# MEDICAL POLICY

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| **POLICY TITLE** | **HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS** |
| **POLICY NUMBER** | **MP 9.042** |

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| **CLINICAL BENEFIT** | ☐ MINIMIZE SAFETY RISK OR CONCERN.<br>☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS.<br>☐ ASSURE APPROPRIATE LEVEL OF CARE.<br>☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS.<br>☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET.<br>☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE. |
| **Effective Date:** | **2/1/2024** |



## I. POLICY

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 HCT, may be considered **medically necessary:**

- 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 CR for those in a chemo-sensitive first or subsequent relapse; or
- To consolidate a first CR in individuals with diffuse large B-cell lymphoma, with an age-adjusted International Prognostic Index score that predicts a high-or high-intermediate risk of relapse.

For individuals with mantle cell lymphoma, the following may be considered **medically necessary.**

- Autologous HCT to consolidate a first remission.
- Allogeneic HCT, myeloablative or reduced-intensity conditioning, as salvage therapy.

For individuals with mantle cell lymphoma, the following are **investigational,** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures:

- Autologous HCT is as salvage therapy.
- Allogeneic HCT to consolidate a first remission.

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

For patients with NHL B-cell subtypes considered indolent, either allogeneic HCT using a myeloablative conditioning regimen or autologous HCT may be considered **medically necessary:**

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

Either autologous HCT or allogeneic HCT is considered **investigational** as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with these procedures:

- As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
- To consolidate a first 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;
- To consolidate a first CR for those with indolent NHL B-cell subtypes.

For individuals with mature T-cell or NK-cell (peripheral T-cell) neoplasms:

- Autologous HCT may be considered **medically necessary** to consolidate a first complete remission in high-risk subtypes (see Policy Guidelines section).
- Autologous or allogeneic HCT (myeloablative or reduced-intensity conditioning) may be considered **medically necessary** as salvage therapy.
- Allogeneic HCT is considered **investigational** to consolidate a first remission, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

For individuals with hepatosplenic T-cell lymphoma:

- Allogenic HCT may be considered **medically necessary** to consolidate a first CR or partial response.
- 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.
- Autologous or allogeneic HCT as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

Reduced-intensity conditioning allogeneic HCT may be considered **medically necessary** as a treatment of NHL in individuals who meet criteria for an allogeneic HCT but who do not qualify for a myeloablative allogeneic HCT (see Policy Guidelines).

Tandem transplants are considered **investigational** to treat individuals with any stage, grade, or subtype of NHL, as there is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

**Note:** Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL). Therefore, SLL is considered along with CLL in MP 9.038. Lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia is considered in MP 9.046.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

**Policy Guidelines**

**National Comprehensive Cancer Network**

Current National Comprehensive Cancer Network (NCCN) guidelines on B-cell lymphomas ( v.2.2023) include the following recommendations:

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

National Comprehensive Cancer Network guidelines on T-cell lymphomas ( v.2.2023) include the following recommendations:'

- "Second-line systemic therapy followed by consolidation with HDT [high-dose therapy]/ASCR [autologous stem cell rescue] or allogeneic HCT for those with a CR [complete response] or PR [partial response] is recommended for patients who are candidates for transplant."
- "Allogeneic HCT should be considered for patients with acute or lymphoma [ATLL] subtype, if donor is available."
- "In patients with acute or lymphoma subtypes who achieve a response to second-therapy, allogeneic HSCT should be considered if a donor is available."
- "In patients [with T-PLL] who achieve a CR or PR following initial therapy, consolidation with allogeneic HCT should be considered. Autologous HCT may be considered, if a donor is not available and if the patient is not physically fit enough to undergo allogeneic HCT."

For hepatosplenic T-Cell Lymphoma (HSTCL), the guidelines state: "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." Furthermore, the guidelines state that: "Long-term remission is primarily or exclusively seen in those who have undergone consolidative HCT."

Of note, the NCCN does acknowledge the following: "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." Nonetheless, they also state: "The goal of initial therapy is to induce complete or near complete response to allow successful bridging to HCT, preferably an allogeneic HCT."

**Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas**

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

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

A chemo-sensitive relapse is defined as relapsed NHL that does not progress during or immediately after standard-dose induction chemotherapy (i.e., 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 (PTCL), salvage therapy includes patients who do not achieve a CR (e.g., achieve only a partial response (PR), have no response, or have progressive disease) with first-line induction chemotherapy (refractory disease) or who relapse after achieving a CR 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 CR or PR 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.

