# Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

**BCBSA Ref. Policy:** 8.01.20

**Effective Date:** May 1, 2019

**Last Revised:** April 18, 2019

**Replaces:** 8.01.20

## RELATED MEDICAL POLICIES:

- 7.01.50 Placental and Umbilical Cord Blood as a Source of Stem Cells
- 8.01.15 Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
- 8.01.21 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- 8.01.22 Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
- 8.01.24 Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- 8.01.25 Hematopoietic Cell Transplantation for Autoimmune Diseases
- 8.01.29 Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- 8.01.511 Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- 8.01.532 Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

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## Introduction

A hematopoietic cell is an immature cell that can mature into different types of blood cells. Certain chemotherapy drugs can destroy the bone marrow, and bone marrow is where blood cells form. Infusing immature blood cells gives the body a chance to restore blood cell production in the bone marrow. When the immature blood cells are taken from the patient it’s known as an autologous hematopoietic cell transplant (HCT). Using immature cells from a donor is known as an allogeneic HCT. This policy discusses when hematopoietic cell transplants may be considered medically necessary for non-Hodgkin lymphoma, a type of immune system cancer.
Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

Small lymphocytic lymphoma may be considered a node-based variant of chronic lymphocytic leukemia. Therefore, small lymphocytic lymphoma is considered along with chronic lymphocytic leukemia in a separate policy. Lymphoplasmacytic lymphoma and Waldenstrom macroglobulinemia are considered in separate policies (see Related Policies).

<table>
<thead>
<tr>
<th>Indication</th>
<th>Coverage Statement</th>
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</thead>
</table>
| Non-Hodgkin lymphoma (NHL) B-cell aggressive subtype (except mantle cell) | Myeloablative autologous, myeloablative allogeneic or reduced-intensity conditioning (RIC) allogeneic HCT with curative intent may be considered medically necessary:  
  • As salvage for patients not in complete remission after first line chemotherapy induction  
  OR  
  • To achieve or consolidate a complete remission in chemotherapy sensitive first or subsequent relapse  
  OR  
  • To consolidate a complete remission in patients with an age-adjusted International Prognostic Index (IPI) that predicts a high or high-intermediate risk of relapse |
| Mantle cell NHL B-cell subtype | Autologous HCT may be considered medically necessary to consolidate a first remission of mantle cell NHL B-cell subtype.  
Allogeneic and RIC allogeneic HCT are considered investigational to consolidate a first remission of mantle cell NHL B-cell subtype.  
Allogeneic or RIC allogeneic HCT with curative intent may be considered medically necessary as salvage for patients with |
<table>
<thead>
<tr>
<th>Indication</th>
<th>Coverage Statement</th>
</tr>
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<tbody>
<tr>
<td>mantle cell NHL B-cell subtype who are not in complete remission after first line chemotherapy.</td>
<td>Myeloablative autologous HCT is considered investigational as salvage for patients with mantle cell NHL B-cell subtype who are not in complete remission after first line chemotherapy.</td>
</tr>
<tr>
<td><strong>NHL B-cell indolent subtypes</strong></td>
<td>Myeloablative autologous, allogeneic, or RIC allogeneic HCT with curative intent may be considered medically necessary:</td>
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<tr>
<td></td>
<td>• As salvage for patients not in complete remission after first line (induction) chemotherapy</td>
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<tr>
<td></td>
<td>OR</td>
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<tr>
<td></td>
<td>• To achieve or consolidate a complete remission in chemotherapy sensitive first or subsequent relapse (regardless of transformation)</td>
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<td></td>
<td><strong>Myeloablative autologous, allogeneic, and RIC allogeneic HCT are considered investigational:</strong></td>
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<td></td>
<td>• As initial therapy (without standard induction chemotherapy) for all B-Cell NHL</td>
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<td></td>
<td>OR</td>
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<td></td>
<td>• To consolidate a first complete remission for low or low-intermediate IPI score diffuse large B-Cell NHL</td>
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<td></td>
<td>OR</td>
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<tr>
<td></td>
<td>• To consolidate a first complete remission for indolent B-cell NHL</td>
</tr>
<tr>
<td><strong>Mature T-cell or NK (peripheral T-cell) lymphoma</strong></td>
<td>Myeloablative autologous HCT may be considered medically necessary:</td>
</tr>
<tr>
<td></td>
<td>• To consolidate a first complete remission in high-risk subtypes (see Table 1 below)</td>
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<tr>
<td></td>
<td><strong>Myeloablative autologous, allogeneic, or reduced-intensity conditioning allogeneic HCT may be considered medically necessary as salvage therapy.</strong></td>
</tr>
<tr>
<td></td>
<td>Myeloablative and reduced-intensity conditioning allogeneic HCT are considered investigational to consolidate a first complete remission.</td>
</tr>
</tbody>
</table>
**Indication**  | **Coverage Statement**  
--- | ---  
Tandem transplants| Tandem transplants are considered investigational to treat patients with any stage, grade, or subtype of NHL.

