PREMERA | BLUE CROSS

MEDICAL POLICY – 8.01.529

Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas

BCBSA Ref. Policy:	8.01.20
Effective Date:	June 10, 2020
Last Revised:	June 9, 2020
Replaces:	8.01.20

RELATED MEDICAL POLICIES:

7.01.50	Placental and Umbilical Cord Blood as a Source of Stem Cells
8.01.15	Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma
8.01.21	Allogeneic Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
8.01.22	Allogeneic Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias
8.01.24	Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
8.01.25	Hematopoietic Cell Transplantation for Autoimmune Diseases
8.01.29	Hematopoietic Cell Transplantation for Hodgkin Lymphoma
8.01.511	Hematopoietic Cell Transplantation for Solid Tumors of Childhood
8.01.532	Hematopoietic Cell Transplantation in the Treatment of Germ-Cell Tumors

Select a hyperlink below to be directed to that section.

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

∞ Clicking this icon returns you to the hyperlinks menu above.

Introduction

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

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

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

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

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

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

Additional Information

Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic hematopoietic cell transplant (HCT), but whose age (typically older than 55 years) or comorbidities (eg, 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.

Documentation Requirements

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

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

Coding

Code	Description
CPT	
38230	Bone marrow harvesting for transplantation; allogeneic
38232	Bone marrow harvesting for transplantation; autologous
38240	Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor
38241	Hematopoietic progenitor cell (HPC); autologous transplantation
HCPCS	
S2140	Cord blood harvesting for transplantation, allogeneic
S2142	Cord blood-derived stem-cell transplantation, allogeneic

Code	Description
S2150	Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post transplant care in the global definition

Related Information

Consideration of Age

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

Definition of Terms

Allogeneic HCT: The conventional ("classical") practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total -body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient.

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

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

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

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

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

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

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

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

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

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

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

Salvage therapy: Chemotherapy given to patients who have either (1) failed to achieve complete remission after initial treatment for newly diagnosed lymphoma, or (2) relapsed after an initial complete remission.

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

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

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

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

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

Benefit Application

The following considerations may supersede this policy:

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

Evidence Review

Description

Hematopoietic cell transplantation (HCT) refers to a procedure by which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or from a donor (allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the cells in it are antigenically "naïve" and thus are associated with a lower incidence of rejection or graft-versus-host disease. Umbilical cord blood is discussed in greater detail in another medical policy (see **Related Policies**).

Background

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.[5] 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[6] and an updated version of the REAL system, the new World Health Organization (WHO) classification.[7] The WHO/REAL classification recognized three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2016 WHO classification (see **Table 2**).[8]

Table 2. Updated WHO Classification (2016)

Classification of Neoplasms	
Mature B-cell neoplasms	Chronic lymphocytic leukemia/small lymphocytic lymphoma
	Monoclonal B-cell lymphocytosis[a]
	B-cell prolymphocytic leukemia
	Splenic marginal zone lymphoma

	Hairy cell leukemia
	• *Splenic lymphoma/leukemia, unclassifiable*
	  ○ *Splenic diffuse red pulp small B-cell lymphoma*
	  ○ *Hairy cell leukemia-variant*

	Lymphoplasmacytic lymphoma • Waldenström macroglobulinemia
	Monoclonal gammogapthy of undetermined significance, IgM[a]
	Heavy chain diseases • Alpha heavy chain disease • Gamma heavy chain disease • Mu heavy chain disease
	Monoclonal gammogapthy of undetermined significance, IgG/IgA[a]
	Plasma cell myeloma
	Solitary plasmacytoma of bone
	Extraosseous plasmacytoma
	Monoclonal immunglobulin deposition diseases[a]
	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
	Nodal marginal zone lymphoma (MZL) • *Pediatric nodal MZL*
	Follicular lymphoma • *In situ follicular neoplasiaa* • *Duodenal-type follicular lymphoma[a]*
	Pediatric type follicular lymphoma[a] • *Large B-cell lymphoma with IRF4 rearrangement[a]*
	Primary cutaneous follicle center lymphoma
	Mantle cell lymphoma • *In situ mantel cell neoplasia[a]*
	Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) • *Germinal center B-cell type[a]* • *Activated B-cell type[a]*

