

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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.

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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.****

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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**.*

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

Policy Guidelines

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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 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 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 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.

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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 3.2025):

- Burkitt Lymphoma
- Classic Follicular Lymphoma
- Diffuse Large B-Cell Lymphoma (DLBCL)
- Extranodal Marginal Zone Lymphoma of Nongastric Sites (Noncutaneous)
- Extranodal Marginal Zone Lymphoma of the Stomach
- 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 2.2025):

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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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

International Prognostic Index (IPI)

- Age greater than or equal to 60 years
- Serum lactate dehydrogenase (LDH) concentration greater than normal
- ECOG performance status 2-4
- 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).

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- 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 patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allogeneic HCT [allo-HCT]). These cells can be harvested from bone marrow, peripheral blood, or 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 patients who are sufficiently medically fit to tolerate substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

required to minimize graft rejection and graft-versus-host disease (GVHD), which increases susceptibility to opportunistic infections.

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

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation

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

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 regulations, other plan medical policies, and accredited national guidelines.

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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 [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 patients 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 patients. 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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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 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 3 types of patients: 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 patients 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 patients with high-risk features; RCTs to confirm this have not been performed. A single retrospective registry study showed a potential survival benefit among patients 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 2 systematic reviews. 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 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 patients with HSTCL. Two small, retrospective studies have shown similar results. A third small, retrospective study showed no significant differences in OS or PFS between allo-HCT and auto-HCT, but the

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

achievement of CR at the time of HCT was associated with improved OS in auto-HCT recipients. 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 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 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 patients 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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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 (v3.2024) include the following recommendations:

- For follicular lymphoma, marginal zone lymphomas, and mantle cell lymphoma, recommend allogeneic HCT as third-line consolidation therapy in select cases, which include mobilization failures and persistent bone marrow involvement. NCCN does note that with approval of CART T-cell therapy for relapsed/refractory mantle cell lymphoma, allogeneic HCT has been deferred to disease relapse following multiple prior therapies in many NCCN member institutions.
- For Diffuse Large B Cell Lymphoma (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 [complete response] 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 (v1.2025) include the following recommendations:

For peripheral T-cell lymphoma:

For first-line consolidation, "Autologous HCT is a reasonable treatment option only in patients with disease responding to induction therapy (although it is associated with a high relapse rate)..Longer follow-up and preferably data from a prospective randomized trial are necessary to evaluate the impact of first-line consolidation therapy with autologous HCT on time-to-treatment failure and overall survival (OS) outcomes."

Relapsed/refractory disease: "Second-line systemic therapy followed by consolidation with autologous or allogeneic HCT for those with a CR or [partial response] PR is recommended for patients who are candidates for transplant. Localized relapse (limited to one or two sites) may be treated with [involved-site radiation therapy] ISRT before or after autologous HCT. Allogeneic HCT, when feasible, should be considered for the majority of patients with relapsed/refractory disease. Autologous HCT may be an appropriate option, particularly those with [anaplastic lymphoma kinase-anaplastic large-cell lymphomas] ALCL and for selected patients with other subtypes with chemosensitive relapsed disease.

For adult T-cell leukemia/lymphoma:

- “Allogeneic HCT should be considered (if a donor is available) for patients with high-risk chronic subtype, acute or lymphoma subtype that is responding to first-line or second-line

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

therapy. Among patients with acute and lymphoma subtypes, the modified prognostic index (discussed above) identified allogeneic HCT as a statistically significant favorable prognostic factor for OS for patients with intermediate and high-risk score." "

For T-cell Prolymphocytic Leukemia: "Allogeneic HCT should be considered for patients who achieve a CR or PR following initial therapy. 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. Autologous HCT has also been shown to provide some benefit for patients when an allogeneic HCT is not feasible. 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 patients with MCL.⁷⁸ The panel of experts, consisting of physicians and investigators, recommended the use of autologous HCT as consolidation therapy in newly diagnosed MCL patients (without TP53 mutation or bi-allelic deletion) who are in complete or partial remission after first-line therapies.

The ASTCT Committee on Practice Guidelines published guidance on transplantation and cellular therapies in 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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- "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.