### Table 1: Allowable Treatment by NHL Type

<table>
<thead>
<tr>
<th>NHL Type</th>
<th>Presenting Stage</th>
<th>Treatment Intent</th>
<th>Autologous HCT</th>
<th>Allogeneic HCT</th>
<th>RIC</th>
<th>Tandem Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-Cell aggressive (not mantle)</td>
<td>Not in CR post 1st Line</td>
<td>Salvage</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Chemo-sensitive 1st or later relapse</td>
<td>Consolidate (CR)</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td>High or high-intermediate IPI</td>
<td>CR</td>
<td>Consolidate</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>1st Remission</td>
<td>Consolidate</td>
<td>Medically Necessary</td>
<td>Investigational</td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not in CR post 1st Line</td>
<td>Salvage</td>
<td>Investigational</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td>Indolent</td>
<td>CR</td>
<td>Consolidate</td>
<td>Investigational</td>
<td>Investigational</td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not in CR post 1st Line</td>
<td>Salvage</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Chemo-sensitive 1st or later relapse</td>
<td>Consolidate (CR)</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td>Mature T-cell or NK cell high risk</td>
<td>1st CR</td>
<td>Consolidate</td>
<td>Medically Necessary</td>
<td>Investigational</td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not CR post Chemo</td>
<td>Salvage</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Medically Necessary</td>
<td>Investigational</td>
</tr>
<tr>
<td>Mature T-cell or NK cell not high risk</td>
<td>1st CR</td>
<td>Consolidate</td>
<td>Investigational</td>
<td>Investigational</td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td>All NHL low or low-intermediate IPI</td>
<td>1st CR</td>
<td>Consolidate</td>
<td>Investigational</td>
<td>Investigational</td>
<td>Investigational</td>
<td></td>
</tr>
</tbody>
</table>

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Additional Information

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic hematopoietic stem-cell transplant (HCT), but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude use of a standard conditioning regimen.

In patients who qualify for a myeloablative allogeneic hematopoietic HCT on the basis of overall health and disease status, allogeneic HCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic HCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic HCT with RIC.

Documentation Requirements

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:

- Diagnosis/condition (including type of non-Hodgkin’s Lymphoma)
- History and physical examination documenting the severity of the condition
- Prior treatment (if any) patient has received
- Any poor-risk features
- History of remission(s) and relapse(s) (if any)

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
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</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td>HCPCS</td>
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</tr>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
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<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<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>
</table>

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**Related Information**

**Consideration of Age**

The ages stated in this policy for which reduced intensity conditioning would be considered an option in patients who meet other criteria for an allogeneic HSCT are based on the risk factors defined by the International Prognostic Index. See Evidence Review section and NCCN.

**Definition of Terms**

**Allogeneic HCT:** The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total -body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient.

**Autologous HCT:** This involves the administration of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. It is typically performed as consolidation therapy when the patient’s disease is in complete remission.

**Chemo-sensitive relapse:** This is defined as relapsed non-Hodgkin lymphoma (NHL) that does not progress during or immediately after standard-dose induction chemotherapy (ie, achieves stable disease or a partial response).

**Complete remission (CR):** This is the disappearance of all the signs of cancer in response to treatment. Also called complete response.
Consolidation therapy: This is treatment that is given after cancer has disappeared following initial therapy with the goal of killing any cancer cells that may be left in the body. Also referred to as intensification therapy and post-remission therapy.

Disease-free survival: This is the length of time after primary treatment for a cancer that the patient survives free of any signs or symptoms of the cancer being treated. Also called relapse-free survival.

