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# MEDICAL POLICY – 8.01.529

# Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

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| BCBSA Ref. Policy: | 8.01.20 |
| Effective Date: | Apr. 1, 2025 |
| Last Revised: | Mar. 10, 2025 |
| Replaces: | 8.01.20 |

RELATED MEDICAL POLICIES:

| | |
|---|---|
| 8.01.15 | Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma |
| 8.01.24 | Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults |
| 8.01.25 | Hematopoietic Cell Transplantation for Autoimmune Diseases |
| 8.01.29 | Hematopoietic Cell Transplantation for Hodgkin Lymphoma |
| 8.01.511 | Hematopoietic Cell Transplantation for Solid Tumors of Childhood |
| 8.01.532 | Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors |
| 8.01.539 | Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms |

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POLICY CRITERIA | DOCUMENTATION REQUIREMENTS | CODING
RELATED INFORMATION | EVIDENCE REVIEW | REFERENCES | HISTORY

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## Introduction

A hematopoietic cell is an immature cell that can mature into different types of blood cells. Certain chemotherapy drugs can destroy the bone marrow, and bone marrow is where blood cells form. Infusing immature blood cells gives the body a chance to restore blood cell production in the bone marrow. When the immature blood cells are taken from the patient it's known as an autologous hematopoietic cell transplant (HCT). Using immature cells from a donor is known as an allogeneic HCT. This policy discusses when hematopoietic cell transplants may be considered medically necessary for non-Hodgkin lymphoma, a type of immune system cancer.

**Note:** The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for

providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

## Policy Coverage Criteria

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

| Indication | Coverage Statement |
|---|---|
| **Non-Hodgkin lymphoma (NHL) B-cell aggressive subtype (except mantle cell)** | **Myeloablative autologous, myeloablative allogeneic or reduced-intensity conditioning (RIC) allogeneic HCT with curative intent may be considered medically necessary:**<br>• As salvage therapy for individuals not in complete remission after a full course of first line chemotherapy induction<br>**OR**<br>• To achieve or consolidate a complete remission in chemotherapy sensitive first or subsequent relapse<br>**OR**<br>• To consolidate a complete remission in individuals with an age-adjusted International Prognostic Index (IPI) that predicts a high or high-intermediate risk of relapse |
| **Mantle cell NHL B-cell subtype** | **Autologous HCT may be considered medically necessary to consolidate a first remission of mantle cell NHL B-cell subtype.**<br><br>**Allogeneic and RIC allogeneic HCT are considered investigational to consolidate a first remission of mantle cell NHL B-cell subtype.**<br><br>**Allogeneic or RIC allogeneic HCT with curative intent may be considered medically necessary as salvage for individuals with mantle cell NHL B-cell subtype who are not in complete remission after first line chemotherapy.** |

| Indication | Coverage Statement |
|---|---|
| | **Myeloablative autologous HCT is considered investigational as salvage for individuals with mantle cell NHL B-cell subtype who are not in complete remission after first line chemotherapy.** |
| **NHL B-cell indolent subtypes** | **Myeloablative autologous, allogeneic, or RIC allogeneic HCT with curative intent may be considered medically necessary:**<br>• As salvage therapy for individuals not in complete remission after a full course of first line (induction) chemotherapy<br>**OR**<br>• To achieve or consolidate a complete remission in chemotherapy sensitive first or subsequent relapse (regardless of transformation)<br><br>**Myeloablative autologous, allogeneic, and RIC allogeneic HCT are considered investigational:**<br>• As initial therapy (without completion of a full course of standard induction chemotherapy) for all B-Cell NHL<br>**OR**<br>• To consolidate a first complete remission for low or low-intermediate IPI score diffuse large B-Cell NHL<br>**OR**<br>• To consolidate a first complete remission for indolent B-cell NHL |
| **Mature T-cell or NK (peripheral T-cell) lymphoma** | **Myeloablative autologous HCT may be considered medically necessary:**<br>• To consolidate a first complete remission in high-risk subtypes (see **Table 1** below)<br><br>**Myeloablative autologous, allogeneic, or reduced intensity conditioning allogeneic HCT may be considered medically necessary as salvage therapy.**<br><br>**Myeloablative and reduced intensity conditioning allogeneic HCT are considered investigational to consolidate a first complete remission.** |
| **Hepatosplenic T-cell lymphoma** | **Allogeneic HCT may be considered medically necessary to consolidate a first CR or partial response.** |