In 2024, ASTCT and EBMT formulated consensus recommendations for HCT and cellular therapies in follicular lymphoma. The following consensus statements were made:

Front-line setting (ie, HCT following first-line chemotherapy):

- The panel does not recommend autologous or allogeneic HCT as consolidation therapy in eligible follicular lymphoma patients in complete or partial remission after first-line therapies.

Early first relapse/progression (ie, first relapse occurred on or within 24 months from receiving front-line chemoimmunotherapy (post-operative day [POD] 24) and without evidence of histological transformation):

- The panel recommends autologous HCT as an option for consolidation therapy in eligible, relapsed POD24 follicular lymphoma patients who have achieved complete or partial remission after second-line therapies.

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- The panel does not recommend autologous HCT as consolidation therapy in eligible, relapsed follicular lymphoma patients who do not achieve complete or partial remission after second or subsequent line therapies.
- The panel does not recommend allogeneic HCT as consolidation therapy in eligible, relapsed POD24 follicular lymphoma patients who have achieved complete or partial remission after second-line therapies.

Late first relapse, second relapse, and beyond settings:

- The panel does not recommend autologous HCT as consolidation therapy in eligible, relapsed follicular lymphoma patients who did not achieve complete or partial remission after second or subsequent line therapies.
- The panel does not recommend autologous HCT as consolidation therapy in eligible, relapsed follicular lymphoma patients who have relapsed after CAR T-cell therapy and did not achieve complete or partial remission to the most recent anti-lymphoma treatment.
- The panel recommends considering allogeneic HCT as consolidation therapy in eligible, relapsed follicular lymphoma patients who have received 3 or more lines of systemic therapy and are in one of the following clinical scenarios:
 - Develop disease relapse early post-autologous HCT and do not have access to CAR T-cell therapy
 - Develop disease relapse post-CAR T-cell therapy
 - Develop therapy-related myeloid neoplasm or bone marrow failure syndrome.
- The panel recommends that allogeneic HCT be considered as a salvage/consolidation therapy only in patients who have achieved complete or partial remission to the most recent anti-lymphoma treatment. Candidacy for allogeneic HCT is dependent on good performance status and adequate organ function.

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:

- 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.

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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

- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
- Adequate cardiac, renal, pulmonary, and hepatic function.

c) Effective ... 2005, when recognized clinical risk factors are employed to select patients for transplantation, high-dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:

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

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
<i>Ongoing</i>			
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	1000	Jul 2025

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

NCT No.	Trial Name	Planned Enrollment	Completion Date
	Safety and Efficacy of Nelarabine in T-ALL Patients		
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 Residual Disease-Negative First Complete Remission	689	Jan 2027

NCT: national clinical trial.

References

1. National Cancer Institute. Adult Non-Hodgkin Lymphoma Treatment (PDQ)Health Professional Version. 2022; <http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional>.
2. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. Sep 01 1994; 84(5): 1361-92. PMID 8068936
3. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November, 1997. Ann Oncol. Dec 1999; 10(12): 1419-32. PMID 10643532
4. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. Jul 2022; 36(7): 1720-1748. PMID 35732829
5. American Cancer Society. Non-Hodgkin Lymphoma (Adults). <https://www.cancer.org/cancer/non-hodgkin-lymphoma/about.html>
6. Laport GG. The role of hematopoietic cell transplantation for follicular non-Hodgkin's lymphoma. Biol Blood Marrow Transplant. Jan 2006; 12(1 Suppl 1): 59-65. PMID 16399587
7. Al Khabori M, de Almeida JR, Guyatt GH, et al. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. Jan 04 2012; 104(1): 18-28. PMID 22190633