***Cross-references:***

**MP 9.001** Placental/Umbilical Cord Blood as a Source of Stem Cells**.**
**MP 9.038** Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
**MP 9.043** Hematopoietic Cell Transplantation for Hodgkin Lymphoma
**MP 9.045** Hematopoietic Cell Transplantation for Primary Amyloidosis
**MP 9.046** Hematopoietic Cell Transplantation for Waldenstrom Macroglobulinemia
**MP 9.050** Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma

## II. PRODUCT VARIATIONS

TOP

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:
https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies

## III. DESCRIPTION/BACKGROUND

TOP

**NON-HODGKIN LYMPHOMA**
A heterogeneous group of lymphoproliferative malignancies, non-Hodgkin lymphoma (NHL) usually originates in lymphoid tissue. Historically, uniform treatment of patients with NHL was hampered by the lack of a uniform classification system. In 1982, the Working Formulation was developed to unify different classification systems into one. 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 and an updated version of the REAL system, the new World Health Organization classification. The World Health Organization (WHO)/REAL classification recognized 3 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 World Health Organization classification (see Table 1).

The most recent lymphoma classification is the 2022 WHO classification (see Table 1).

**Table 1. 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* |
| • B-lymphoblastic leukaemia/lymphoma, NOS |
| • B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy[a] |

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|---|
| B-lymphoblastic leukaemia/lymphoma with hypodiploidy |
| • B-lymphoblastic leukaemia/lymphoma with iAMP21 |
| B-lymphoblastic leukaemia/lymphoma with BCR::ABL1 fusion[a] |
| B-lymphoblastic leukaemia/lymphoma with BCR::ABL1-like features[a] |
| • B-lymphoblastic leukaemia/lymphoma with KMT2A rearrangement[a] |
| • B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1 fusion[a] |
| • B-lymphoblastic leukaemia/lymphoma with ETV6::RUNX1-like features[a] |
| B-lymphoblastic leukaemia/lymphoma with TCF3::PBX1 fusion[a] |
| B-lymphoblastic leukaemia/lymphoma with IGH::IL3 fusion[a] |
| B-lymphoblastic leukaemia/lymphoma with TCF3::HLF fusion[a] |
| B-lymphoblastic leukaemia/lymphoma with other defined genetic abnormalities |
| **Mature B-cell neoplasms** |
| *Pre-neoplastic and neoplastic small lymphocytic proliferations* |
| Monoclonal B-cell lymphocytosis |
| • Chronic lymphocytic leukaemia/small lymphocytic lymphoma |
| *Splenic B-cell lymphomas and leukaemias* |
| • Hairy cell leukaemia |
| • Splenic marginal zone lymphoma |
| Splenic diffuse red pulp small B-cell lymphoma |
| • Splenic B-cell lymphoma/leukaemia with prominent nucleoli[a] |
| *Lymphoplasmacytic lymphoma* |
| Lymphoplasmacytic lymphoma |
| • *Marginal zone lymphoma* |
| Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue |
| • Primary cutaneous marginal zone lymphoma[a] |
| • Nodal marginal zone lymphoma |
| Paediatric marginal zone lymphoma |
| Follicular lymphoma |
| In situ follicular B-cell neoplasm[a] |
| Follicular lymphoma |
| Paediatric-type follicular lymphoma |
| Duodenal-type follicular lymphoma |
| *Cutaneous follicle centre lymphoma* |
| Primary cutaneous follicle centre lymphoma |
| *Mantle cell lymphoma* |
| In situ mantle cell neoplasm[a] |
| Mantle cell lymphoma |
| Leukaemic non-nodal mantle cell lymphoma |
| *Transformations of indolent B-cell lymphomas* |
| Transformations of indolent B-cell lymphomas[a] |
| *Large B-cell lymphomas* |

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|---|
| Diffuse large B-cell lymphoma, NOS |
| T-cell/histiocyte-rich large B-cell lymphoma |
| 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* |
| 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] |

ALK: anaplastic lymphoma kinase; GI: gastrointestinal; Ig: immunoglobulin; NK: natural killer.[a] Changes from 2016 WHO classification. Provisional entities are listed in italics.

In the United States, B-cell lymphomas represent 80% to 85% of cases of NHL, and T-cell lymphomas represent 15% to 20%. Natural killer lymphomas are relatively rare.

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: diffuse large B-cell lymphoma (DLBCL) 31%, follicular lymphoma 22%, small lymphocytic lymphoma and chronic lymphocytic leukemia 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma of mucosa-

associated lymphoid tissue lymphoma 5%. All other subtypes each represents fewer than 2% of cases of NHL.

