

MEDICAL POLICY

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

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	5/1/2026

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.

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**

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- 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:

- Allogeneic 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.

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**.

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POLICY GUIDELINES

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

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

A chemosensitive relapse is defined as relapsed non-Hodgkin lymphoma that does not progress during or immediately after standard-dose induction chemotherapy (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 individuals with refractory or relapsed disease. For individuals with peripheral T-cell lymphoma, salvage therapy includes patients 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 patients who relapse after a complete or partial response after initial induction chemotherapy, or individuals who fail a previous autologous HCT.

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

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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**

PRODUCT VARIATIONS

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

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

DESCRIPTION/BACKGROUND

Treatment for Non-Hodgkin Lymphoma

Hematopoietic Cell Transplantation

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

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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

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Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

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
<i>B-cell lymphoblastic leukaemias/lymphomas</i>
<ul style="list-style-type: none"> • B-lymphoblastic leukaemia/lymphoma, NOS • B-lymphoblastic leukaemia/lymphoma with high hyperdiploidy^a
B-lymphoblastic leukaemia/lymphoma with hypodiploidy
<ul style="list-style-type: none"> • 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
<ul style="list-style-type: none"> • 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

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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
<i>Pre-neoplastic and neoplastic small lymphocytic proliferations</i>
Monoclonal B-cell lymphocytosis
<ul style="list-style-type: none"> Chronic lymphocytic leukaemia/small lymphocytic lymphoma
<i>Splenic B-cell lymphomas and leukaemias</i>
<ul style="list-style-type: none"> Hairy cell leukaemia Splenic marginal zone lymphoma
Splenic diffuse red pulp small B-cell lymphoma
<ul style="list-style-type: none"> Splenic B-cell lymphoma/leukaemia with prominent nucleoli^a
<i>Lymphoplasmacytic lymphoma</i>
Lymphoplasmacytic lymphoma
<ul style="list-style-type: none"> <i>Marginal zone lymphoma</i>
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
<ul style="list-style-type: none"> 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
<i>Cutaneous follicle centre lymphoma</i>
Primary cutaneous follicle centre lymphoma
<i>Mantle cell lymphoma</i>
In situ mantle cell neoplasm ^a
Mantle cell lymphoma
Leukaemic non-nodal mantle cell lymphoma
<i>Transformations of indolent B-cell lymphomas</i>
Transformations of indolent B-cell lymphomas ^a
<i>Large B-cell lymphomas</i>
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

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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
<ul style="list-style-type: none"> • High-grade B-cell lymphoma, NOS • <i>Burkitt lymphoma</i>
Burkitt lymphoma
<i>KSHV/HHV8-associated B-cell lymphoid proliferations and lymphomas</i>
Primary effusion lymphoma
KSHV/HHV8-positive diffuse large B-cell lymphoma ^a
KSHV/HHV8-positive germinotropic lymphoproliferative disorder ^a
<i>Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation</i>
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

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again if their disease remains of the indolent type. Indolent NHL may transform into a more aggressive form, which is generally treated with regimens that are used for aggressive, recurrent NHL. Histologic transformation to higher grade lymphoma occurs in up to 70% of patients with low-grade lymphoma, and median survival with conventional chemotherapy is 1 year or less.

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

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

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

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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

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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/ μ L
 - One point each for age 50 to 59 years, LDH ratio of 0.67-0.99 U/L, WBC of 6700-9999/ μ L
 - 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/ μ L
 - Three points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15,000/ μ L 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

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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 TCR δ and TCR $\gamma\delta$.^{5,10,11} In rare cases, neoplastic cells may express TCR $\alpha\beta$.¹²⁻¹⁴ TCR $\gamma\delta$ variant predominantly affects patients assigned male at birth, with a median age of 35 years, whereas TCR $\alpha\beta$ 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.

RATIONALE

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.

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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.

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For individuals who have hepatosplenic T-cell lymphoma (HSTCL) who receive autologous or allo-HCT as consolidation therapy after first response (complete or partial), the evidence includes observational studies and systematic reviews. Relevant outcomes are OS, DSS, change in disease status, morbid events, and treatment-related mortality and morbidity. Two meta-analyses using patient-level data found that consolidation therapy with HCT improves survival in patients with HSTCL. Two small, retrospective studies have shown similar results. A third small, retrospective study showed no significant differences in OS or PFS between allo-HCT and autologous-HCT, but the achievement of CR at the time of HCT was associated with improved OS in autologous-HCT recipients. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

DEFINITIONS

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 allogeneic 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.

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

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CODING INFORMATION

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								

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POLICY HISTORY

MP 9.042	03/13/2020 Consensus Review. No change to Policy Statements. References reviewed and updated. Definitions to Acronyms added.
	03/22/2021 Consensus Review. Added NCCN statement. Updated Summary of Evidence and References. No changes to coding.
	09/01/2021 Administrative Update. New code C84.7A added. Effective 10/01/2021
	02/08/2022 Consensus Review. No changes to policy statements. References, description/background section, and summary of evidence section updated.
	03/20/2023 Minor Review. Added statement regarding hepatosplenic T cell lymphoma, both MN and INV. Updated policy guidelines, and background. New definitions and references.
	03/27/2024 Consensus Review. No change to policy statement. New references.
	08/30/2024 Administrative Update. Several ICD10 codes deleted, effective 10/01/2024
	02/20/2025 Consensus review. No change to policy statement. Removed NCCN statement.
	06/24/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	01/28/2026 Consensus review. No change to policy intent. Updated rationale and references.

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