Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062
Original Effective Date: 01/28/2002
Current Effective Date: 10/09/2019

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma is addressed separately in medical policy 00052.

Note: Hematopoietic Cell Transplantation Hodgkin Lymphoma is addressed separately in medical policy 00057.

Note: Hematopoietic Cell Transplantation for Primary Amyloidosis or Waldenström Macroglobulinemia is addressed separately in medical policy 00138.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

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

Based on review of available data, the Company may consider for patients with non-Hodgkin lymphoma (NHL) B-cell subtypes aggressive (except mantle cell lymphoma), either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous hematopoietic cell transplantation (HCT) to be eligible for coverage.**

Patient Selection Criteria

Coverage eligibility for the use of hematopoietic cell transplantation (HCT) for non-Hodgkin lymphomas (NHLs) will be considered when ANY of the following criteria are met:

- As salvage therapy for patients who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy; OR
- To achieve or consolidate a complete remission (CR) for those in a chemosensitive first or subsequent relapse; OR

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- To consolidate a first complete remission (CR) in patients with diffuse large B-cell lymphoma, with an age-adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.

For Patients with Mantle Cell Lymphoma:
Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to consolidate a first remission to be eligible for coverage.**

Based on review of available data, the Company may consider allogeneic hematopoietic cell transplantation (HCT), myeloablative or reduced-intensity conditioning (RIC) as salvage therapy to be eligible for coverage.**

For Patients with Non-Hodgkin Lymphoma (NHL) B-Cell Subtypes:
Based on review of available data, the Company may consider patients with non-Hodgkin lymphoma (NHL) B-cell subtypes indolent, either allogeneic hematopoietic cell transplantation (HCT) using a myeloablative conditioning regimen or autologous hematopoietic cell transplantation (HCT) to be eligible for coverage:**

- As salvage therapy for patients who do not achieve complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy; OR
- To achieve or consolidate complete remission (CR) for those in a first or subsequent chemosensitive relapse, whether or not their lymphoma has undergone transformation to a higher grade.

Based on review of available data, the Company may consider reduced-intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) as a treatment of non-Hodgkin lymphoma (NHL) in patients who meet criteria for an allogeneic hematopoietic cell transplantation (HCT) but who do not qualify for a myeloablative allogeneic hematopoietic cell transplantation (HCT) to be eligible for coverage.** (see Policy Guidelines).

For Patients with Mature T-Cell or Natural Killer (NK)-Cell (Peripheral T-Cell) Neoplasms:
Based on review of available data, the Company may consider autologous hematopoietic cell transplantation (HCT) to consolidate a first complete remission (CR) in high-risk subtypes to be eligible for coverage.** (see Policy Guidelines).
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Based on review of available data, the Company may consider autologous or allogeneic hematopoietic cell transplantation (HCT) (myeloablative or reduced-intensity conditioning [RIC]) as salvage therapy to be eligible for coverage.**

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

Based on review of available data, the Company considers either autologous hematopoietic cell transplantation (HCT) or allogeneic hematopoietic cell transplantation (HCT) to be investigational.*

- As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any non-Hodgkin lymphoma (NHL); OR
- To consolidate a first complete remission (CR) for patients with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse; OR
- To consolidate a first complete remission (CR) for those with indolent non-Hodgkin lymphoma (NHL) B-cell subtypes.

Based on review of available data, the Company considers tandem transplants to treat patients with any stage, grade, or subtype of non-Hodgkin lymphoma (NHL) to be investigational.*

For Patients with Mature T-Cell or Natural Killer (NK)-Cell (Peripheral T-Cell) Neoplasms:
Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to consolidate a first remission to be investigational.*

For Patients with Mantle Cell Lymphoma (MCL):
Based on review of available data, the Company considers autologous hematopoietic cell transplantation (HCT) as salvage therapy to be investigational.*

Based on review of available data, the Company considers allogeneic hematopoietic cell transplantation (HCT) to consolidate a first remission to be investigational.*
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Note: 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 evidence review 00052. Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia is considered in evidence review 00138.