First-line therapy: This is the first treatment given for a disease and is often part of a standard set of treatments, which may include surgery followed by chemotherapy and radiation.

Hematopoietic stem-cell transplantation (HCT): This refers to a procedure in which hematopoietic 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 cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT).

International Prognostic Index (IPI): This model was developed for predicting outcomes in patients with aggressive non-Hodgkin’s lymphoma based on the patients’ clinical characteristics before treatment.

Myeloablative chemotherapy: This is high-dose chemotherapy that kills all cells in the bone marrow, including the cancer cells. It is generally followed by bone marrow or stem-cell transplant to rebuild the bone marrow.

Reduced-intensity conditioning (RIC): This 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.

Relapse: The return of a disease or the signs and symptoms after a period of improvement.

Salvage therapy: Chemotherapy given to patients who have either (1) failed to achieve complete remission after initial treatment for newly diagnosed lymphoma, or (2) relapsed after an initial complete remission.

Tandem transplants: These are usually defined as the planned administration of 2 successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic cells.
Transformation: This term describes a lymphoma whose histologic pattern has evolved to a higher-grade lymphoma. Transformed lymphomas typically evolve from a nodular pattern to a diffuse pattern.

High-Risk (Aggressive) T-Cell and NK-Cell Neoplasms:

The T-cell and NK-cell neoplasms are a clinically heterogeneous group of rare disorders, most of which have an aggressive clinical course and poor prognosis. The exception would include the following subtypes which typically have a relatively indolent and protracted course:

- T-cell large granulocyte leukemia (T-LGL),
- Chronic lymphoproliferative disorder of NK cells,
- Early stage mycosis fungoides,
- Primary cutaneous ALCL, and
- ALK+ ALCL.\textsuperscript{11}

Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health.
- Some plans may participate in voluntary programs offering coverage for patients participating in clinical trials approved by the National Institutes of Health assessing cancer chemotherapy, including autologous bone marrow transplantation.
- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.
Description

Hematopoietic stem-cell transplantation (HCT) refers to a procedure in which hematopoietic 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 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 cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in another medical policy (see Related Policies).

Background

Non-Hodgkin Lymphoma

A heterogeneous group of lymphoproliferative malignancies, non-Hodgkin lymphoma (NHL) usually originates in lymphoid tissue. Historically, uniform treatment of patients with NHL was hampered by the lack of a uniform classification system. In 1982, the Working Formulation was developed to unify different classification systems into one.¹ The Working Formulation divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Because our understanding of NHL has improved, the diagnosis has become more sophisticated and includes the incorporation of new immunophenotyping and genetic techniques. As a result, the Working Formulation has become outdated.

European and American pathologists proposed a new classification, the Revised European-American Lymphoma (REAL) Classification² and an updated version of the REAL system, the new World Health Organization (WHO) classification.³ The WHO/REAL classification recognized three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2016 WHO classification (see Table 2).⁴
### Table 2. Updated WHO Classification (2016)

<table>
<thead>
<tr>
<th>Classification of Neoplasms</th>
<th>Chronic lymphocytic leukemia/small lymphocytic lymphoma</th>
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</thead>
<tbody>
<tr>
<td>Mature B-cell neoplasms</td>
<td></td>
</tr>
<tr>
<td>Monoclonal B-cell lymphocytosis&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>B-cell prolymphocytic leukemia</td>
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<tr>
<td>Splenic marginal zone lymphoma</td>
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<tr>
<td>Hairy cell leukemia</td>
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<tr>
<td>• <em>Spleenic lymphoma/leukemia, unclassifiable</em></td>
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<tr>
<td>o <em>Splenic diffuse red pulp small B-cell lymphoma</em></td>
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<tr>
<td>o <em>Hairy cell leukemia-variant</em></td>
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<tr>
<td>Lymphoplasmacytic lymphoma</td>
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<tr>
<td>• Waldenström macroglobulinemia</td>
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<tr>
<td>Monoclonal gammagopathy of undetermined significance, IgM&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Heavy chain diseases</td>
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<td>• Alpha heavy chain disease</td>
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<td>• Gamma heavy chain disease</td>
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<td>• Mu heavy chain disease</td>
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<tr>
<td>Monoclonal gammagopathy of undetermined significance, IgG/IgA&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Plasma cell myeloma</td>
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<tr>
<td>Solitary plasmacytoma of bone</td>
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<tr>
<td>Extraosseous plasmacytoma</td>
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<tr>
<td>Monoclonal immunglobulin deposition diseases&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
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<tr>
<td>Nodal marginal zone lymphoma (MZL)</td>
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<tr>
<td>• <em>Pediatric nodal MZL</em></td>
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<tr>
<td>Follicular lymphoma</td>
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<tr>
<td>• <em>In situ follicular neoplasia</em></td>
<td></td>
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<tr>
<td>• <em>Duodenal-type follicular lymphoma</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Pediatric type follicular lymphoma&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>• <em>Large B-cell lymphoma with IRF4 rearrangement</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Primary cutaneous follicle center lymphoma</td>
<td></td>
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<tr>
<td>Mantle cell lymphoma</td>
<td></td>
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<tr>
<td>• <em>In situ mantel cell neoplasia</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)</td>
<td></td>
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<tr>
<td>• <em>Germinal center B-cell type</em>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>• <em>Activated B-cell type</em>&lt;sup&gt;a&lt;/sup&gt;</td>
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</tbody>
</table>
## Classification of Neoplasms