Classification of Neoplasms	
	T-cell/histiocyte-rich large B-cell lymphoma
	DLBCL associated with chronic inflammation
	Lymphomatoid granulomatosis
	Primary mediastinal (thymic) large B-cell lymphoma
	Intravascular large B-cell lymphoma
	Primary cutaneous DLBCL, leg type
	ALK [anaplastic lymphoma kinase]-positive large B-cell lymphoma
	Plasmablastic lymphoma
	Primary effusion lymphoma
	HHV8 DLBCL NOS[a]
	Burkitt lymphoma
	Burkitt-like lymphoma with 11q aberration[a]
	High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements[a]
	High-grade B-cell lymphoma, NOS[a]
	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
	T-cell prolymphocytic leukemia
	T-cell large granular lymphocytic leukemia
	Chronic lymphoproliferative disorder of NK cells
	Aggressive NK-cell leukemia
	Systemic Epstein-Barr virus-positive T-cell lymphoproliferative of childhood[a]
	Hydroa vacciniforme-like lymphoproliferative disorder[a]
	Adult T-cell leukemia/ lymphoma
	Extranodal NK/T-cell lymphoma, nasal type
	Enteropathy-associated T-cell lymphoma
	Monomorphic epitheliotropic intestinal T-cell lymphoma[a]
	Indolent T-cell lymphoproliferative disorder of the GI tract[a]
	Hepatosplenic T-cell lymphoma
	Subcutaneous panniculitis-like T-cell lymphoma
	Mycosis fungoides
	Sézary syndrome

Classification of Neoplasms	
Mature T-cell and NK-cell neoplasms	Primary cutaneous CD30-positive T-cell lymphoproliferative disorder • Lymphomatoid papulosis • Primary cutaneous anaplastic large-cell lymphoma
	Primary cutaneous gamma-delta T-cell lymphoma
	Primary cutaneous aggressive epidermotropic CD8-positive cytotoxic T-cell lymphoma[a]
	Primary cutaneous acral CD8+ T-cell lymphoma[a]
	Primary cutaneous small/medium CD4-positive T-cell lymphoproliferative disorder[a]
	Peripheral T-cell lymphoma, NOS
	Angioimmunoblastic T-cell lymphoma
	Follicular T-cell lymphoma[a]
	Nodal peripheral T-cell lymphoma with TFH phenotype[a]
	Anaplastic large-cell lymphoma (ALCL), ALK-positive
	Anaplastic large-cell lymphoma (ALCL), ALK-negative[a]
	Breast implant–associated anaplastic large-cell lymphoma[a]

ALK: anaplastic lymphoma kinase; GI: gastrointestinal; Ig: immunoglobulin; NK: natural killer.

[a] Changes from 2008 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.[9]

The International Lymphoma Classification Project identified the most common NHL subtypes as follows: DLBCL 31%, follicular lymphoma (FL) 22%, small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) 6%, mantle cell lymphoma (MCL) 6%, peripheral T-cell lymphoma (PTCL) 6%, and marginal zone B-cell lymphoma/MALT lymphoma 5%. All other subtypes each represent less than 2% of cases of NHL.[9]

Types of NHL

In general, the NHL can be divided into two prognostic groups, indolent and aggressive. Indolent NHL has a relatively good prognosis, with a median survival of 10 years; however, it is not curable in advanced clinical stages.[5] Early stage indolent NHL (stage I or II) may be effectively treated with radiation alone.[5] Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages.[5] 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,[10] and median survival with conventional chemotherapy is 1 year or less.