| Indication | Coverage Statement |
|---|---|
| | **Autologous HCT may be considered medically necessary to consolidate a first response if a suitable donor is not available or for individuals who are ineligible for allogeneic HCT.**<br><br>**Autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) is considered investigational.** |
| **Tandem transplants** | **Tandem transplants are considered investigational to treat individuals with any stage, grade, or subtype of NHL.** |

**Table 1: Allowable Treatment by NHL Type**

| NHL Type | Presenting Stage | Treatment Intent | Autologous HCT | Allogeneic HCT | RIC | Tandem Transplant |
|---|---|---|---|---|---|---|
| **B-Cell aggressive (not mantle)** | Not in CR post 1st Line | Salvage | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |
| | Chemo-sensitive 1st or later relapse | Consolidate (CR) | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |
| **High or high-intermediate IPI** | CR | Consolidate | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |
| **Mantle cell** | 1st Remission | Consolidate | Medically Necessary | Investigational | Investigational | Investigational |
| | Not in CR post 1st Line | Salvage | Investigational | Medically Necessary | Medically Necessary | Investigational |
| **Indolent** | CR | Consolidate | Investigational | Investigational | Investigational | Investigational |
| | Not in CR post 1st Line Chemo | Salvage | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |
| | Chemo-sensitive 1st or later relapse | Consolidate (CR) | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |

## Table 1: Allowable Treatment by NHL Type

| NHL Type | Presenting Stage | Treatment Intent | Autologous HCT | Allogeneic HCT | RIC | Tandem Transplant |
|---|---|---|---|---|---|---|
| **Mature T-cell or NK cell high risk** | 1st CR | Consolidate | Medically Necessary | Investigational | Investigational | Investigational |
| | Not CR post Chemo | Salvage | Medically Necessary | Medically Necessary | Medically Necessary | Investigational |
| **Mature T-cell or NK cell not high risk** | 1st CR | Consolidate | Investigational | Investigational | Investigational | Investigational |
| **All NHL low or low-intermediate IPI** | 1st CR | Consolidate | Investigational | Investigational | Investigational | Investigational |

## Additional Information

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

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

## Documentation Requirements

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

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

## Coding

| Code | Description |
|---|---|
| **CPT** | |
| 38230 | Bone marrow harvesting for transplantation; allogeneic |
| 38232 | Bone marrow harvesting for transplantation; autologous |
| 38240 | Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor |
| 38241 | Hematopoietic progenitor cell (HPC); autologous transplantation |
| **HCPCS** | |
| S2142 | Cord blood-derived stem-cell transplantation, allogeneic |
| S2150 | Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition |

**Note**: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

## Related Information

### Consideration of Age

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

### Definition of Terms

**Allogeneic HCT:** The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total -

body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient.

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

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

**Complete remission (CR)**: This is the disappearance of all the signs of cancer in response to treatment. Also called complete response.

**Consolidation therapy:** This is treatment that is given after cancer has disappeared following initial therapy with the goal of killing any cancer cells that may be left in the body. Also referred to as intensification therapy and post-remission therapy.

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

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

**Hematopoietic cell transplantation (HCT):** This refers to a procedure in which hematopoietic cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs with or without whole-body radiation therapy. Hematopoietic cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT).

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

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

**Reduced-intensity conditioning (RIC):** This refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments.

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

**Salvage therapy:** This 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 (e.g., 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.

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

**Transformation:** This term describes a lymphoma whose histologic pattern has evolved to a higher-grade lymphoma. Transformed lymphomas typically evolve from a nodular pattern to a diffuse pattern.

