

## Corporate Medical Policy

### Hematopoietic Cell Transplantation for Hodgkin Lymphoma

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#### Description of Procedure or Service

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##### **Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation (HCT) 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 radiation therapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic 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 of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers 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).

##### **Conditioning for HCT**

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 prior to 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 prior to engraftment, but not GVHD.

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., 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

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fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

## **Reduced-Intensity Conditioning for Allogeneic HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in 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. 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 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 reduced-intensity conditioning will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (traditional) regimens.

## **Hodgkin Lymphoma**

Hodgkin Lymphoma (HL) is a relatively uncommon B-cell lymphoma. In 2011, an estimated 8,830 new diagnoses and 1,300 deaths will occur in the U.S. 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 and older.

The World Health Organization (WHO) classification divides HL into two main types:

1. "Classical" HL (CHL)
  - Nodular sclerosis
  - Mixed cellularity
  - Lymphocyte depleted
  - 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. NLPHL lacks Reed-Sternberg cells, but is characterized by the presence of lymphocytic and histiocytic cells termed "popcorn cells".

The following staging system for HL recognizes the fact 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 HL who can be treated with extended field radiation from those who require systemic chemotherapy.

## **Staging for Hodgkin Lymphoma**

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Staging for HL 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 including 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 two 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., II<sub>2</sub>).

## **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 one 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 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 radiation therapy 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 radiation therapy.

HL is highly responsive to conventional chemotherapy, and up to 80% of newly diagnosed patients can be cured with combination chemotherapy and/or radiation therapy. 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

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12 months from the time of remission, respectively. Approximately 70% of patients with late first relapse can be salvaged by autologous HCT, but not more than 40% with early first relapse.

Only approximately 25%-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 less than 12 months.

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**BCBSNC will provide coverage for hematopoietic cell transplantation for Hodgkin lymphoma when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

**If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**Some health benefit plans may exclude benefits for transplantation.**

## When Hematopoietic Cell Transplantation for Hodgkin Lymphoma is covered

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

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 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).

## When Hematopoietic Cell Transplantation for Hodgkin Lymphoma is not covered

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A second autologous cell transplantation (HCT) for relapsed lymphoma after a prior autologous HCT is considered **investigational**.

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

## Policy Guidelines

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Refer to the individual member's benefit plan for prior review requirements

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## **Autologous HCT**

For individuals who have Hodgkin lymphoma who receive autologous HCT as initial therapy, the evidence includes randomized controlled trials (RCTs). Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid status, morbid events, treatment-related mortality, and treatment related morbidity. RCTs of autologous HCT as first-line treatment have reported that autologous HCT does not have 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/refractory Hodgkin lymphoma who receive autologous HCT, the evidence includes randomized controlled trials (RCTs), non randomized 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.

## **Allogeneic HCT**

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

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

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

For individuals who have relapsed or refractory Hodgkin lymphoma who receive reduced-intensity conditioning (RIC) with allo-HCT, the evidence includes case series, cohort studies, and a systematic review. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. A 2015 systematic review cited a

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number of studies, including some with comparison groups, showing acceptable outcomes after RIC allo-HCT in patients with relapsed or refractory Hodgkin lymphoma. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## **Tandem Autologous HCT**

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

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

## **Billing/Coding/Physician Documentation Information**

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcsnc.com](http://www.bcsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, 38243, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## **Scientific Background and Reference Sources**

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### **Bone Marrow Transplant for Hodgkin's Disease**

BCBSA Medical Policy Reference Manual, 12/1/1999; 8.01.29

TEC Assessment, August, 2000; Volume 15, No. 9

BCBSA Medical Policy Reference Manual, 8/18/2000; 8.01.29

The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, Centennial Edition, Section 11, Hematology and Oncology, Chapter 139, Lymphomas. [www.merck.com](http://www.merck.com)

Specialty Matched Consultant Advisory Panel - 11/2002

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 4/29/2003

Specialty Matched Consultant Advisory Panel - 11/2004

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 3/7/06

# Hematopoietic Cell Transplantation for Hodgkin Lymphoma

Specialty Matched Consultant Advisory Panel - 11/2006

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 6/12/08

Specialty Matched Consultant Advisory Panel - 11/2008

## **Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma**

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 11/12/2009

Medical Director – 8/2010

Specialty Matched Consultant Advisory Panel – 11/2010

Specialty Matched Consultant Advisory Panel – 11/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 11/10/2011

Specialty Matched Consultant Advisory Panel – 12/2012

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 11/8/2012

Specialty Matched Consultant Advisory Panel – 11/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 12/12/2013