Policy Guidelines
Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for allogeneic hematopoietic cell transplantation (HCT), but whose age (typically >55 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy) preclude the use of a standard conditioning regimen.

In patients who qualify for a myeloablative allogeneic 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.

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

Transformation 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.

Tandem transplants usually are defined as the planned administration of two successive cycles of high-dose myeloablative chemotherapy, each followed by infusion of autologous hematopoietic stem cells, whether or not there is evidence of persistent disease following the first treatment cycle. Sometimes, the second cycle may use nonmyeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

The term salvage therapy describes therapy given to patients with refractory or relapsed disease. For patients with peripheral T-cell lymphoma, salvage therapy includes patients who do not achieve a complete response (eg, achieve only a partial response, have no response, or have progressive disease) with first-line induction chemotherapy (refractory disease) or who relapse after achieving a
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complete response with first-line induction chemotherapy. For mantle cell lymphoma, salvage therapy includes patients with progressive disease with first-line induction chemotherapy (refractory disease) or in patients who relapse after a complete or partial response after initial induction chemotherapy, or patients who fail a previous autologous HCT.

High-risk (aggressive) T-cell and natural killer cell neoplasms are a clinically heterogeneous group of rare disorders, most of which have an aggressive clinical course and poor prognosis. The exception includes the following subtypes, which typically have a relatively indolent and protracted course: T-cell large granulocyte leukemia, chronic lymphoproliferative disorder of natural killer cells, early-stage mycosis fungoides, primary cutaneous anaplastic large-cell lymphoma, and anaplastic lymphoma kinase-anaplastic large-cell lymphomas.

**Background/Overview**

**Non-Hodgkin Lymphoma**

A heterogeneous group of lymphoproliferative malignancies, 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. 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 immune phenotyping 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) Classification, and an updated version of the REAL system, the new World Health Organization classification. 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 1).
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Table 1. Updated WHO Classification (2016)

<table>
<thead>
<tr>
<th>Classification of Neoplasms</th>
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</thead>
<tbody>
<tr>
<td>Mature B-cell neoplasms</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma</td>
</tr>
<tr>
<td>Monoclonal B-cell lymphocytosisa</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td>Splenic lymphoma/leukemia, unclassifiable</td>
</tr>
<tr>
<td>- Splenic diffuse red pulp small B-cell lymphoma</td>
</tr>
<tr>
<td>- Hairy cell leukemia-variant</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Classification of Neoplasms</th>
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<tbody>
<tr>
<td>• Waldenström macroglobulinemia</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance, IgM&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Heavy chain diseases</td>
</tr>
<tr>
<td>• Alpha heavy chain disease</td>
</tr>
<tr>
<td>• Gamma heavy chain disease</td>
</tr>
<tr>
<td>• Mu heavy chain disease</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance, IgG/IgA&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Plasma cell myeloma</td>
</tr>
<tr>
<td>Solitary plasmacytoma of bone</td>
</tr>
<tr>
<td>Extraosseous plasmacytoma</td>
</tr>
<tr>
<td>Monoclonal immunoglobulin deposition diseases&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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### Classification of Neoplasms

<table>
<thead>
<tr>
<th>Neoplasm Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)</td>
</tr>
<tr>
<td>Nodal marginal zone lymphoma (MZL)</td>
</tr>
<tr>
<td>• Pediatric nodal MZL</td>
</tr>
<tr>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>• In situ follicular neoplasia</td>
</tr>
<tr>
<td>• Duodenal-type follicular lymphoma</td>
</tr>
<tr>
<td>Pediatric type follicular lymphoma</td>
</tr>
<tr>
<td>• Large B-cell lymphoma with IRF4 rearrangement</td>
</tr>
<tr>
<td>Primary cutaneous follicle center lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>• In situ mantel cell neoplasia</td>
</tr>
</tbody>
</table>
Classification of Neoplasms

- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS)
  - Germinal center B-cell type
  - Activated B-cell type

- 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
### Classification of Neoplasms

<table>
<thead>
<tr>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary effusion lymphoma</td>
</tr>
<tr>
<td><em>HHV8 DLBCL NOS</em></td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
</tr>
<tr>
<td><em>Burkitt-like lymphoma with 11q aberration</em></td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, with <em>MYC</em> and <em>BCL2</em> and/or <em>BCL6</em> rearrangements</td>
</tr>
<tr>
<td>High-grade B-cell lymphoma, NOS</td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>Mature T-cell and NK-cell neoplasms</td>
</tr>
<tr>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>T-cell large granular lymphocytic leukemia</td>
</tr>
<tr>
<td><em>Chronic lymphoproliferative disorder of NK cells</em></td>
</tr>
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</table>
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<table>
<thead>
<tr>
<th>Classification of Neoplasms</th>
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</thead>
<tbody>
<tr>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood(^a)</td>
</tr>
<tr>
<td>Hydroa vacciniforme-like lymphoproliferative disorder(^a)</td>
</tr>
<tr>
<td>Adult T-cell leukemia/ lymphoma</td>
</tr>
<tr>
<td>Extranodal NK/T-cell lymphoma, nasal type</td>
</tr>
<tr>
<td>Enteropathy-associated T-cell lymphoma</td>
</tr>
<tr>
<td>Monomorphic epitheliotropic intestinal T-cell lymphoma(^a)</td>
</tr>
<tr>
<td><em>Indolent T-cell lymphoproliferative disorder of the GI tract</em>(^a)</td>
</tr>
<tr>
<td>Hepatosplenic T-cell lymphoma</td>
</tr>
<tr>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
</tr>
</tbody>
</table>

\(^a\) Indicates a diagnosis associated with a specific condition.
### Classification of Neoplasms

<table>
<thead>
<tr>
<th>Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sézary syndrome</td>
</tr>
<tr>
<td>Primary cutaneous CD30-positive T-cell lymphoproliferative disorder</td>
</tr>
<tr>
<td>• Lymphomatoid papulosia</td>
</tr>
<tr>
<td>• Primary cutaneous anaplastic large-cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous gamma-delta T-cell lymphoma</td>
</tr>
<tr>
<td><em>Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma</em></td>
</tr>
<tr>
<td><em>Primary cutaneous acral CD8+ T-cell lymphoma</em></td>
</tr>
<tr>
<td><em>Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder</em></td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td><em>Follicular T-cell lymphoma</em></td>
</tr>
</tbody>
</table>
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Classification of Neoplasms

<table>
<thead>
<tr>
<th>Nodal peripheral T-cell lymphoma with TFH phenotype(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic large-cell lymphoma (ALCL), ALK-positive</td>
</tr>
<tr>
<td>Anaplastic large-cell lymphoma (ALCL), ALK-negative(^a)</td>
</tr>
<tr>
<td>Breast implant-associated anaplastic large-cell lymphoma(^a)</td>
</tr>
</tbody>
</table>

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

\(^a\) Changes from 2008 WHO classification. Provisional entities are listed in italics.

In the United States, 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.

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: DLBCL 31%, follicular lymphoma 22%, small lymphocytic lymphoma and chronic lymphocytic leukemia 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue lymphoma 5%. All other subtypes each represents fewer than 2% of cases of NHL.

Types of NHL

In general, NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of ten years; however, it is not curable in advanced clinical stages. Early-stage indolent NHL (stage I or II) may be effectively treated with radiotherapy alone. Although indolent NHL is responsive to radiotherapy and chemotherapy, a continuous rate of relapse is seen in advanced stages. These patients can often be treated again 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 is the most common indolent NHL (70%-80% of cases), and often the terms indolent lymphoma and follicular lymphoma 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). Before its development in 1993, the 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 by a 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 and OS at 5 years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger patients with localized disease.
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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 follicular lymphoma, which has multiple independent risk factors for relapse after first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index contains 5 adverse prognostic factors:

1. Age older than 60 years
2. Ann Arbor stage III or IV disease
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 three categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).