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

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

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

## Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health.
- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

# Evidence Review

## Description

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 from 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 cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease.

## Background

## Non-Hodgkin Lymphoma

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

and includes the incorporation of new immunophenotyping and genetic techniques. As a result, the Working Formulation has become outdated.

European and American pathologists proposed a new classification, the Revised European-American Lymphoma (REAL) Classification[2] and an updated version of the REAL system, the new World Health Organization (WHO) classification.[3] The WHO/REAL classification recognized three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2022 WHO classification (see **Table 2**).[4]

## Table 2. Updated WHO Classification (2022)

| **Tumour-like lesions with B-cell predominance** |
|---|
| Reactive B-cell-rich lymphoid proliferations that can mimic lymphoma[a] |
| IgG4-related disease[a] |
| Unicentric Castleman disease[a] |
| Idiopathic multicentric Castleman disease[a] |
| KSHV/HHV8-associated multicentric Castleman disease[a] |
| **Precursor B-cell neoplasms** |
| B-cell lymphoblastic leukaemias/lymphomas<br>• B-lymphoblastic leukaemia/lymphoma, NOS<br>• B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy[a]<br>• B-lymphoblastic leukaemia/lymphoma with hypodiploidy<br>• B-lymphoblastic leukaemia/lymphoma with iAMP21<br>• B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion[a]<br>• B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features[a]<br>• B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement[a]<br>• B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion[a]<br>• B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features[a]<br>• B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion[a]<br>• B-lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion[a]<br>• B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion[a]<br>• B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities |

| Mature B-cell neoplasms |
| --- |
| Pre-neoplastic and neoplastic small lymphocytic proliferations<br>• Monoclonal B-cell lymphocytosis<br>• Chronic lymphocytic leukaemia/small lymphocytic lymphoma |
| Splenic B-cell lymphomas and leukaemias<br>• Hairy cell leukaemia<br>• Splenic marginal zone lymphoma<br>• Splenic diffuse red pulp small B-cell lymphoma<br>• Splenic B-cell lymphoma/leukaemia with prominent nucleoli[a] |
| Lymphoplasmacytic lymphoma |
| Marginal zone lymphoma<br>• Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue<br>• Primary cutaneous marginal zone lymphoma[a]<br>• Nodal marginal zone lymphoma<br>• Paediatric marginal zone lymphoma<br>• Follicular lymphoma<br>• In situ follicular B-cell neoplasm[a]<br>• Follicular lymphoma<br>• Paediatric-type follicular lymphoma<br>• Duodenal-type follicular lymphoma |
| Cutaneous follicle centre lymphoma<br>• Primary cutaneous follicle centre lymphoma |
| Mantle cell lymphoma<br>• In situ mantle cell neoplasm[a]<br>• Mantle cell lymphoma<br>• Leukaemic non-nodal mantle cell lymphoma |
| Transformations of indolent B-cell lymphomas<br>• Transformations of indolent B-cell lymphomas[a] |
| Large B-cell lymphomas<br>• Diffuse large B-cell lymphoma, NOS<br>• T-cell/histiocyte-rich large B-cell lymphoma<br>• Diffuse large B-cell lymphoma/ high grade B-cell lymphoma with MYC and BCL2 rearrangements[a] |

- ALK-positive large B-cell lymphoma
- Large B-cell lymphoma with IRF4 rearrangement
- High-grade B-cell lymphoma with 11q aberrations[a]
- Lymphomatoid granulomatosis
- EBV-positive diffuse large B-cell lymphoma[a]
- Diffuse large B-cell lymphoma associated with chronic inflammation
- Fibrin-associated large B-cell lymphoma[a]
- Fluid overload-associated large B-cell lymphoma[a]
- Plasmablastic lymphoma
- Primary large B-cell lymphoma of immune-privileged sites[a]
- Primary cutaneous diffuse large B-cell lymphoma, leg type
- Intravascular large B-cell lymphoma
- Primary mediastinal large B-cell lymphoma
- Mediastinal grey zone lymphoma[a]
- High-grade B-cell lymphoma, NOS

