Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062
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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 individuals with non-Hodgkin lymphoma (NHL) B-cell subtypes considered 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 individuals 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

- To consolidate a first complete remission (CR) in individuals 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 Individuals 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 Individuals with Non-Hodgkin Lymphoma (NHL) B-Cell Subtypes:
Based on review of available data, the Company may consider individuals 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 individuals 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 transformed 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 individuals 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 Individuals 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).

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.****

For individuals with hepatosplenic T-cell lymphoma:
Based on review of available data, the Company may consider Allogenic HCT to consolidate a first CR or partial response to be **eligible for coverage.****

Based on review of available data, the Company may consider Autologous HCT to consolidate a first response if a suitable donor is not available or for individuals who are ineligible for allogeneic HCT 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 individuals 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 individuals with any stage, grade, or subtype of non-Hodgkin lymphoma (NHL) to be **investigational.***

For Individuals 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 Individuals 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.***

***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.*

For individuals with hepatosplenic T-cell lymphoma:
Based on review of available data, the Company considers autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) to be **investigational.***

Policy Guidelines

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
Reduced-intensity conditioning (RIC) would be considered an option in individuals 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 individuals 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 individuals 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 2 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 individuals with refractory or relapsed disease. For individuals with peripheral T-cell lymphoma, salvage therapy includes individuals 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 complete response with first-line induction chemotherapy. For mantle cell lymphoma, salvage therapy includes individuals with progressive disease with first-line induction chemotherapy (refractory disease) or in individuals who relapse after a complete or partial response after initial induction chemotherapy, or individuals 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

Throughout the years, the methods to classify the various types of lymphomas have been modified as technology and understanding of the role of genetics and immunology have increased. The historical table of classifying NHL by the International Working Formulation (IWF) had been updated by the Revised European American Lymphoma (REAL) classification. Subsequently, the classification has been updated as a result of collaboration between the European and American hematology and pathology societies and World Health Organization (WHO). For clinical utility, NHL can also be divided into indolent or aggressive lymphomas (NCI, 2021). The use of a particular

classification is based on the practitioner's preference. A widely utilized tool as a prognostic indicator for NHL is the International Prognostic Indicator. The index was developed based on clinical characteristics to predict the outcome of aggressive NHL.

Individuals with indolent lymphoma may experience a relapse with a more aggressive histology. Documentation of conversion to a more aggressive histology requires an appropriate change to a therapy applicable to that histologic type. Histologic conversions or transformations are typically treated with the regimens prescribed for aggressive NHL.

B-cell Lymphomas (NCCN guidelines v 5.2023):

- Burkitt Lymphoma
- Castleman Disease
- Diffuse Large B-Cell Lymphoma
- Extranodal Marginal Zone Lymphoma of Nongastric Sites (Noncutaneous)
- Extranodal Marginal Zone Lymphoma of the Stomach
- Follicular Lymphoma (grade 1-2)
- High-Grade B-Cell Lymphomas
- Histologic Transformation of Indolent Lymphomas to Diffuse Large B-Cell Lymphoma
- HIV-Related B-Cell Lymphomas
- Lymphoblastic Lymphoma
- Mantle Cell Lymphoma
- Nodal Marginal Zone Lymphoma
- Post-Transplant Lymphoproliferative Disorders
- Primary Mediastinal Large B-Cell Lymphoma
- Splenic Marginal Zone Lymphoma

T-cell Lymphomas (NCCN guidelines v 1.2023):

- Adult T-Cell Leukemia/Lymphoma
- Breast Implant-Associated ALCL
- Extranodal NK/T-Cell Lymphomas
- Hepatosplenic T-Cell Lymphoma
- Peripheral T-Cell Lymphomas

- T-Cell Large Granular Lymphocytic Leukemia
- T-Cell Prolymphocytic Leukemia

Modified REAL Classification of Lymphoproliferative Diseases (NCI, 2023): Non-Hodgkin indolent lymphoma/leukemia

- Follicular lymphoma.
- Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia).
- Marginal zone lymphoma.
- Splenic marginal zone lymphoma.
- Primary cutaneous anaplastic large cell lymphoma.