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

8. Schaaf M, Reiser M, Borchmann P, et al. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. *Cochrane Database Syst Rev*. Jan 18 2012; 1(1): CD007678. PMID 22258971
9. Ladetto M, De Marco F, Benedetti F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. *Blood*. Apr 15 2008; 111(8): 4004-13. PMID 18239086
10. Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Blood*. Oct 15 2006; 108(8): 2540-4. PMID 16835383
11. Deconinck E, Foussard C, Milpied N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. *Blood*. May 15 2005; 105(10): 3817-23. PMID 15687232
12. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. *Blood*. Nov 01 2004; 104(9): 2667-74. PMID 15238420
13. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. *J Clin Oncol*. Nov 01 2003; 21(21): 3918-27. PMID 14517188
14. Bozkaya Y, Uncu D, Dağdaş S, et al. Evaluation of Lymphoma Patients Receiving High-Dose Therapy and Autologous Stem Cell Transplantation: Experience of a Single Center. *Indian J Hematol Blood Transfus*. Sep 2017; 33(3): 361-369. PMID 28824238
15. Jiménez-Ubieto A, Grande C, Caballero D, et al. Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure who reach complete response after rescue treatment. *Hematol Oncol*. Dec 2018; 36(5): 765-772. PMID 30129233
16. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. Sep 30 1993; 329(14): 987-94. PMID 8141877
17. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. *Blood*. Sep 01 2004; 104(5): 1258-65. PMID 15126323
18. Greb A, Bohlius J, Schiefer D, et al. High-dose chemotherapy with autologous stem cell transplantation in the first line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. *Cochrane Database Syst Rev*. Jan 23 2008; 2008(1): CD004024. PMID 18254036
19. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol*. Mar 1997; 15(3): 1131-7. PMID 9060555
20. Kaiser U, Uebelacker I, Abel U, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for "aggressive" lymphoma. *J Clin Oncol*. Nov 15 2002; 20(22): 4413-9. PMID 12431962
 21. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. *J Natl Cancer Inst*. Jan 03 2001; 93(1): 22-30. PMID 11136838
 22. Sweetenham JW, Santini G, Qian W, et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission therapy for adult patients with lymphoblastic lymphoma: results of a randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. *J Clin Oncol*. Jun 01 2001; 19(11): 2927-36. PMID 11387366
 23. Fisher RI. Autologous stem-cell transplantation as a component of initial treatment for poor-risk patients with aggressive non-Hodgkin's lymphoma: resolved issues versus remaining opportunity. *J Clin Oncol*. Nov 15 2002; 20(22): 4411-2. PMID 12431961
 24. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non-Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a groupe d'Etude des lymphomes de l'Adulte study. *J Clin Oncol*. Aug 2000; 18(16): 3025-30. PMID 10944137
 25. Fisher RI. Autologous bone marrow transplantation for aggressive non-Hodgkin's lymphoma: lessons learned and challenges remaining. *J Natl Cancer Inst*. Jan 03 2001; 93(1): 4-5. PMID 11136829
 26. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. *Biol Blood Marrow Transplant*. 2001; 7(6): 308-31. PMID 11464975
 27. Kimby E, Brandt L, Nygren P, et al. A systematic overview of chemotherapy effects in aggressive non-Hodgkin's lymphoma. *Acta Oncol*. 2001; 40(2-3): 198-212. PMID 11441932
 28. Philip T, Biron P. High-dose chemotherapy and autologous bone marrow transplantation in diffuse intermediate- and high-grade non-Hodgkin lymphoma. *Crit Rev Oncol Hematol*. Feb 2002; 41(2): 213-23. PMID 11856597
 29. Betticher DC, Martinelli G, Radford JA, et al. Sequential high dose chemotherapy as initial treatment for aggressive sub-types of non-Hodgkin lymphoma: results of the international randomized phase III trial (MISTRAL). *Ann Oncol*. Oct 2006; 17(10): 1546-52. PMID 16888080
 30. 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, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMOH report. *Acta Haematol*. 2006; 115(1-2): 15-21. PMID 16424644