**Types of NHL**
In general, NHL can be divided into 2 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. Early-stage indolent NHL (stage I or II) may be effectively treated with radiotherapy alone. Although indolent NHL is responsive to radiotherapy and chemotherapy, a continuous rate of relapse is seen in advanced stages. These patients can often be treated again if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, and median survival with conventional chemotherapy is 1 year or less.

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

Aggressive NHL has a shorter natural history; however, 30% to 60% of these patients can be cured with intensive combination chemotherapy regimens[5]. Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large-cell lymphoma, and Burkitt lymphoma.

**Staging**

The Ann Arbor staging classification is commonly used to stage lymphomas. Originally developed for Hodgkin disease, the classification was later expanded to include NHL (see Table 2).

| 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 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 |

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

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

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

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

Patients with 2 or more risk factors have a less than 50% chance of relapse-free survival and overall survival at 5 years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger patients with localized disease.

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

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

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

These 5 factors are used to stratify patients into 3 categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).

**Mantle Cell Lymphoma**
Mantle Cell Lymphomas (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 in 1992 by Banks et al. The number of therapeutic trials is not as numerous for MCL as for other NHL, because it was not widely recognized until the REAL classification. MCL shows a strong predilection for senior men, and most cases (70%) present with disseminated (stage IV) disease; extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately 2 to 4 years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs—often within 12 to 18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

***Risk Assessment***

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

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

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

MCL International Prognostic Index allows separation of 3 groups with significantly different prognoses:

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

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

**Hepatosplenic T-cell Lymphoma**
Hepatosplenic T-cell lymphoma (HSTCL) is a rare lymphoproliferative disorder associated with an aggressive clinical course and a worse prognosis. HSTCL accounts for less than or equal to 2% of all cases of T-cell lymphomas diagnosed worldwide and in up to 20% of cases develops in the setting of chronic immune suppression or immune dysregulation, particularly inflammatory bowel disease (IBD), hematologic malignancies, and previous solid organ transplant. The concomitant use of tumor necrosis factor-alpha (TNF-α) inhibitors and thiopurine-based immunomodulators has been identified as a risk factor for developing HSTCL among patients with IBD.

HSTCL is most often characterized by spleen, liver, and bone marrow involvement. Lymphadenopathy is uncommon and patients frequently present with systemic symptoms, hepatosplenomegaly, cytopenias, and sometimes hemophagocytic lymphohistiocytosis (HLH). Clinical presentation is highly non-specific and high index of suspicion is required to make the diagnosis. In the majority of cases, the neoplastic cells typically arise from lymphocytes having the surface expression of TCRδ and TCRɣδ.5,10,11 In rare cases, neoplastic cells may express TCRαβ.12-14 TCRɣδ variant predominantly affects patients assigned male at birth, with a median age of 35 years, whereas TCRαβ variant occurs more commonly in patients assigned female at birth older than 50 years. 4 Both are considered as immunophenotypic variants of the same disease and are managed in the same way. Per the NCCN, long-term remission of hepatosplenic T-cell lymphoma is primarily or exclusively seen in those who have undergone consolidative HCT.

**Treatment for NHL**

***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. Cord blood is discussed in detail in MP-9.001.

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 critical for achieving a good outcome. 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.

**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 initial eradication of malignant cells and the subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. Intense conditioning regimens are limited to patients 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 also increase 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 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 susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

***Reduced-Intensity Conditioning for Allogeneic HCT***

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiotherapy that 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 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.

### REGULATORY STATUS

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

## IV. RATIONALE

TOP

### SUMMARY OF EVIDENCE

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

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

For individuals who have NHL, excluding MCL, who receive tandem autologous and allogeneic HCT, the evidence includes several nonrandomized trials. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. No

randomized studies have been conducted on the use of tandem HCT for the treatment of NHL, and the published evidence comprises a limited number of patients. Presently, conclusions on the use of tandem transplants cannot be made about autologous and allogeneic HCT. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have MCL who receive autologous, allogeneic, or tandem HCT, the evidence includes case series and RCTs. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Case series and RCTs have shown long-term disease control of this aggressive lymphoma with autologous HCT (with rituximab) to consolidate a first remission; however, the use of autologous HCT in the relapsed setting has not shown improved outcomes. Allo-HCT has shown prolonged disease control in the relapsed or refractory setting. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have peripheral T-cell lymphoma (PTCL) who receive autologous or allo-HCT, the evidence includes prospective trials and case reports/series. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of patients; moreover, the patient populations were heterogeneous and included good- and poor-risk patients in the same study. Patient population and characteristics of the studies can be explained partially by the rarity and heterogeneity of the particular group of lymphomas addressed. Additionally, studies of this nature often mix three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase-positive anaplastic large-cell lymphomas, which has a better prognosis-even with conventional chemotherapy regimens; and a third type has anaplastic lymphoma kinase negative anaplastic large-cell lymphomas, which has a worse prognosis than anaplastic lymphoma kinase positive anaplastic large-cell lymphomas (but better than patients with PTCL not otherwise specified). 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; randomized trials 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. Patients with relapsed or refractory PTCL are generally considered incurable with chemotherapy alone. In the salvage setting, data have shown that the use of HCT may improve survival outcomes similar to the results seen in corresponding aggressive B-cell lymphomas in the same treatment setting. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have hepatosplenic T cell lymphoma (HSTCL) who receive autologous or allogeneic HCT, the evidence includes two meta-analyses using patient-level data. Findings