Non-Hodgkin aggressive lymphoma/leukemia

- Diffuse large B-cell lymphoma.
- Mediastinal large B-cell lymphoma (primary mediastinal large B-cell lymphoma).
- Follicular large cell lymphoma.
- Anaplastic large cell lymphoma.
- Extranodal NK–/T-cell lymphoma.
- Lymphomatoid granulomatosis.
- Angioimmunoblastic T-cell lymphoma.
- Peripheral T-cell lymphoma.
- Enteropathy-type intestinal T-cell lymphoma.
- Intravascular large B-cell lymphoma (intravascular lymphomatosis).
- Burkitt lymphoma/diffuse small noncleaved-cell lymphoma.
- Lymphoblastic lymphoma.
- Adult T-cell leukemia/lymphoma.
- Mantle cell lymphoma.
- Polymorphic post transplantation lymphoproliferative disorder.
- True histiocytic lymphoma.
- Primary effusion lymphoma.
- Plasmablastic lymphoma.

International Prognostic Index (IPI)

- Age greater than 60 years
- Serum lactate dehydrogenase (LDH) concentration greater than normal
- ECOG performance status equal to 2
- Ann Arbor clinical stage III or IV
- Number of involved extranodal disease sites greater than 1

In this system, one point is given for each of the above characteristics present in the individual, for a total score ranging from zero to five, representing increasing degrees of risk:

- Low risk. IPI score of zero or one (0 to 1)
- Low intermediate risk. IPI score of two (2)
- High intermediate risk. IPI score of three (3)
- High risk. IPI score of four or five (4 to 5)

Age adjusted IPI

For this score, all of the prognostic factors listed above, with the exception of age and number of extranodal sites, were given one point, for a score ranging from zero to three, representing increased degrees of risk:

- Low risk. Age-adjusted IPI score of zero
- Low intermediate risk. Age-adjusted IPI score of one
- High intermediate risk. Age-adjusted IPI score of two
- High risk. Age-adjusted IPI score of three

ECOG Performance Status: A scale used to determine the individual's level of functioning:

0= Fully active, able to carry on all pre-disease performance without restriction
1= Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2= Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3= Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4= Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5= Dead

The Ann Arbor staging system is commonly used for individuals with NHL.

- Stage I: involvement of a single lymph node region (I) or localized involvement of a single extralymphatic organ or site (IE).
- Stage II: involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of a single associated extralymphatic organ or site and its regional lymph nodes with or without other lymph node regions on the same side of the diaphragm (IIE).
- Stage III: involvement of lymph node regions on both sides of the diaphragm (III) that may also be accompanied by localized involvement of an extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS+E).
- Stage IV: disseminated (multifocal) involvement of 1 or more extralymphatic sites with or without associated lymph node involvement or isolated extralymphatic organ involvement with distant (nonregional) nodal involvement.

Treatment for Non-Hodgkin Lymphoma

Hematopoietic Cell Transplantation

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

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

Conditioning for Hematopoietic Cell Transplantation
Conventional Conditioning
The conventional ("classical") practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of the initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to individuals who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of the bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

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

convert to full-donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

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

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Hematopoietic cell transplantation (HCT) refers to a procedure by which hematopoietic stem cells are infused to restore bone marrow function in cancer individuals who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). 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.

Summary of Evidence

For individuals who have indolent B-cell non-Hodgkin lymphoma (NHL) who receive autologous hematopoietic cell transplant (HCT) as first-line therapy, the evidence includes observational studies, randomized controlled trials (RCTs), and systematic reviews. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), change in disease status, morbid events, and treatment-related mortality and morbidity. The RCTs have not shown a survival advantage with HCT as first-line therapy for indolent B-cell lymphomas; however, RCTs have shown a survival benefit