| T-cell/histiocyte-rich large B-cell lymphoma |
| DLBCL associated with chronic inflammation |
| Lymphomatoid granulomatosis |
| Primary mediastinal (thymic) large B-cell lymphoma |
| Intravascular large B-cell lymphoma |
| **Primary cutaneous DLBCL, leg type** |
| ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma |
| Plasmablastic lymphoma |
| Primary effusion lymphoma |
| **HHV8 DLBCL NOS** |
| Burkitt lymphoma |
| **Burkitt-like lymphoma with 11q aberration** |
| High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements |
| High-grade B-cell lymphoma, NOS |
| B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma |
| T-cell prolymphocytic leukemia |
| T-cell large granular lymphocytic leukemia |
| **Chronic lymphoproliferative disorder of NK cells** |
| Aggressive NK-cell leukemia |
| Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood |
| Hydroa vacciniforme-like lymphoproliferative disorder |
| Adult T-cell leukemia/ lymphoma |
| Extranodal NK/T-cell lymphoma, nasal type |
| Enteropathy-associated T-cell lymphoma |
| Monomorphic epitheliotropic intestinal T-cell lymphoma |
| **Indolent T-cell lymphoproliferative disorder of the GI tract** |
| Hepatosplenic T-cell lymphoma |
| Subcutaneous panniculitis-like T-cell lymphoma |
| Mycosis fungoides |
| Mature T-cell and Sézary syndrome |
### Classification of Neoplasms

**NK-cell neoplasms**
- Primary cutaneous CD30-positive T-cell lymphoproliferative disorder
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large-cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- **Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma**
- **Primary cutaneous acral CD8+ T-cell lymphoma**
- **Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder**

**Peripheral T-cell lymphoma, NOS**
- Angioimmunoblastic T-cell lymphoma
- **Follicular T-cell lymphoma**
- **Nodal peripheral T-cell lymphoma with TFH phenotype**
- Anaplastic large-cell lymphoma (ALCL), ALK-positive
- Anaplastic large-cell lymphoma (ALCL), ALK-negative
- **Breast implant–associated anaplastic large-cell lymphoma**

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ALK: anaplastic lymphoma kinase; GI: gastrointestinal; Ig: immunoglobulin; NK: natural killer.

* Changes from 2008 WHO classification. Provisional entities are listed in italics.

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In the U.S., B-cell lymphomas represent 80% to 85% of cases of NHL, and T-cell lymphomas represent 15% to 20%. Natural killer lymphomas are relatively rare.\(^5\)

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: DLBCL 31%, follicular lymphoma (FL) 22%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma/MALT lymphoma 5%. All other subtypes each represent less than 2% of cases of NHL.\(^5\)

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**Types of NHL**

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.\(^1\) Early stage indolent NHL (stage 1 or 2) may be effectively treated with radiation alone.\(^1\) Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages.\(^1\) These patients can often be re-treated if their disease remains of the indolent type. Indolent NHL may transform...
into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, and median survival with conventional chemotherapy is 1 year or less.