demonstrated that that consolidation therapy with HCT improves survival in patients with hepatosplenic t-cell lymphoma (HTCL). Two small, retrospective studies have shown similar results. Generally, outcomes are improved when non-CHOP regimens are used for induction therapy. In the absence of data from prospective and randomized studies, the results of this largest meta-analysis support the use of induction therapy with non–CHOP-based regimens followed by consolidation with allogeneic HCT as an effective treatment approach (associated with improved survival) for all eligible patients with HSTCL. Autologous HCT has also been shown to provide some benefit for patients when an allogeneic HCT is not feasible. In a retrospective series of 14 patients with HSTCL, induction therapy with ICE or IVAC followed by consolidation with autologous HCT was associated with improved outcomes compared with CHOP or CHOP-like regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

## V. DEFINITIONS

TOP

**ALLOGENIC** refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor, after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA). Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor effect. Their disadvantage is the risk of graft-versus host disease (GVHD), which increases with great HLA disparity and recipient age.

**AUTOLOGOUS** refers to originating within an individual, i.e., self-donation. These stem cells are harvested from patients prior to myeloablative therapy.

**REDUCED-INTENSITY ALLOGENIC STEM CELL TRANSPLANTATION** uses lower doses of chemotherapy than standard allogenic transplant, it does not completely inactivate the patient's immune system or treat the ALL as aggressively. Older, sicker patients may be helped with this type of treatment.

## VI. BENEFIT VARIATIONS

TOP

The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

## VII. DISCLAIMER

TOP

*Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.*

## VIII. CODING INFORMATION

TOP

**Note:** This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

**Covered when medically necessary:**

| Procedure Codes | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| S2140 | S2142 | S2150 | 38204 | 38205 | 38206 | 38207 | 38208 | 38209 |
| 38210 | 38211 | 38212 | 38213 | 38214 | 38215 | 38230 | 38232 | 38240 |
| 38241 | | | | | | | | |