Mantle Cell Lymphoma
MCL comprises 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). The number of therapeutic trials is not as numerous for MCL as for other NHL, because it was not widely recognized until the REAL classification. MCL shows a strong predilection for senior men, and most cases (70%) present with disseminated (stage IV) disease; 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 Follicular Lymphoma International Prognostic Index system to patients with MCL has shown limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and Follicular Lymphoma International Prognostic Index risk factors, including the
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. Therefore, a new prognostic index for patients with MCL was developed and should prove useful in comparing clinical trial results for MCL.

The MCL IPI is based on the following risk factors prognostic for OS:
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 to age younger than 50 years, ECOG Performance Status score of 0-1, LDH ratio of less than 0.67 U/L, WBC of less than 6700/µL
   - One point each for age 50 to 59 years, LDH ratio of 0.67-0.99 U/L, WBC of 6700-9999/µL
   - Two points each for age 60 to 69 years, ECOG Performance Status score of 2-4, LDH ratio of 1.00-1.49 U/L, WBC of 10000-14999/µL
   - Three points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15000/µL or more.

MCL IPI allows separation of 3 groups with significantly different prognoses:
- 0-3 points denote low-risk, which affects 44% of patients, who have a 5-year OS rate of 60% (median OS, not reached)
- 4-5 points denote intermediate risk, which affects 35% of patients, who have a median OS of 51 months
- 6-11 points denote high-risk, which affects 21% of patients, who have a median OS of 29 months

Peripheral T-Cell Lymphoma
Most PTCLs are aggressive and fall into the category of PTCL, unspecified PTCL, or PTCL not otherwise survival, angioimmunoblastic or anaplastic large-cell, which combined make up 60% to 70% of all T-cell lymphomas. PTCLs are less responsive to standard chemotherapy than DLBCLs and carry a worse prognosis than aggressive B-cell counterparts. Survival rates at 5 years with standard chemotherapy regimens range from 20% to 35%. The poor results with conventional
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Chemotherapy have prompted exploration of the role of hematopoietic cell transplantation (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 (see Table 2).

Table 2. 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 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 allogeneic 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 (except 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 the subsequent graft-versus-malignancy (GVM) 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 GVM 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 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 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 GVM 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 radiotherapy) 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

RIC refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is two-fold: to reduce disease burden, and to minimize treatment-related morbidity and nonrelapse mortality 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 nonrelapse mortality and relapse due to residual disease. RIC regimens can be viewed as a continuum—from nearly total 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, RIC refers to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
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.

Rationale/Source

Hematopoietic cell transplantation (HCT) refers to a procedure by which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although umbilical cord blood is an allogeneic source, the stem cells in it are antigenically “naive” and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in evidence review.
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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 NHL, 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 OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the randomized trials offer conflicting results, some data have revealed an OS 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 also shown an OS 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 NHL, excluding MCL, who receive tandem autologous and allogeneic HCT, the evidence includes several nonrandomized trials. The relevant outcomes are OS, DSS, 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 NHL, 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 MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. The relevant outcomes are OS, DSS, 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 for MCL 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
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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. The relevant outcomes are OS, DSS, 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; moreover, 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 addressed. Additionally, studies of this nature often mix three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas, which has a better prognosis—even with conventional chemotherapy regimens; and a third type has anaplastic lymphoma kinase-negative anaplastic large-cell lymphomas, which has a worse prognosis than anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas (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 first-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.

Supplemental Information
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.
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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 recommendations:

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

- “Second line systematic therapy followed by consolidation with HDT [high-dose therapy]/ASCR [autologous stem cell rescue] or allogeneic HCT 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.”