Follicular lymphoma (FL) is the most common indolent NHL (70%-80% of cases), and often the terms indolent lymphoma and FL are used synonymously. Also included in the indolent NHL are small lymphocytic lymphoma/chronic lymphocytic lymphoma, lymphoplasmacytic lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.

Aggressive NHL has a shorter natural history; however, 30% to 60% of these patients can be cured with intensive combination chemotherapy regimens. Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

**Risk Assessment**

Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI). Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the following 5 risk factors prognostic of overall survival (OS) and adjusted for patient age, the IPI defines 4 risk groups: low, low-intermediate, high-intermediate, and high-risk:

1. Age older than 60 years
2. Elevated serum lactate dehydrogenase (LDH) level
3. Ann Arbor stage III or IV disease
4. Eastern Cooperative Oncology Group (ECOG) performance status of 2, 3, or 4
5. Involvement of more than 1 extranodal site

Risk groups are stratified according to the number of adverse factors as follows: 0 or 1 is low risk, 2 is low intermediate, 3 is high intermediate, and 4 or 5 are high risk.

Patients with 2 or more risk factors have a less than 50% chance of relapse-free survival (RFS) and OS at 5 years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger patients with localized disease.
Adverse risk factors for age-adjusted IPI include stage III or IV disease, elevated LDH and ECOG performance status of 2 or greater and can be calculated as follows: 0 is low risk, 1 is low intermediate, 2 is high intermediate, and 3 is high risk.

With the success of the IPI, a separate prognostic index was developed for FL, which has multiple independent risk factors for relapse after a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains 5 adverse prognostic factors:

1. Age older than 60 years
2. Ann Arbor stage III–IV
3. Hemoglobin level less than 12.0 g/dL
4. More than 4 lymph node areas involved
5. Elevated serum LDH level

These five factors are used to stratify patients into 3 categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).8

**Mantle Cell Lymphoma**

Mantle Cell Lymphoma (MCL) comprises approximately 65% to 68% of NHL and has been recognized for some time now as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed by Banks et al(1992).9 The number of therapeutic trials is not as numerous for MCL as for other NHL, as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2 to 4 years, and although most patients achieve remission with first -line therapy, relapse inevitably occurs, often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.
**Risk Assessment**

Not until recently has a prognostic index been established for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL.\(^\text{10}\) Therefore, a new prognostic index for patients with MCL was developed and should prove useful in comparing clinical trial results for MCL.

The MCL International Prognostic Index (MIPI) is based on the following risk factors prognostic for overall survival.

1. **Age**
2. **ECOG performance status**
3. **Serum LDH** (calculated as a ratio of LDH to a laboratory’s upper limit of normal)
4. **White blood cell (WBC) count**
   - Zero points each are assigned for age younger than 50 years, ECOG performance 0-1, LDH ratio less than 0.67, WBC less than 6700
   - One point each for age 50 to 59 years, LDH ratio 0.67-0.99, WBC 6700-9999
   - Two points each for age 60 to 69 years, ECOG 2-4, LDH ratio 1.00-1.49, WBC 10,000-14,999
   - Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

MIPI allows separation of 3 groups with significantly different prognoses\(^\text{10}\):

- 0-3 points=low risk, 44% of patients, median OS not reached and a 5-year OS rate of 60%
- 4-5 points=intermediate risk, 35% of patients, median OS, 51 months
- 6-11 points=high risk, 21% of patients, median OS, 29 months
Peripheral T-Cell Lymphoma

Most peripheral T-cell lymphomas (PTCL) are aggressive and fall into the category of PTCL, unspecified (PTCL-u) or not otherwise specified (PTCL-NOS), angioimmunoblastic or anaplastic large cell which, combined make up approximately 60% to 70% of T-cell lymphomas. PTCLs are less responsive to standard chemotherapy than DLBCLs and carry a worse prognosis than aggressive Bcell counterparts. Survival rates at 5 years with standard chemotherapy regimens range from 20% to 35%. The poor results with conventional chemotherapy have prompted exploration of the role of HCT as therapy.

Staging

The Ann Arbor staging classification is commonly used to stage lymphomas. Originally developed for Hodgkin disease, the classification was later expanded to include NHL.