| ICD-10-CM Diagnosis Codes | Description |
|---|---|
| C82.01 | Follicular lymphoma grade I, lymph nodes of head, face, and neck |
| C82.02 | Follicular lymphoma grade I, intrathoracic lymph nodes |
| C82.03 | Follicular lymphoma grade I, intra-abdominal lymph nodes |
| C82.04 | Follicular lymphoma grade I, lymph nodes of axilla and upper limb |
| C82.05 | Follicular lymphoma grade I, lymph nodes of inguinal region and lower limb |
| C82.06 | Follicular lymphoma grade I, intrapelvic lymph nodes |
| C82.07 | Follicular lymphoma grade I, spleen |
| C82.08 | Follicular lymphoma grade I, lymph nodes of multiple sites |
| C82.09 | Follicular lymphoma grade I, extranodal and solid organ sites |
| C82.11 | Follicular lymphoma grade II, lymph nodes of head, face, and neck |
| C82.12 | Follicular lymphoma grade II, intrathoracic lymph nodes |
| C82.13 | Follicular lymphoma grade II, intra-abdominal lymph nodes |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C82.14 | Follicular lymphoma grade II, lymph nodes of axilla and upper limb |
| C82.15 | Follicular lymphoma grade II, lymph nodes of inguinal region and lower limb |
| C82.16 | Follicular lymphoma grade II, intrapelvic lymph nodes |
| C82.17 | Follicular lymphoma grade II, spleen |
| C82.18 | Follicular lymphoma grade II, lymph nodes of multiple sites |
| C82.19 | Follicular lymphoma grade II, extranodal and solid organ sites |
| C82.31 | Follicular lymphoma grade IIIa, lymph nodes of head, face, and neck |
| C82.32 | Follicular lymphoma grade IIIa, intrathoracic lymph nodes |
| C82.33 | Follicular lymphoma grade IIIa, intra-abdominal lymph nodes |
| C82.34 | Follicular lymphoma grade IIIa, lymph nodes of axilla and upper limb |
| C82.35 | Follicular lymphoma grade IIIa, lymph nodes of inguinal region and lower limb |
| C82.36 | Follicular lymphoma grade IIIa, intrapelvic lymph nodes |
| C82.37 | Follicular lymphoma grade IIIa, spleen |
| C82.38 | Follicular lymphoma grade IIIa, lymph nodes of multiple sites |
| C82.39 | Follicular lymphoma grade IIIa, extranodal and solid organ sites |
| C82.41 | Follicular lymphoma grade IIIb, lymph nodes of head, face, and neck |
| C82.42 | Follicular lymphoma grade IIIb, intrathoracic lymph nodes |
| C82.43 | Follicular lymphoma grade IIIb, intra-abdominal lymph nodes |
| C82.44 | Follicular lymphoma grade IIIb, lymph nodes of axilla and upper limb |
| C82.45 | Follicular lymphoma grade IIIb, lymph nodes of inguinal region and lower limb |
| C82.46 | Follicular lymphoma grade IIIb, intrapelvic lymph nodes |
| C82.47 | Follicular lymphoma grade IIIb, spleen |
| C82.48 | Follicular lymphoma grade IIIb, lymph nodes of multiple sites |
| C82.49 | Follicular lymphoma grade IIIb, extranodal and solid organ sites |
| C82.51 | Diffuse follicle center lymphoma, lymph nodes of head, face, and neck |
| C82.52 | Diffuse follicle center lymphoma, intrathoracic lymph nodes |
| C82.53 | Diffuse follicle center lymphoma, intra-abdominal lymph nodes |
| C82.54 | Diffuse follicle center lymphoma, lymph nodes of axilla and upper limb |
| C82.55 | Diffuse follicle center lymphoma, lymph nodes of inguinal region and lower limb |
| C82.56 | Diffuse follicle center lymphoma, intrapelvic lymph nodes |
| C82.57 | Diffuse follicle center lymphoma, spleen |
| C82.58 | Diffuse follicle center lymphoma, lymph nodes of multiple sites |
| C82.59 | Diffuse follicle center lymphoma, extranodal and solid organ sites |
| C82.61 | Cutaneous follicle center lymphoma, lymph nodes of head, face, and neck |
| C82.62 | Cutaneous follicle center lymphoma, intrathoracic lymph nodes |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C82.63 | Cutaneous follicle center lymphoma, intra-abdominal lymph nodes |
| C82.64 | Cutaneous follicle center lymphoma, lymph nodes of axilla and upper limb |
| C82.65 | Cutaneous follicle center lymphoma, lymph nodes of inguinal region, and lower limb |
| C82.66 | Cutaneous follicle center lymphoma, intrapelvic lymph nodes |
| C82.67 | Cutaneous follicle center lymphoma, spleen |
| C82.68 | Cutaneous follicle center lymphoma, lymph nodes of multiple sites |
| C82.69 | Cutaneous follicle center lymphoma, extranodal and solid organ sites |
| C82.81 | Other types of follicular lymphoma, lymph nodes of head, face, and neck |
| C82.82 | Other types of follicular lymphoma, intrathoracic lymph nodes |
| C82.83 | Other types of follicular lymphoma, intra-abdominal lymph nodes |
| C82.84 | Other types of follicular lymphoma, lymph nodes of axilla and upper limb |
| C82.85 | Other types of follicular lymphoma, lymph nodes of inguinal region and lower limb |
| C82.86 | Other types of follicular lymphoma, intrapelvic lymph nodes |