for relapsed disease. Observational studies have shown similar results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have aggressive B-cell NHL, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first complete remission (CR), the evidence includes RCTs and a systematic review. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the RCTs offer conflicting results, some data have revealed an OS benefit in individuals with aggressive B-cell lymphomas (at high- or high-intermediate risk of relapse) who receive HCT to consolidate a first CR. The RCTs of HCT for relapsed aggressive B-cell lymphomas have also shown an OS benefit with the previously described approach. Results of a retrospective study comparing autologous and allo-HCT for relapsed or refractory B-cell NHL showed more positive outcomes for autologous HCTs. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have NHL, excluding MCL, who receive tandem autologous and allo-HCT, the evidence includes several nonrandomized trials. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No RCTs have been conducted on the use of tandem HCT for the treatment of NHL, and the published evidence comprises of a limited number of individuals. Presently, conclusions on the use of tandem transplants cannot be made about autologous and allo-HCT. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series and RCTs. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Case series and RCTs 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. Allo-HCT has shown prolonged disease control in the relapsed or refractory setting. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous or allo-HCT, the evidence mainly includes prospective trials and case reports/series. 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 individuals; moreover, the patient populations were heterogeneous and included good- and poor-risk individuals 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 3 types of individuals: 1 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 individuals with PTCL not otherwise specified). For first-line therapy, autologous and allo-HCT were compared in a phase 3 trial, and there were comparable OS and PFS rates between the two groups. Results from recent phase 2 studies with autologous HCT as consolidation offers the best survival outcomes for individuals with high-risk features; RCTs to confirm this have not been performed. A single retrospective registry study showed a potential survival benefit among individuals treated with allo-HCT in the front-line setting; however, prospective studies are not available. Similarly, high-dose chemotherapy plus consolidation with autologous HCT as the first-line therapy for adults with nodal PTCL demonstrated improved OS and progression-free (PFS) in a systematic review. Individuals 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 an improvement in the net health outcome.

For individuals who have hepatosplenic T-cell lymphoma (HSTCL) who receive autologous or allo-HCT as consolidation therapy after first response (complete or partial), the evidence includes observational studies and systematic reviews. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Two meta-analyses using patient-level data found that consolidation therapy with HCT improves survival in individuals with HSTCL. Two small, retrospective studies have shown similar results. The evidence is sufficient to determine that the technology results in an 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.

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 individuals 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 individuals with non-Hodgkin lymphoma who do not qualify for a myeloablative allogeneic HCT. One reviewer responded on the medical necessity of HCT in individuals 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 1 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 individuals is coming into question.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines on B-cell lymphomas (v6.2023) include the following recommendations:

- For follicular lymphoma, marginal zone lymphomas, and mantle cell lymphoma, recommend allogeneic HCT as second-line consolidation therapy in select cases, which include mobilization failures and persistent bone marrow involvement. NCCN does note that with recent approval of CART T-cell therapy for relapsed/refractory MCL, allogeneic HCT has been deferred to disease relapse following multiple prior therapies in many NCCN member institutions.
- For DLBCL, "[a]llogeneic HCT should be considered in selected patients with mobilization failures and persistent bone marrow involvement or lack of adequate response to second-line therapy, though patients should be in CR or near CR at the time of transplant."
- For Burkitt lymphoma, allogeneic HCT is an option for selected patients who achieve a complete or partial response to second-line therapy.

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v1.2023) include the following recommendations:
For peripheral T-cell lymphoma: "Second-line systemic 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."

For adult T-cell leukemia/lymphoma:

- "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."

For T-cell Prolymphocytic Leukemia: "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."

For hepatosplenic T-Cell Lymphoma (HSTCL):

- "Consolidation therapy with allogeneic HCT is recommended for eligible patients with complete response or partial response after initial induction therapy or second-line therapy. Consolidation therapy with autologous HCT can be considered if a suitable donor is not available or for patients who are ineligible for allogeneic HCT."
- "Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT."
- "Few studies have reported improved survival outcomes with autologous or allogeneic HCT as consolidation therapy for patients with disease in first or second remission. Some studies have also reported that graft-versus-lymphoma effect associated with allogeneic HCT may result in long-term survival in a significant proportion of patients with HSTCL and active disease at the time of transplant was not necessarily associated with poor outcomes."
- "The goal of initial therapy is to induce complete or near complete response to allow successful bridging to HCT, preferably an allogeneic HCT."

The American Society of Transplantation and Cellular Therapy

In 2021, the American Society of Transplantation and Cellular Therapy (ASTCT), Center of International Blood and Marrow Transplant Research (CIBMTR), and the European Society for Blood and Marrow Transplantation (EBMT) formulated consensus recommendations regarding autologous HCT, allogeneic HCT, and chimeric antigen receptor (CAR) T-cell therapy for individuals with MCL. The panel of experts, consisting of physicians and investigators, recommended the use of autologous HCT as consolidation therapy in newly diagnosed MCL individuals (without TP53 mutation or bi-allelic deletion) who are in complete or partial remission after first-line therapies.