Burkitt lymphoma

KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas

- Primary effusion lymphoma
- KSHV/HHV8-positive diffuse large B-cell lymphoma[a]
- KSHV/HHV8-positive germinotropic lymphoproliferative disorder[a]

Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation

- Hyperplasias arising in immune deficiency/dysregulation[a]
- Polymorphic lymphoproliferative disorders arising in immune deficiency/dysregulation[a]
- EBV-positive mucocutaneous ulcer
- Lymphomas arising in immune deficiency / dysregulation[a]
- Inborn error of immunity-associated lymphoid proliferations and lymphomas[a]

Hodgkin lymphoma

- Classic Hodgkin lymphoma
- Nodular lymphocyte predominant Hodgkin lymphoma

## Plasma cell neoplasms and other diseases with paraproteins

Monoclonal gammopathies

- Cold agglutinin disease[a]

| |
|---|
| • IgM monoclonal gammopathy of undetermined significance<br>• Non-IgM monoclonal gammopathy of undetermined significance<br>• Monoclonal gammopathy of renal significance[a] |
| Diseases with monoclonal immunoglobulin deposition<br>• Immunoglobulin-related (AL) amyloidosis[a]<br>• Monoclonal immunoglobulin deposition disease[a] |
| Heavy chain diseases<br>• Mu heavy chain disease<br>• Gamma heavy chain disease<br>• Alpha heavy chain disease |
| Plasma cell neoplasms<br>• Plasmacytoma<br>• Plasma cell myeloma<br>• Plasma cell neoplasms with associated paraneoplastic syndrome[a]<br>• POEMS syndrome<br>• TEMPI syndrome<br>• AESOP syndrome |

[a]Changes from 2016 WHO classification. AESOP: adenopathy and extensive skin patch overlying a plasmacytoma; ALK: anaplastic lymphoma kinase; EBV: Epstein-Barr virus; HHV: human herpes virus; KSHV: Kaposi's sarcoma-associated herpesvirus; NOS: not otherwise specified; POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes; TEMPI: telangiectasias, elevated erythropoietin level and erythrocytosis, monoclonal gammopathy, perinephric fluid collections, and intrapulmonary shunting.

In the US, B-cell lymphomas represent 85% of cases of NHL, and T-cell lymphomas represent 15%.[5] Natural killer lymphomas are relatively rare.[1]

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: DLBCL 31%, follicular lymphoma (FL) 22%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma/MALT lymphoma 5%. All other subtypes each represent less than 2% of cases of NHL.[1]

## Types of Non-Hodgkin lymphoma

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.[1] Early-stage indolent NHL (stage I or II) may be effectively treated with radiation alone. Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages. These individuals can often be treated again if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of individuals with low-grade lymphoma,[6] and median survival with conventional chemotherapy is 1 year or less.

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

Aggressive NHL has a shorter natural history; however, 30% to 60% of these individuals can be cured with intensive combination chemotherapy regimens.[1] Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt lymphoma.

## Risk Assessment

Oncologists developed a clinical tool to aid in predicting the prognosis of individuals with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI).[16] Before its development in 1993, prognosis was predominantly based on disease stage.

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

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

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

Individuals with two or more risk factors have a less than 50% chance of relapse-free survival (RFS) and OS at 5 years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger individuals with localized disease.

Adverse risk factors for age-adjusted IPI include stage III or IV disease, elevated LDH and ECOG Performance Status of 2 or greater and can be calculated as follows: 0 is low risk, 1 is low intermediate, 2 is high intermediate, and 3 is high risk.