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

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

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:
   1. Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
   2. Resistant non-Hodgkin’s lymphomas or those presenting with poor prognostic features following an initial response;
   3. Recurrent or refractory neuroblastoma; or,
   4. 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:
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- 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%.”

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.

References
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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 PMID

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. PMID


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35. Baldissera RC, Nucci M, Vigorito AC, et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk,
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**Policy History**

Original Effective Date: 01/28/2002
Current Effective Date: 10/09/2019
12/06/2001 Medical Policy Committee review
03/25/2002 Managed Care Advisory Council approval
06/24/2002 Format revision. No substance change to policy
05/07/2004 Medical Director Review

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05/18/2004 Medical Policy Committee review. Format revision. High-Dose Chemotherapy and Hematopoietic Stem-Cell Support for Non-Hodgkin’s Lymphoma policy developed separately from current HDC with Hematopoietic Stem-cell Support policy. No substance change to policy
06/28/2004 Managed Care Advisory Council approval
08/03/2005 Medical Director review
08/16/2005 Medical Policy Committee review. Format revision. Appendix A added Coverage eligibility unchanged
08/24/2005 Managed Care Advisory Council approval
07/07/2006 Format revision including addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/02/2006 Medical Director review
08/09/2006 Medical Policy Committee approval. Background and rationale/source updated to reflect current literature review.
07/10/2007 Medical Director review
07/18/2007 Medical Policy Committee approval. Coverage eligibility unchanged.
07/02/2008 Medical Director review
07/16/2008 Medical Policy Committee review. Older WHO/REAL and IWF classification schemes replaced by updated WHO/REAL classification and Ann Arbor staging schemes. Minor, nonsubstantive wording changes made to the Policy statements to de-emphasize the older classification systems; “peripheral T-cell lymphoma (PTCL) at any stage of disease” added as investigational indication. Information about non-myeloablative (RIC) regimens added. “High-Dose Chemotherapy” removed from policy title.
07/02/2009 Medical Director review
07/22/2009 Medical Policy Committee review. Policy statement revised to indicate that autologous SCT may be considered medically necessary in some cases of mantle cell lymphoma and that reduced-intensity chemotherapy allogeneic SCT may be medically necessary under specific conditions.
07/01/2010 Medical Policy Committee approval
07/21/2010 Medical Policy Implementation Committee approval. No change to coverage.
08/04/2011 Medical Policy Committee approval
08/17/2011 Medical Policy Implementation Committee approval. Policy statements revised to specifically break out mantle cell lymphoma (investigational statements added for
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autologous as salvage therapy and allogeneic to consolidate a first remission and medically necessary statement added for allogeneic as salvage therapy) and peripheral T-cell lymphoma (added statements as medically necessary for autologous to consolidate first remission in specific situations and autologous and allogeneic as salvage therapy, and as investigational regarding allogeneic HSCT to consolidate a first complete remission).

08/02/2012  Medical Policy Committee review
08/15/2012  Medical Policy Implementation Committee approval. Coverage eligibility statement clarification that peripheral T-cell lymphomas encompass mature T-cell and NK-cell neoplasms.
03/04/2013  Coding updated
08/01/2013  Medical Policy Committee review
08/21/2013  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/04/2014  Medical Policy Committee review
08/03/2015  Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015  Medical Policy Committee review
10/06/2016  Medical Policy Committee review
10/19/2016  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017  Coding update: Removing ICD-9 Diagnosis Codes
10/05/2017  Medical Policy Committee review
10/18/2017  Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/04/2018  Medical Policy Committee review
10/03/2019  Medical Policy Committee review
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Next Scheduled Review Date: 10/2020

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| ICD-10 Diagnosis | C82.00-C82.99, C83.00-C83.99, C84.40-C84.99, C84.A0-C84.A9, C84.Z0-C84.Z9, C85.10-C85.99, C86.0-C86.66, C88.4 |

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