deaths. The disease has a bimodal distribution, with most patients diagnosed between the ages of 20 and 39 years, with a second peak in adults aged 65 years and older.

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

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

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

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

Each stage is subdivided into A and B categories. "A" indicates no systemic symptoms are present and "B" indicates the presence of systemic symptoms, which include unexplained weight loss of more than 10% of body weight, unexplained fevers >38°C, or drenching night sweats (see Table 1).

Table 1. Ann Arbor Staging System for Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Area of Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Single lymph node region (I) or localized involvement of a single extralymphatic organ or site (I&lt;sub&gt;E&lt;/sub&gt;)</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&lt;sub&gt;E&lt;/sub&gt;). The number of lymph node regions involved should be indicated by a subscript (eg, II&lt;sub&gt;2&lt;/sub&gt;).</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions or structures on both sides of the diaphragm, which may involve an extralymphatic organ or site (III&lt;sub&gt;E&lt;/sub&gt;), spleen (III&lt;sub&gt;S&lt;/sub&gt;), or both (III&lt;sub&gt;E+S&lt;/sub&gt;)</td>
</tr>
<tr>
<td>IV</td>
<td>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</td>
</tr>
</tbody>
</table>

Patients with HL are generally classified into 3 groups: early-stage favorable (stage I-II with no B symptoms, large mediastinal lymphadenopathy, or other unfavorable factors), early-stage unfavorable (stage I-II with a large mediastinal mass, multiple involved nodal regions, B symptoms, extranodal involvement, or elevated erythrocyte sedimentation rate ≥50), and advanced-stage disease (stage III-IV).
Treatment

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

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

In patients with relapse, the results of salvage therapy vary depending on a number of prognostic factors, as follows: the length of the initial remission, stage at recurrence, and the severity of anemia at the time of relapse. Early and late relapse are defined as less or more than 12 months from the time of remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous hematopoietic cell transplantation (HCT) but not more than 40% with early first relapse.

Only 25% to 35% of patients with primary progressive or poor-risk recurrent HL achieve durable remission after autologous HCT, with most failures being due to disease progression after transplant. Most relapses after transplant occur within 1 to 2 years, and once relapse occurs posttransplant, median survival is less than 12 months.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in policy #285.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for Hematopoietic Cell Transplantation

Conventional Conditioning

The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.
The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

**Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation**
Reduced-Intensity Conditioning (RIC) refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial GVM effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

**Targeted Chemotherapy and Autologous Hematopoietic Cell Transplantation for the Treatment of Hodgkin Lymphoma**
A recent important development in the Hodgkin lymphoma treatment landscape is the emergence of several novel agents that are now being used as alternatives to stem cell transplantation in patients at high-risk for relapse after chemotherapy or relapse following autologous HCT. These agents include brentuximab vedotin, a CD30-directed antibody-drug conjugate, and nivolumab and pembrolizumab which are 2 programmed death receptor-1 (PD-1) blocking antibodies. The U.S. Food and Drug Administration (FDA) regulatory status of these agents for the treatment of HL is summarized in Table 2.

Brentuximab vedotin was evaluated in a large, phase 3, multinational, double-blind randomized controlled trial known as the AETHERA trial (abbreviation definition unknown). Moskowitz et al (2015)\(^\text{10}\) reported on the outcomes for 329 individuals with HL with risk factors for post-transplantation relapse or progression (eg, primary refractory HL, relapse <12 months after initial therapy, and/or relapse with extranodal disease). Results showed that early consolidation with brentuximab vedotin after autologous HCT significantly improved 2-year progression-free survival (PFS) versus placebo (63% versus 51%, hazard ratio [HR] 0.57; 95% confidence interval [CI], 0.40 to 0.81). At 5-year follow-up, the significant PFS benefit for brentuximab vedotin persisted (59% versus 41%; HR 0.52; 95% CI, 0.38 to 0.72).\(^\text{11}\) In addition, a study by Smith et al (2018)\(^\text{12}\) of tandem autologous HCT observed that the 2-year PFS of 63% for brentuximab vedotin demonstrated in the AETHERA RCT “matches” the 2-year PFS rates for tandem autologous HCT.

A survival benefit with novel agents has been found in the setting of relapse post-autologous HCT. Bair et al (2017) reported a retrospective comparative analysis that evaluated the outcomes of 87 individuals with relapsed/refractory HL who had relapsed post-autologous HCT.\(^\text{13}\) Compared to individuals who did not receive any novel agents, those that received novel agents, including brentuximab vedotin or nivolumab, experienced a significant improvement in median overall survival (85.6 versus 17.1 months; \(P<.001\)). The availability of safe and effective targeted systemic therapy represents an alternative to the use of a second autologous transplant or planned tandem autologous HCT for HL consolidation treatment or relapse/refractory disease treatment.

**Summary**
Hodgkin lymphoma (HL) results from a clonal expansion of a B-cell lineage, characterized by the presence of Reed-Sternberg cells on pathology. Standard treatment is based on the stage at presentation...
and may involve chemotherapy with or without radiotherapy. Hematopoietic cell transplantation (HCT) has been used for HL, particularly in the setting of relapse or refractory disease.

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

For individuals who have relapsed or refractory Hodgkin lymphoma who receive autologous HCT, the evidence includes RCTs, a meta-analysis, nonrandomized comparative studies, and case series. Relevant outcomes are OS, DSS, change in disease status, morbid events, and 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 OS. The evidence is sufficient to determine that the technology results in an 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 OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs or nonrandomized comparative studies were identified. In a 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 that the technology results in an improvement in the net health outcome.

**Allogeneic Hematopoietic Cell Transplantation**
For individuals who have Hodgkin lymphoma (HL) who receive allogeneic stem cell transplant (allo-HCT) as first-line therapy, the evidence includes no published studies. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No studies specifically addressing allo-HCT as first-line treatment for HL were identified. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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 OS, DSS, 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 HL. The pooled analysis found a 6-month OS rate of 83% and a 3-year OS of 50%. The evidence is sufficient to determine that the technology results in an 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 OS, DSS, 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 followed by allo-HCT was significantly associated with higher 1- and 2-year OS rates and significantly higher recurrence-free survival rates at 1 year compared with no previous autologous HCT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

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

Additional Information

2020 Input
Clinical input was sought to help determine whether the use of either second autologous HCT for relapsed HL or tandem autologous HCT for HL would provide a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 4 respondents, including 3 complete responses including 2 physician-level responses identified through specialty societies and 1 physician-level response identified through an academic medical center.

For individuals with relapsed HL after an autologous HCT who receive second autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

For individuals with HL who receive tandem autologous HCT, clinical input does not support a clinically meaningful improvement in net health outcome and does not indicate this use is consistent with generally accepted medical practice.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>1/2021</td>
<td>Medicare information removed. See MP #132 Medicare Advantage Management for local coverage determination and national coverage determination reference.</td>
</tr>
<tr>
<td>4/2020</td>
<td>Bone marrow harvesting codes were removed. Outpatient prior authorization is not required.</td>
</tr>
<tr>
<td>1/2019</td>
<td>Outpatient prior authorization is required for all commercial products including Medicare Advantage. Effective 1/1/2019.</td>
</tr>
<tr>
<td>3/2018</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>2/2018</td>
<td>Coding information clarified.</td>
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<tr>
<td>9/2015</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>6/2014</td>
<td>Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.</td>
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<tr>
<td>12/2012</td>
<td>Updated to add new CPT code 38243.</td>
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<td>Date</td>
<td>Details</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