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

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

These five factors are used to stratify individuals into three categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).[17]

## Mantle Cell Lymphoma

Mantle Cell Lymphoma (MCL) comprises 65% to 68% of NHL and has been recognized for some time now as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed by Banks et al(1992)[43] The number of therapeutic trials is not as numerous for MCL as for other NHL, because it was not widely recognized until the REAL classification. MCL shows a strong predilection for senior men, and most cases (70%) present with disseminated (stage IV) disease; extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2 to 4 years, and although most individuals achieve remission with first-line therapy, relapse inevitably occurs, often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

**Risk Assessment**

A prognostic index has recently been established for individuals with MCL. Application of the IPI or FLIPI system to individuals with MCL has shown limitations, which included no separation of some important risk groups. In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in individuals with MCL.[44] Therefore, a new prognostic index for individuals with MCL was developed and is useful in comparing clinical trial results for MCL.

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

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

MCL IPI allows separation of 3 groups with significantly different prognoses[44]:

- 0-3 points denotes low risk, which affects 44% of individuals, who have a 5-year OS rate of 60% (median OS, not reached)
- 4-5 points denotes intermediate risk, which affects 35% of individuals, who have a median OS of 51 months
- 6-11 points denotes high risk, which affects 21% of individuals, who have a median OS of 29 months

## Peripheral T-Cell Lymphoma

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

## Staging

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

## Table 3. Ann Arbor Classification

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

## Treatment for NHL

### Hematopoietic Cell Transplantation

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is

critical for achieving a good outcome with allogenic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

### *Conventional Preparative Conditioning for HCT*

The conventional ("classical") practice of allogeneic 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 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 extant disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to individuals who are sufficiently medically fit to tolerate substantial adverse events. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by the cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy (with or without radiation) to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow 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 individual's disease is in complete remission. Individuals who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment but not graft-versus-host disease.

### Reduced-Intensity Conditioning for Allogeneic HCT

RIC refers to the pretransplant use of lower doses 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 totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Individuals who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism. For the purposes of this policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be nonmyeloablative.

## Summary of Evidence

For individuals who have indolent B-cell NHL who receive autologous HCT as first-line therapy, the evidence includes observational studies, randomized controlled trials (RCTs), and systematic reviews. The relevant outcomes are overall survival (OS), disease-specific survival, 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, the evidence includes RCTs and a systematic review. The relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the RCTs offer conflicting results, some of the data has 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 complete remission. The RCTs of HCT for relapsed aggressive B-cell lymphomas have 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 allogeneic HCT, the evidence includes several nonrandomized trials. The relevant outcomes are OS, disease-specific survival, 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 a limited number of individuals. Presently, conclusions on the use of tandem transplants cannot be made about autologous and

allogeneic 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. The relevant outcomes are OS, disease-specific survival, 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 allogeneic HCT, the evidence includes prospective trials and case reports/series. The relevant outcomes are OS, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of individuals; moreover, the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas addressed. Additionally, studies of this nature often mix three types of individuals: one type of individual has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphomas (ALCL), which has a better prognosis—even with conventional chemotherapy regimens; and a third type has ALK-negative ALCL, which has a worse prognosis than ALK-positive ALCL (but better than 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 progression-free survival (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; randomized trials 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 PFS in two systematic reviews. 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 a meaningful 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. A third small, retrospective study showed no significant differences in OS or PFS between allo-HCT and auto-HCT, but the 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.

## Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished phase III 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 4**.

## Table 4. 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 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| 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.

## 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 three physician specialty societies and three academic medical centers while this policy was under review in 2011. Input was solicited particularly for the use of 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 one physician specialty society and one 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 RIC 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 one reviewer commented that with the increasing use of rituximab and its success in improving patient outcomes, the role of HCT in consolidating first complete response in high-risk patients is coming into question.

## Practice Guidelines and Position Statements

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the policy conclusions.

Guidelines or position statements will be considered for inclusion 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 (v.3.2024) include the following recommendations[76]:

- 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 MCL, 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 complete response (CR) or near CR at the time of transplant."

- For Burkitt lymphoma, allogeneic HCT is an option for selected patients to achieve a complete or partial response to second-line therapy.

National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.1.2025) include the following recommendations:[77]

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 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. 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.[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 Diffuse Large B Cell Lymphoma (DLBCL) in 2023.[79] 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.