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

31. Olivieri A, Santini G, Patti C, et al. Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin's lymphoma: long-term results by the NHLCSG. *Ann Oncol.* Dec 2005; 16(12): 1941-8. PMID 16157621
32. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* Oct 31 2013; 369(18): 1681-90. PMID 24171516
33. Casasnovas RO, Ysebaert L, Thieblemont C, et al. FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study. *Blood.* Sep 14 2017; 130(11): 1315-1326. PMID 28701367
34. Strüßmann T, Fritsch K, Baumgarten A, et al. Favourable outcomes of poor prognosis diffuse large B-cell lymphoma patients treated with dose-dense Rituximab, high-dose Methotrexate and six cycles of CHOP-14 compared to first-line autologous transplantation. *Br J Haematol.* Sep 2017; 178(6): 927-935. PMID 28643323
35. Qualls D, Sullivan A, Li S, et al. High-dose Thiotepa, Busulfan, Cyclophosphamide, and Autologous Stem Cell Transplantation as Upfront Consolidation for Systemic Non-Hodgkin Lymphoma With Synchronous Central Nervous System Involvement. *Clin Lymphoma Myeloma Leuk.* Dec 2017; 17(12): 884-888. PMID 28870642
36. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. *Hematology Am Soc Hematol Educ Program.* 2009: 523-31. PMID 20008237
37. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. *N Engl J Med.* Dec 07 1995; 333(23): 1540-5. PMID 7477169
38. Fujita N, Kobayashi R, Atsuta Y, et al. Hematopoietic stem cell transplantation in children and adolescents with relapsed or refractory B-cell non-Hodgkin lymphoma. *Int J Hematol.* Apr 2019; 109(4): 483-490. PMID 30701466
39. Monjanel H, Deconinck E, Perrodeau E, et al. Long-term follow-up of tandem high-dose therapy with autologous stem cell support for adults with high-risk age-adjusted international prognostic index aggressive non-Hodgkin Lymphomas: a GOELAMS pilot study. *Biol Blood Marrow Transplant.* Jun 2011; 17(6): 935-40. PMID 21109011
40. Papadopoulos KP, Noguera-Irizarry W, Wiebe L, et al. Pilot study of tandem high-dose chemotherapy and autologous stem cell transplantation with a novel combination of regimens in patients with poor risk lymphoma. *Bone Marrow Transplant.* Sep 2005; 36(6): 491-7. PMID 16044139
41. Tarella C, Zanni M, Di Nicola M, et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early-intensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). *Leukemia.* Aug 2007; 21(8): 1802-11. PMID 17554382
42. Satwani P, Jin Z, Martin PL, et al. Sequential myeloablative autologous stem cell transplantation and reduced intensity allogeneic hematopoietic cell transplantation is safe and feasible in

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- children, adolescents and young adults with poor-risk refractory or recurrent Hodgkin and non-Hodgkin lymphoma. *Leukemia*. Feb 2015; 29(2): 448-55. PMID 24938649
43. Banks PM, Chan J, Cleary ML, et al. Mantle cell lymphoma. A proposal for unification of morphologic, immunologic, and molecular data. *Am J Surg Pathol*. Jul 1992; 16(7): 637-40. PMID 1530105
44. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*. Jan 15 2008; 111(2): 558-65. PMID 17962512
45. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: results of a prospective randomized trial of the European MCL Network. *Blood*. Apr 01 2005; 105(7): 2677-84. PMID 15591112
46. Dreyling M, Doorduijn J, Giné E, et al. Ibrutinib combined with immunochemotherapy with or without autologous stem-cell transplantation versus immunochemotherapy and autologous stem-cell transplantation in previously untreated patients with mantle cell lymphoma (TRIANGLE): a three-arm, randomised, open-label, phase 3 superiority trial of the European Mantle Cell Lymphoma Network. *Lancet*. May 25 2024; 403(10441): 2293-2306. PMID 38705160
47. Zoellner AK, Unterhalt M, Stilgenbauer S, et al. Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial. *Lancet Haematol*. Sep 2021; 8(9): e648-e657. PMID 34450102
48. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. *Leuk Lymphoma*. Jun 2008; 49(6): 1062-73. PMID 18452065
49. García-Noblejas A, Cannata-Ortiz J, Conde E, et al. Autologous stem cell transplantation (ASCT) in patients with mantle cell lymphoma: a retrospective study of the Spanish lymphoma group (GELTAMO). *Ann Hematol*. Aug 2017; 96(8): 1323-1330. PMID 28536895
50. Metzner B, Müller TH, Casper J, et al. Long-term outcome in patients with mantle cell lymphoma following high-dose therapy and autologous stem cell transplantation. *Eur J Haematol*. Aug 2023; 111(2): 220-228. PMID 37094812
51. Villanueva ML, Vose JM. The role of hematopoietic stem cell transplantation in non-Hodgkin lymphoma. *Clin Adv Hematol Oncol*. Jul 2006; 4(7): 521-30. PMID 17147239
52. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. *J Clin Oncol*. Dec 01 2003; 21(23): 4407-12. PMID 14645431
53. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. *Blood*. Dec 01 2004; 104(12): 3535-42. PMID 15304387
54. Krüger WH, Hirt C, Basara N, et al. Allogeneic stem cell transplantation for mantle cell lymphoma-update of the prospective trials of the East German Study Group Hematology/Oncology (OSHO#60 and #74). *Ann Hematol*. Jun 2021; 100(6): 1569-1577. PMID 33829299