Table 3. Ann Arbor Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Involvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE)</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localized involvement of extralymphatic organ or site (IIIE) or by involvement of the spleen (IIIS) or both (IIISE)</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement</td>
</tr>
</tbody>
</table>

Treatment for NHL

Hematopoietic Cell Transplantation

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allogenic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA
refers to the tissue type expressed at the HLA-A, -B, and -DR 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 HCT**

The conventional practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation; this is performed at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect that is 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 graft-versus-malignancy effect is considered 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 medically fit to tolerate substantial adverse events 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 allogeneic HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increase susceptibility to opportunistic infections. The immune reactivity between donor T cells and malignant cells is responsible for the graft-versus-malignancy effect; it also leads to acute and chronic graft-versus-host disease.

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy (with or without radiation) to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

**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 conventional full-dose myeloablative conditioning treatments. The goal of RIC is 2-fold: to reduce disease burden, and
to minimize treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly totally myeloablative to minimally myeloablative with lymphoablation—because it tailors its intensity 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 evidence review, reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

Summary of Evidence

For individuals who have indolent B-cell non-Hodgkin lymphomas who receive autologous HCT as first-line therapy, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Randomized trials have not shown a survival advantage with HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit for relapsed disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have indolent B-cell non-Hodgkin lymphomas (NHL) who receive autologous HCT as first-line therapy, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality and morbidity. Randomized trials have not shown a survival advantage with HCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit for relapsed disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have aggressive B-cell non-Hodgkin lymphomas, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first complete remission, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the randomized trials offer conflicting results, some of the data has revealed an overall survival benefit in patients with aggressive B-cell lymphomas (at high or high-intermediate risk of relapse) who receive HCT to
consolidate a first complete remission. Randomized studies of HCT for relapsed aggressive B-cell lymphomas have shown an overall survival benefit with the previously described approach. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have non-Hodgkin lymphomas, excluding MCL, who receive tandem autologous and allogeneic HCT, the evidence includes several nonrandomized trials. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. No randomized studies have been conducted on the use of tandem HCT for the treatment of non-Hodgkin lymphoma, and the published evidence comprises a limited number of patients. Presently, conclusions on the use of tandem transplants cannot be made about autologous and allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have mantle cell lymphoma who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Due in part to the rarity of this disease, randomized trials on the use of HCT in mantle cell lymphoma have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allogeneic HCT has shown prolonged disease control in the relapsed or refractory setting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous or allogeneic HCT, the evidence includes prospective trials and case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of patients; further the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas in which the study addresses. Additionally, studies of this nature often mix of three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphomas (ALCL), which has a better prognosis—even with conventional chemotherapy regimens; and a third type has ALK-negative ALCL, which has a worse prognosis than ALK-positive ALCL (but better than patients with PTCL not otherwise specified). There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (ie, some randomized studies
have included PTCL with aggressive B-cell lymphomas. For front-line therapy, results from recent phase 2 studies with autologous HCT as consolidation offers the best survival outcomes for patients with high-risk features; randomized trials to confirm this have not been performed. No relevant data for the use of allogeneic HCT in the first-line setting are available. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, data have shown that the use of HCT may improve survival outcomes similar to the results seen in corresponding aggressive B-cell lymphomas in the same treatment setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished phase 3 trials that might influence this review are listed in National Cancer Institute’s Physician Data Query database.

**Clinical Input From Physician Specialty Societies and Academic Medical Centers**

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

**2011 Input**

In response to requests, input was received from 3 physician specialty societies and 3 academic medical centers while this policy was under review in 2011. Input was solicited particularly for the use of hematopoietic cell transplantation (HCT) in mantle cell lymphoma (MCL) and peripheral T-cell lymphoma. There was a uniform agreement for the use of autologous HCT to consolidate the first remission in MCL. There was a general agreement for the use of allogeneic HCT as salvage therapy for MCL, with less agreement on the use of autologous HCT in the salvage setting. For peripheral T-cell lymphoma, there was general agreement on the use of autologous HCT to consolidate a complete remission in high-risk patients and the salvage setting. Input was split on the use of allogeneic HCT to consolidate a first complete remission or
as salvage therapy, but there was more support to consider it medically necessary in both settings.