| C82.87 | Other types of follicular lymphoma, spleen |
| C82.88 | Other types of follicular lymphoma, lymph nodes of multiple sites |
| C82.89 | Other types of follicular lymphoma, extranodal and solid organ sites |
| C83.01 | Small cell B-cell lymphoma, lymph nodes of head, face, and neck |
| C83.02 | Small cell B-cell lymphoma, intrathoracic lymph nodes |
| C83.03 | Small cell B-cell lymphoma, intra-abdominal lymph nodes |
| C83.04 | Small cell B-cell lymphoma, lymph nodes of axilla and upper limb |
| C83.05 | Small cell B-cell lymphoma, lymph nodes of inguinal region and lower limb |
| C83.06 | Small cell B-cell lymphoma, intrapelvic lymph nodes |
| C83.07 | Small cell B-cell lymphoma, spleen |
| C83.08 | Small cell B-cell lymphoma, lymph nodes of multiple sites |
| C83.09 | Small cell B-cell lymphoma, extranodal and solid organ sites |
| C83.11 | Mantle cell lymphoma, lymph nodes of head, face, and neck |
| C83.12 | Mantle cell lymphoma, intrathoracic lymph nodes |
| C83.13 | Mantle cell lymphoma, intra-abdominal lymph nodes |
| C83.14 | Mantle cell lymphoma, lymph nodes of axilla and upper limb |
| C83.15 | Mantle cell lymphoma, lymph nodes of inguinal region and lower limb |
| C83.16 | Mantle cell lymphoma, intrapelvic lymph nodes |
| C83.17 | Mantle cell lymphoma, spleen |
| C83.18 | Mantle cell lymphoma, lymph nodes of multiple sites |
| C83.19 | Mantle cell lymphoma, extranodal and solid organ sites |
| C83.31 | Diffuse large B-cell lymphoma, lymph nodes of head, face, and neck |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C83.32 | Diffuse large B-cell lymphoma, intrathoracic lymph nodes |
| C83.33 | Diffuse large B-cell lymphoma, intra-abdominal lymph nodes |
| C83.34 | Diffuse large B-cell lymphoma, lymph nodes of axilla and upper limb |
| C83.35 | Diffuse large B-cell lymphoma, lymph nodes of inguinal region and lower limb |
| C83.36 | Diffuse large B-cell lymphoma, intrapelvic lymph nodes |
| C83.37 | Diffuse large B-cell lymphoma, spleen |
| C83.38 | Diffuse large B-cell lymphoma, lymph nodes of multiple sites |
| C83.39 | Diffuse large B-cell lymphoma, extranodal and solid organ sites |
| C83.51 | Lymphoblastic (diffuse) lymphoma, lymph nodes of head, face, and neck |
| C83.52 | Lymphoblastic (diffuse) lymphoma, intrathoracic lymph nodes |
| C83.53 | Lymphoblastic (diffuse) lymphoma, intra-abdominal lymph nodes |
| C83.54 | Lymphoblastic (diffuse) lymphoma, lymph nodes of axilla and upper limb |
| C83.55 | Lymphoblastic (diffuse) lymphoma, lymph nodes of inguinal region and lower limb |
| C83.56 | Lymphoblastic (diffuse) lymphoma, intrapelvic lymph nodes |
| C83.57 | Lymphoblastic (diffuse) lymphoma, spleen |
| C83.58 | Lymphoblastic (diffuse) lymphoma, lymph nodes of multiple sites |
| C83.59 | Lymphoblastic (diffuse) lymphoma, extranodal and solid organ sites |
| C83.71 | Burkitt lymphoma, lymph nodes of head, face, and neck |
| C83.72 | Burkitt lymphoma, intrathoracic lymph nodes |
| C83.73 | Burkitt lymphoma, intra-abdominal lymph nodes |
| C83.74 | Burkitt lymphoma, lymph nodes of axilla and upper limb |
| C83.75 | Burkitt lymphoma, lymph nodes of inguinal region and lower limb |
| C83.76 | Burkitt lymphoma, intrapelvic lymph nodes |
| C83.77 | Burkitt lymphoma, spleen |
| C83.78 | Burkitt lymphoma, lymph nodes of multiple sites |
| C83.79 | Burkitt lymphoma, extranodal and solid organ sites |
| C83.81 | Other non-follicular lymphoma, lymph nodes of head, face, and neck |
| C83.82 | Other non-follicular lymphoma, intrathoracic lymph nodes |
| C83.83 | Other non-follicular lymphoma, intra-abdominal lymph nodes |
| C83.84 | Other non-follicular lymphoma, lymph nodes of axilla and upper limb |
| C83.85 | Other non-follicular lymphoma, lymph nodes of inguinal region and lower limb |
| C83.86 | Other non-follicular lymphoma, intrapelvic lymph nodes |
| C83.87 | Other non-follicular lymphoma, spleen |
| C83.88 | Other non-follicular lymphoma, lymph nodes of multiple sites |
| C83.89 | Other non-follicular lymphoma, extranodal and solid organ sites |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C84.01 | Mycosis fungoides, lymph nodes of head, face, and neck |
| C84.02 | Mycosis fungoides, intrathoracic lymph nodes |
| C84.03 | Mycosis fungoides, intra-abdominal lymph nodes |
| C84.04 | Mycosis fungoides, lymph nodes of axilla and upper limb |
| C84.05 | Mycosis fungoides, lymph nodes of inguinal region and lower limb |
| C84.06 | Mycosis fungoides, intrapelvic lymph nodes |
| C84.07 | Mycosis fungoides, spleen |
| C84.08 | Mycosis fungoides, lymph nodes of multiple sites |
| C84.09 | Mycosis fungoides, extranodal and solid organ sites |