In 2024, ASTCT and EBMT formulated consensus recommendations for HCT and cellular therapies in follicular lymphoma.[80] The following consensus statements were made:

- Front-line setting (i.e., 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 (i.e., 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.

- 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.

## Medicare National Coverage

Medicare has the following national coverage determination for the use of autologous cell transplantation for Hodgkin and non-Hodgkin lymphomas.[81]

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

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

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

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

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

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

## Regulatory Status

The US Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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## History

| Date | Comments |
|---|---|
| 04/14/14 | New PR policy; replaces 8.01.20. Policy updated with literature search through December 23, 2013. Policy section reworded and reformatted. Policy statements changed as follows: NHL B-cell – RIC is now medically necessary; B-cell Indolent – RIC is now investigational (previously medically necessary); Mature T-cell or NK – RIC is now investigational to consolidate CR (previously medically necessary). References 37 and 42 added; reference 66 updated. |
| 06/24/14 | Update Related Policies. Remove 8.01.35, 8.01.42 and 8.01.54, then add 8.01.532 |
| 12/03/14 | Update Related Policies. Remove 8.01.17 and 8.01.26. |
| 04/24/15 | Annual Review. Policy updated with literature review; no change in policy statements. |
| 08/09/16 | Update Related Policies. Remove 8.01.27 as it was archived. |
| 11/04/16 | Coding update. Removed codes that are transplant benefit related. |
| 12/01/16 | Annual review, approved November 8, 2016. Added references 68 and 69. No changes to policy statement. |
| 04/01/17 | Updated titles in Related Policies. |
| 08/01/17 | Updated title of Related Policy 8.01.511. |
| 12/01/17 | Annual Review, approved November 9, 2017. Updated WHO classifications and Summary of Evidence section. No changes to policy statement. |
| 05/01/18 | Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017. Policy statements unchanged. |
| 09/01/18 | Minor update. Re-adding Consideration of Age information which was inadvertently removed during a previous update. |
| 04/01/19 | Minor update, added Documentation Requirements section. |
| 05/01/19 | Annual Review, approved April 18, 2019. Policy updated with literature review through November 2018; reference 60 added. Policy statements unchanged. |
| 05/01/20 | Annual Review, approved April 23, 2020. Policy updated with literature review through November 2019; references added. Policy statements unchanged. |
| 05/06/20 | Delete policy, approved May 5, 2020. This policy will be deleted effective July 2, 2020 and replaced with InterQual criteria for dates of service on or after July 2, 2020. |
| 06/10/20 | Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020. |

| Date | Comments |
|---|---|
| 04/01/21 | Annual Review, approved March 23, 2021. Policy updated with literature review through November 19, 2020; references added. Update Related Policies, removed reference to policy 8.01.22 and replaced with policy 8.01.538. |
| 05/01/21 | Update Related Policies. Removed policy 7.01.50 as it was archived. |
| 04/01/22 | Annual Review, approved March 21, 2022. Policy updated with literature review through December 6, 2021; references added. Policy statements unchanged. |
| 10/01/22 | Coding update. Removed HCPC code S2140. |
| 05/01/23 | Annual Review, approved April 11, 2023. Policy updated with literature review through December 1, 2022; references added. New medically necessary policy statement added for hepatosplenic T-cell lymphoma. Minor editorial refinements made to other policy statements; intent unchanged. Changed the wording from "patient" to "individual" throughout the policy for standardization. |
| 05/01/24 | Annual Review, approved April 8, 2024. Policy updated with literature review through November 15, 2023; references added. Policy statements unchanged. Updated Related Policy section; removed 8.01.21 and replaced with 8.01.539 Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms. |
| 10/09/24 | Minor update. Removed policy 8.01.538 Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias from the Related Policy section. |
| 04/01/25 | Annual Review, approved March 10, 2025. Policy updated with literature review through December 3, 2024; references added. Policy statements unchanged. |



**Scope**: Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.