2009 Input

In response to requests, input was received from 1 physician specialty society and 1 academic medical center while this policy was under review in 2009. There was general agreement with the policy statements. Both reviewers agreed that allogeneic HCT with reduced-intensity conditioning should be considered medically necessary in patients with non-Hodgkin lymphoma who do not qualify for a myeloablative allogeneic HCT. One reviewer responded on the medical necessity of HCT in patients with MCL in the first remission and recently published literature supported this. There was conflicting input on whether HCT should be considered investigational for peripheral T-cell lymphoma. Also, the one reviewer commented that with the increasing use of rituximab and its success in improving patient outcomes, the role of HCT in consolidating first complete response in high-risk patients is coming into question.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines on B-cell lymphomas (v.1.2019) include the following recommendations71:

“Second-line chemotherapy ... followed by high-dose therapy and autologous HSCT [hematopoietic stem cell transplantation] or allogeneic HSCT ... may be considered in selected patients with a reasonable remission duration.”

“Treatment of relapsed or refractory HIV-associated lymphomas remains a challenge, with autologous HSCT being the only potentially curative strategy.”

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.2.2019) include the following recommendations72:

“Second-line systematic therapy followed by consolidation with HDT [high-dose therapy]/ASCR [autologous stem cell rescue] or allogeneic HSCT for those with a CR [complete response] or PR [partial response] is recommended for patients who are candidates for transplant.”
“Allogeneic HCT should be considered for patients with acute or lymphoma [ATLL] subtype, if donor is available.”

“In patients with acute or lymphoma subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available.”

“In patients [with T-PLL] who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT.”

**Medicare National Coverage**

Medicare has the following national coverage determination for the use of autologous cell transplantation for Hodgkin and non-Hodgkin lymphomas.73

“a) Effective .... 1989, AuSCT [autologous stem cell transplantation] is considered reasonable and necessary ... for the following conditions and is covered under Medicare for patients with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
- Resistant non-Hodgkin’s lymphomas or those presenting with poor prognostic features following an initial response;
- Recurrent or refractory neuroblastoma; or,
- Advanced Hodgkin’s disease who have failed conventional therapy and have no HLA-matched donor.

b) Effective ... 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function.
c) Effective ... 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

- Amyloid deposition in 2 or fewer organs; and,
- Cardiac left ventricular ejection fraction (EF) greater than 45%.”

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 title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

References


13. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy with autologous stem-cell support or allogeneic stem-cell support for follicular non-Hodgkin’s lymphoma. TEC Assessments 1995;Volume 10:Tab 28

14. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments 2000;Volume 15:Tab 9.


<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tr>
<td>04/14/14</td>
<td>New PR policy; replaces 8.01.20. Policy updated with literature search through December 23, 2013. Policy section reworded and reformatted. Policy statements changed as follows: NHL B-cell – RIC is now medically necessary; B-cell Indolent – RIC is now investigational (previously medically necessary); Mature T-cell or NK – RIC is now investigational to consolidate CR (previously medically necessary). References 37 and 42 added; reference 66 updated.</td>
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<td>06/24/14</td>
<td>Update Related Policies. Remove 8.01.35, 8.01.42 and 8.01.54, then add 8.01.532</td>
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<tr>
<td>12/03/14</td>
<td>Update Related Policies. Remove 8.01.17 and 8.01.26.</td>
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<td>04/24/15</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements.</td>
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<tr>
<td>08/09/16</td>
<td>Update Related Policies. Remove 8.01.27 as it was archived.</td>
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<tr>
<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
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<td>12/01/16</td>
<td>Annual review, approved November 8, 2016. Added references 68 and 69. No changes to policy statement.</td>
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<td>04/01/17</td>
<td>Updated titles in Related Policies.</td>
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<tr>
<td>08/01/17</td>
<td>Updated title of Related Policy 8.01.511.</td>
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<td>12/01/17</td>
<td>Annual Review, approved November 9, 2017. Updated WHO classifications and Summary of Evidence section. No changes to policy statement.</td>
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<td>09/01/18</td>
<td>Minor update. Re-adding Consideration of Age information which was inadvertently removed during a previous update.</td>
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<tr>
<td>04/01/19</td>
<td>Minor update, added Documentation Requirements section.</td>
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<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 18, 2019. Policy updated with literature review through November 2018; reference 60 added. Policy statements unchanged.</td>
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