| C84.11 | Sezary disease, lymph nodes of head, face, and neck |
| C84.12 | Sezary disease, intrathoracic lymph nodes |
| C84.13 | Sezary disease, intra-abdominal lymph nodes |
| C84.14 | Sezary disease, lymph nodes of axilla and upper limb |
| C84.15 | Sezary disease, lymph nodes of inguinal region and lower limb |
| C84.16 | Sezary disease, intrapelvic lymph nodes |
| C84.17 | Sezary disease, spleen |
| C84.18 | Sezary disease, lymph nodes of multiple sites |
| C84.19 | Sezary disease, extranodal and solid organ sites |
| C84.41 | Peripheral T-cell lymphoma, not classified, lymph nodes of head, face, and neck |
| C84.42 | Peripheral T-cell lymphoma, not classified, intrathoracic lymph nodes |
| C84.43 | Peripheral T-cell lymphoma, not classified, intra-abdominal lymph nodes |
| C84.44 | Peripheral T-cell lymphoma, not classified, lymph nodes of axilla and upper limb |
| C84.45 | Peripheral T-cell lymphoma, not classified, lymph nodes of inguinal region and lower limb |
| C84.46 | Peripheral T-cell lymphoma, not classified, intrapelvic lymph nodes |
| C84.47 | Peripheral T-cell lymphoma, not classified, spleen |
| C84.48 | Peripheral T-cell lymphoma, not classified, lymph nodes of multiple sites |
| C84.49 | Peripheral T-cell lymphoma, not classified, extranodal and solid organ sites |
| C84.61 | Anaplastic large cell lymphoma, ALK-positive, lymph nodes of head, face, and neck |
| C84.62 | Anaplastic large cell lymphoma, ALK-positive, intrathoracic lymph nodes |
| C84.63 | Anaplastic large cell lymphoma, ALK-positive, intra-abdominal lymph nodes |
| C84.64 | Anaplastic large cell lymphoma, ALK-positive, lymph nodes of axilla and upper limb |
| C84.65 | Anaplastic large cell lymphoma, ALK-positive, lymph nodes of inguinal region and lower limb |
| C84.66 | Anaplastic large cell lymphoma, ALK-positive, intrapelvic lymph nodes |
| C84.67 | Anaplastic large cell lymphoma, ALK-positive, spleen |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C84.68 | Anaplastic large cell lymphoma, ALK-positive, lymph nodes of multiple sites |
| C84.69 | Anaplastic large cell lymphoma, ALK-positive, extranodal and solid organ sites |
| C84.71 | Anaplastic large cell lymphoma, ALK-negative, lymph nodes of head, face, and neck |
| C84.72 | Anaplastic large cell lymphoma, ALK-negative, intrathoracic lymph nodes |
| C84.73 | Anaplastic large cell lymphoma, ALK-negative, intra-abdominal lymph nodes |
| C84.74 | Anaplastic large cell lymphoma, ALK-negative, lymph nodes of axilla and upper limb |
| C84.75 | Anaplastic large cell lymphoma, ALK-negative, lymph nodes of inguinal region and lower limb |
| C84.76 | Anaplastic large cell lymphoma, ALK-negative, intrapelvic lymph nodes |
| C84.77 | Anaplastic large cell lymphoma, ALK-negative, spleen |
| C84.78 | Anaplastic large cell lymphoma, ALK-negative, lymph nodes of multiple sites |
| C84.79 | Anaplastic large cell lymphoma, ALK-negative, extranodal and solid organ sites |
| C84.7A | Anaplastic large cell lymphoma, ALK-negative, breast |
| C84.Z1 | Other mature T/NK-cell lymphomas, lymph nodes of head, face, and neck |
| C84.Z2 | Other mature T/NK-cell lymphomas, intrathoracic lymph nodes |
| C84.Z3 | Other mature T/NK-cell lymphomas, intra-abdominal lymph nodes |
| C84.Z4 | Other mature T/NK-cell lymphomas, lymph nodes of axilla and upper limb |
| C84.Z5 | Other mature T/NK-cell lymphomas, lymph nodes of inguinal region and lower limb |
| C84.Z6 | Other mature T/NK-cell lymphomas, intrapelvic lymph nodes |
| C84.Z7 | Other mature T/NK-cell lymphomas, spleen |
| C84.Z8 | Other mature T/NK-cell lymphomas, lymph nodes of multiple sites |
| C84.Z9 | Other mature T/NK-cell lymphomas, extranodal and solid organ sites |
| C85.21 | Mediastinal (thymic) large B-cell lymphoma, lymph nodes of head, face, and neck |
| C85.22 | Mediastinal (thymic) large B-cell lymphoma, intrathoracic lymph nodes |
| C85.23 | Mediastinal (thymic) large B-cell lymphoma, intra-abdominal lymph nodes |
| C85.24 | Mediastinal (thymic) large B-cell lymphoma, lymph nodes of axilla and upper limb |
| C85.25 | Mediastinal (thymic) large B-cell lymphoma, lymph nodes of inguinal region and lower limb |
| C85.26 | Mediastinal (thymic) large B-cell lymphoma, intrapelvic lymph nodes |
| C85.27 | Mediastinal (thymic) large B-cell lymphoma, spleen |
| C85.28 | Mediastinal (thymic) large B-cell lymphoma, lymph nodes of multiple sites |
| C85.29 | Mediastinal (thymic) large B-cell lymphoma, extranodal and solid organ sites |
| C85.81 | Other specified types of non-Hodgkin lymphoma, lymph nodes of head, face, and neck |
| C85.82 | Other specified types of non-Hodgkin lymphoma, intrathoracic lymph nodes |