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

55. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. *Blood*. Apr 30 2009; 113(18): 4144-52. PMID 19168784
56. Geisler C. Mantle cell lymphoma: are current therapies changing the course of disease?. *Curr Oncol Rep*. Sep 2009; 11(5): 371-7. PMID 19679012
57. Zhai Y, Wang J, Jiang Y, et al. The efficiency of autologous stem cell transplantation as the first-line treatment for nodal peripheral T-cell lymphoma: results of a systematic review and meta-analysis. *Expert Rev Hematol*. Mar 2022; 15(3): 265-272. PMID 35152814
58. Girard L, Koh YJ, Koh LP, et al. Role of upfront autologous transplant for peripheral T-cell lymphoma patients achieving a complete remission with first-line therapy: a systematic review and meta-analysis. *Bone Marrow Transplant*. Jun 2024; 59(6): 838-848. PMID 38443704
59. Schmitz N, Truemper L, Bouabdallah K, et al. A randomized phase 3 trial of autologous vs allogeneic transplantation as part of first-line therapy in poor-risk peripheral T-NHL. *Blood*. May 13 2021; 137(19): 2646-2656. PMID 33512419
60. Reimer P. Impact of autologous and allogeneic stem cell transplantation in peripheral T-cell lymphomas. *Adv Hematol*. 2010; 2010: 320624. PMID 21253465
61. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. *Leukemia*. Sep 2006; 20(9): 1533-8. PMID 16871285
62. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. *Ann Oncol*. May 2008; 19(5): 958-63. PMID 18303032
63. Rodríguez J, Conde E, Gutiérrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T-cell lymphoma: a prospective study from The Gel-Tamo Study Group. *Eur J Haematol*. Jul 2007; 79(1): 32-8. PMID 17598836
64. Wang J, Wei L, Ye J, et al. Autologous hematopoietic stem cell transplantation may improve long-term outcomes in patients with newly diagnosed extranodal natural killer/T-cell lymphoma, nasal type: a retrospective controlled study in a single center. *Int J Hematol*. Jan 2018; 107(1): 98-104. PMID 28856590
65. Wu M, Wang F, Zhao S, et al. Autologous hematopoietic stem cell transplantation improves survival outcomes in peripheral T-cell lymphomas: a multicenter retrospective real-world study. *Ann Hematol*. Nov 2023; 102(11): 3185-3193. PMID 37700194
66. Mamez AC, Dupont A, Blaise D, et al. Allogeneic stem cell transplantation for peripheral T cell lymphomas: a retrospective study in 285 patients from the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). *J Hematol Oncol*. May 19 2020; 13(1): 56. PMID 32429979
67. Du J, Yu D, Han X, et al. Comparison of Allogeneic Stem Cell Transplant and Autologous Stem Cell Transplant in Refractory or Relapsed Peripheral T-Cell Lymphoma: A Systematic Review and Meta-analysis. *JAMA Netw Open*. May 03 2021; 4(5): e219807. PMID 34042995