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The ASTCT Committee on Practice Guidelines published guidance on transplantation and cellular therapies in Diffuse Large B Cell Lymphoma (DLBCL) in 2023. The committee made the following recommendations:

- "The panel does not recommend autologous HCT in DLBCL (regardless of IPI score) as consolidation in complete remission after first-line (R-CHOP or similar) therapy." Grading: A
- "Autologous HCT may be considered for eligible patients with DLBCL with secondary CNS involvement at diagnosis achieving complete remission and with undetectable CNS disease after first-line therapy." Grading: C
- "The panel recommends consolidation with autologous HCT for eligible primary CNS lymphoma patients in CR1." Grading: A
- "In DLBCL patients with early relapse who achieve a complete remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients." Grading: B
- "In DLBCL patients with early relapse who achieve a partial remission with salvage therapy, the panel considers autologous HCT an acceptable consolidation therapy in eligible patients." Grading: B
- "In DLBCL patients with late relapse, the panel recommends autologous HCT consolidation therapy in eligible patients who have achieved a complete or partial remission after second-line therapies." Grading: A
- "The panel recommends allogeneic HCT in eligible DLBCL patients relapsing/progressing after CAR-T therapy if they achieve a complete or partial remission with subsequent antilymphoma therapies." Grading: C
- "The panel recommends allogeneic HCT in eligible relapsed or refractory DLBCL patients after autologous HCT failure in regions without access to CAR-T therapy, and in those with CAR T cell manufacturing failure, ideally after achieving a complete or partial remission with subsequent antilymphoma therapies." Grading: C

Grading of recommendations: A, There is good research-based evidence to support the recommendation; B, There is fair research-based evidence to support the recommendation; C, The recommendation is based on expert opinion and panel consensus; X, There is evidence of harm from this intervention.

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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 individuals with:

- Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte 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 individuals that fit the following requirements:

- Newly diagnosed or responsive multiple myeloma. This includes those individuals 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 individuals 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.

Other currently unpublished trials that might influence this review are listed in Table 1.

Table 1. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01827605	A Phase III Multicenter,Randomized Study Comparing Consolidation With 90yttrium-Labeled Ibritumomab Tiuxetan (Zevalin®)‡ Radioimmunotherapy Vs Autologous Stem Cell Transplantation (ASCT) in Patients With Relapsed/Refractory Follicular Lymphoma (FL) Aged 18-65 Years	159	Jan 2024
NCT02881086	Treatment Optimization in Adult Patients With Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma by Individualised, Targeted and Intensified Treatment - a Phase IV-trial With a Phase III-part to Evaluate Safety and Efficacy of Nelarabine in T-ALL Patients	1000	Jul 2025
NCT00882895	Tandem Stem Cell Transplantation for Non-Hodgkin's Lymphoma	18	Jun 2028
NCT03267433	A Randomized Phase III Trial of Consolidation With Autologous Hematopoietic Cell Transplantation Followed by Maintenance Rituximab vs. Maintenance Rituximab Alone for Patients With Mantle Cell Lymphoma in Minimal	689	Jan 2032

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Residual Disease-Negative First Complete Remission		
Unpublished			

NCT: national clinical trial.

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Policy History

Original Effective Date: 01/28/2002
Current Effective Date: 11/11/2024

Policy # 00062
Original Effective Date: 01/28/2002
Current Effective Date: 11/11/2024

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
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 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
09/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
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

10/17/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/03/2019	Medical Policy Committee review
10/09/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/01/2020	Medical Policy Committee review
10/07/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. New policy statements added for hepatosplenic T-cell lymphoma. "Based on review of available data, the Company may consider Allogenic HCT to consolidate a first CR or partial response to be eligible for coverage" and "Based on review of available data, the Company may consider Autologous HCT to consolidate a first response if a suitable donor is not available or for individuals who are ineligible for allogeneic HCT to be eligible for coverage." Added investigational statement: 'Based on review of available data, the Company considers autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) to be investigational." Background and NCCN guidelines updated and added staging systems.
10/03/2024	Medical Policy Committee review
10/08/2024	Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 10/2025

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38232, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.