| POLICY TITLE | HEMATOPOIETIC CELL TRANSPLANTATION FOR NON-HODGKIN LYMPHOMAS |
|---|---|
| POLICY NUMBER | MP 9.042 |

| Procedure Codes | |
|---|---|
| C85.83 | Other specified types of non-Hodgkin lymphoma, intra-abdominal lymph nodes |
| C85.84 | Other specified types of non-Hodgkin lymphoma, lymph nodes of axilla and upper limb |
| C85.85 | Other specified types of non-Hodgkin lymphoma, lymph nodes of inguinal region and lower limb |
| C85.86 | Other specified types of non-Hodgkin lymphoma, intrapelvic lymph nodes |
| C85.87 | Other specified types of non-Hodgkin lymphoma, spleen |
| C85.88 | Other specified types of non-Hodgkin lymphoma, lymph nodes of multiple sites |
| C85.89 | Other specified types of non-Hodgkin lymphoma, extranodal and solid organ sites |
| C86.0 | Extranodal NK/T-cell lymphoma, nasal type |
| C86.1 | Hepatosplenic T-cell lymphoma |
| C86.2 | Enteropathy-type (intestinal) T-cell lymphoma |
| C86.3 | Subcutaneous panniculitis-like T-cell lymphoma |
| C86.4 | Blastic NK-cell lymphoma |
| C86.5 | Angioimmunoblastic T-cell lymphoma |
| C86.6 | Primary cutaneous CD30-positive T-cell proliferations |

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78. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 8.01.20, Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas. March 2023*

## X. POLICY HISTORY

TOP

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|---|---|
| **MP 9.042** | **CAC 5/20/14** Minor. Information on HSCT for Non-Hodgkin Lymphomas extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Policy guidelines and Rationale section added. |
| | **CAC 6/2/15. Consensus review.** No change to policy statements. References and rationale updated. |
| | **CAC 5/31/16 Consensus review**. No change to policy statements. References and rationale reviewed. Coding reviewed. |
| | **Admin update 1/1/17:** Product variation section reformatted. |
| | **CAC 7/25/17 Consensus review.** No change to the policy statements. References reviewed**.** Coding reviewed. |
| | **1/1/18 Admin Update:** Medicare variations removed from Commercial Policies |
| | **4/27/18 Consensus review.** "Stem" removed from title and policy. HSCT changed to HCT in Policy and Policy Guidelines. Policy statements otherwise unchanged. Background and references updated. Rationale condensed. |
| | **3/25/19 Consensus review.** No change to policy statements. Background and summary of evidence review. References updated. 6/6/19 Coding reviewed, no changes. |
| | **3/13/20 Consensus review**. No change to Policy Statements. References reviewed and updated. Definitions to Acronyms added. |
| | **3/22/21 Consensus review.** Added NCCN statement. Updated Summary of Evidence and References. No changes to coding. |
| | **9/1/21 Administrative update.** New code C84.7A added. Effective 10/1/2021 |
| | **2/8/22 Consensus review.** No changes to policy statements. References, description/background section, and summary of evidence section updated. |
| | **3/20/2023 Minor review.** Added statement regarding hepatosplenic T cell lymphoma, both MN and INV. Updated policy guidelines, and background. New definitions and references. |

Top