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

68. Song KW, Mollee P, Keating A, et al. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. *Br J Haematol.* Mar 2003; 120(6): 978-85. PMID 12648067
69. Rodríguez J, Conde E, Gutiérrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. *Haematologica.* Aug 2007; 92(8): 1067-74. PMID 17640855
70. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. *J Clin Oncol.* Aug 20 2009; 27(24): 3951-8. PMID 19620487
71. Klebaner D, Koura D, Tzachanis D, et al. Intensive Induction Therapy Compared With CHOP for Hepatosplenic T-cell Lymphoma. *Clin Lymphoma Myeloma Leuk.* Jul 2020; 20(7): 431-437.e2. PMID 32284297
72. Rashidi A, Cashen AF. Outcomes of allogeneic stem cell transplantation in hepatosplenic T-cell lymphoma. *Blood Cancer J.* Jun 05 2015; 5(6): e318. PMID 26047388
73. Voss MH, Lunning MA, Maragulia JC, et al. Intensive induction chemotherapy followed by early high-dose therapy and hematopoietic stem cell transplantation results in improved outcome for patients with hepatosplenic T-cell lymphoma: a single institution experience. *Clin Lymphoma Myeloma Leuk.* Feb 2013; 13(1): 8-14. PMID 23107915
74. Tanase A, Schmitz N, Stein H, et al. Allogeneic and autologous stem cell transplantation for hepatosplenic T-cell lymphoma: a retrospective study of the EBMT Lymphoma Working Party. *Leukemia.* Mar 2015; 29(3): 686-8. PMID 25234166
75. Moustafa MA, Ramdial JL, Tsalatsanis A, et al. A US Multicenter Collaborative Study on Outcomes of Hematopoietic Cell Transplantation in Hepatosplenic T-Cell Lymphoma. *Transplant Cell Ther.* May 2024; 30(5): 516.e1-516.e10. PMID 38431075
76. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
77. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf.
78. Munshi PN, Hamadani M, Kumar A, et al. ASTCT, CIBMTR, and EBMT clinical practice recommendations for transplant and cellular therapies in mantle cell lymphoma. *Bone Marrow Transplant.* Dec 2021; 56(12): 2911-2921. PMID 34413469
79. Epperla N, Kumar A, Abutalib SA, et al. ASTCT Clinical Practice Recommendations for Transplantation and Cellular Therapies in Diffuse Large B Cell Lymphoma. *Transplant Cell Ther.* Sep 2023; 29(9): 548-555. PMID 37419325
80. Iqbal M, Kumar A, Dreger P, et al. Clinical Practice Recommendations for Hematopoietic Cell Transplantation and Cellular Therapies in Follicular Lymphoma: A Collaborative Effort on Behalf of the American Society for Transplantation and Cellular Therapy and the European

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- Society for Blood and Marrow Transplantation. Transplant Cell Ther. Sep 2024; 30(9): 832-843. PMID 38972511
81. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&DocID=110.23&list_type=ncd&bc=gAAAAAgAAAAAAA%3d%3d&.
82. NIH National Cancer Institute. Indolent B-Cell Non-Hodgkin Lymphoma Treatment (PDQ®)–Health Professional Version. May 14, 2025.
83. SEER Training Modules. Lymphoma: Morphology. U.S. National Institutes of Health, National Cancer Institute. <https://training.seer.cancer.gov/lymphoma/abstract-code-stage/morphology/real.html>
84. National Cancer Institute. NCCN International Prognostic Index (IPI) – Lymphoma. NAACCR Site-Specific Data Items (SSDI). Published May 31, 2024. https://apps.naacr.org/ssdi/input/lymphoma/intern_prog_index/

Policy History

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

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 Allogeneic 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.
10/02/2025	Medical Policy Committee review
10/08/2025	Medical Policy Implementation Committee approval. Coverage eligibility unchanged. NCCN guidelines updated.

Next Scheduled Review Date: 10/2026

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 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.

The responsibility for the content of Louisiana Blue Medical Policy Coverage Guidelines is with Louisiana Blue and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Louisiana Blue Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Louisiana Blue Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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 Delete codes effective 11/01/2025: 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

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

Policy # 00062

Original Effective Date: 01/28/2002

Current Effective Date: 11/01/2025

- 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.

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

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.

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.