Specialty Matched Consultant Advisory Panel – 11/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 12/11/2014

Specialty Matched Consultant Advisory Panel – 11/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 1/14/2016

Specialty Matched Consultant Advisory Panel – 11/2016

## **Hematopoietic Cell Transplantation for Hodgkin Lymphoma**

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 1/12/2017

Medical Director review 1/2017

Specialty Matched Consultant Advisory Panel – 11/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.29, 2/8/2018

Specialty Matched Consultant Advisory Panel – 11/2018

## **Policy Implementation/Update Information**

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### **Bone Marrow Transplant for Hodgkin's Disease**

1/01 Specialty Matched Consultant Advisory Group.

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- 2/01 Original policy issued.
- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.
- 1/04 Benefits Application and Billing/Coding sections updated for consistency.
- 2/04 Individual CPT codes listed for CPT code ranges 38240-38242 under Billing/Coding section.
- 7/29/04 HCPCS code S2150 added to Billing/Coding section.
- 12/23/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. Revised Description of procedure or Service section. Reworded 2nd bullet under When Bone Marrow Transplant for Hodgkin's Disease is covered to "Relapsed Hodgkin's disease" from "Hodgkin's disease relapsing less than one year after completion of an initial course of chemotherapy". Removed the statement, "or its use in patients with disease recurrence after a prolonged (greater than 1 year) initial remission" from the 2nd bullet under When Bone Marrow Transplant for Hodgkin's Disease is not covered. Added policy number to Policy Key Words section. "Hematopoietic" and "Opportunistic" added to Definitions. References added.
- 12/11/06 Specialty Matched Consultant Advisory Panel review 11/6/2006. No changes to policy statement. Added the following statement to the "Policy" section; "If the medical criteria and guidelines are not met, some patients may be eligible for coverage under Clinical Trials. Refer to the policy, Clinical Trial Services for Life-Threatening Conditions." References added.
- 12/22/08 Specialty Matched Consultant Advisory Panel review 11/13/2008. No changes to policy statement. References added. (btw)
- 6/22/10 Policy Number(s) removed. (amw)

## **Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma**

- 9/28/10 Policy named changed from "Bone Marrow Transplant for Hodgkin's Disease" to "Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma". "Description" revised. Removed the statement in the "Benefit Application" section that indicated "Services for or related to the search for a donor are not covered." Changed reference to "bone marrow transplant with high dose chemotherapy with stem cell support" to "hematopoietic stem-cell transplantation" where appropriate. Added to the "When covered" section the following: "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)." And "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) or \*when insufficient stem cells are collected for an autologous HSCT." Updated "Policy Guidelines". References added. (btw)



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- 1/4/11 Specialty Matched Consultant Advisory Panel review 11/29/2010. No change to policy statement.
- 1/10/12 Specialty Matched Consultant Advisory Panel review 11/30/2011. No change to policy statement. (btw)
- 2/7/12 Added new 2012 CPT code, 39232 to Billing/Coding section. Reference added. (btw)
- 12/28/12 Specialty Matched Consultant Advisory Panel review 12/4/2012. No change to policy intent. Added new 2013 CPT code, 38243 to Billing/Coding section. Reference added. (btw)
- 12/10/13 Specialty Matched Consultant Advisory Panel review 11/20/13. No change to policy intent. (btw)
- 2/25/14 Reference added. (btw)
- 12/9/14 Specialty Matched Consultant Advisory Panel review 11/24/2014. No change to policy intent. (lpr)
- 2/10/15 Reference added. (lpr)
- 12/30/15 Specialty Matched Consultant Advisory Panel review 11/18/2015. No change to policy statement. (lpr)
- 4/1/2016 Updated Policy Guidelines section. No change to policy intent. Reference added. (lpr)
- 12/30/16 Specialty Matched Consultant Advisory Panel review 11/30/2016. No change to policy intent. (lpr)

## **Hematopoietic Cell Transplantation for Hodgkin Lymphoma**

- 4/28/17 Policy title changed from “Hematopoietic Stem-Cell Transplantation for Hodgkin Lymphoma” to “Hematopoietic Cell Transplantation for Hodgkin Lymphoma” Description and Policy Guidelines sections revised. Reference added. No change to policy intent. Medical Director review 1/2017. (lpr)
- 12/15/17 Specialty Matched Consultant Advisory Panel review 11/2017. No change to policy statement. (lpr)
- 1/15/19 Specialty Matched Consultant Advisory Panel review 11/2018. Reference added. No change to policy statement. (lpr)

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