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

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

Risk Assessment

Oncologists developed a clinical tool to aid in predicting the prognosis of patients with aggressive NHL (specifically DLBCL), referred to as the International Prognostic Index (IPI).[11] Before its development in 1993, prognosis was predominantly based on disease stage.

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

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

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

Patients with two or more risk factors have a less than 50% chance of relapse-free survival (RFS) and OS at 5 years. Age-adjusted IPI and stage-adjusted modifications of this IPI are used for younger 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 FL, which has multiple independent risk factors for relapse after a first complete remission. The proposed and validated Follicular Lymphoma International Prognostic Index (FLIPI) contains five adverse prognostic factors:

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

These five factors are used to stratify patients into three categories of risk: low (0-1 risk factor), intermediate (2 risk factors), or poor (3 or more risk factors).[12]

Mantle Cell Lymphoma

Mantle Cell Lymphoma (MCL) comprises 65% to 68% of NHL and has been recognized for some time now as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t(11;14), and the term mantle cell lymphoma was proposed by Banks et al(1992)[46] 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 IPI or FLIPI system to patients with MCL showed limitations, which included no separation of

some important risk groups. In addition, some of the individual IPI and FLIPI risk factors, including number of extranodal sites and number of involved nodal areas showed no prognostic relevance, and hemoglobin showed no independent prognostic relevance in patients with MCL.[47] 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 (MIPI) 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
    - 0 points each are assigned for age younger than 50 years, ECOG Performance Status score of 0-1, LDH ratio of less than 0.67 U/L, WBC of less than 6700/mL
    - 1 point each for age 50 to 59 years, LDH ratio of 0.67-0.99 U/L, WBC 6700-9999/mL
    - 2 points each for age 60 to 69 years, ECOG Performance Status score of 2-4, LDH ratio of 1.00-1.49 U/L, WBC of 10,000-14,999/m:
    - 3 points each for age 70 years or older, LDH ratio of 1.5 U/L or greater, WBC of 15,000m/L or more

MCL IPI allows separation of 3 groups with significantly different prognoses[47]:

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

Peripheral T-Cell Lymphoma

Most peripheral T-cell lymphomas (PTCL) are aggressive and fall into the category of PTCL, unspecified (PTCL-u) or not otherwise specified (PTCL-NOS), angioimmunoblastic or anaplastic large cell, which combined make up approximately 60% to 70% of 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 HCT as therapy.

Staging

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

Table 3. Ann Arbor Classification

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

Treatment for NHL

Hematopoietic Cell Transplantation

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is critical for achieving a good outcome with allogenic HCT. Compatibility is established by typing of human leukocyte antigens (HLAs) using cellular, serologic, or molecular techniques. HLA

refers to the tissue type expressed at the HLA-A, -B, and -DR loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

Conventional Preparative Conditioning for HCT

The conventional practice of allogeneic HCT involves administration of cytotoxic agents (eg, cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy effect mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered the potentially curative component, it may be overwhelmed by extant disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to 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 increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy (with or without radiation) to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the 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 of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and nonrelapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC

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

Summary of Evidence

For individuals who have indolent B-cell non-Hodgkin lymphomas (NHL) who receive autologous HCT as first-line therapy, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have aggressive B-cell non-Hodgkin lymphomas, excluding mantle cell lymphoma (MCL), who receive autologous HCT as consolidation therapy after first complete remission, the evidence includes randomized trials and systematic reviews. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. While the data from the randomized trials offer conflicting results, some of the data has revealed an overall survival 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 shown an overall survival benefit with the previously described approach. Results of a retrospective study comparing autologous and allo-HCT for relapsed or refractory 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 non-Hodgkin lymphomas, excluding MCL, who receive tandem autologous and allogeneic HCT, the evidence includes several nonrandomized trials. The relevant outcomes are overall survival, disease-specific survival, 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 non-Hodgkin lymphoma, 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 mantle cell lymphoma who receive autologous, allogeneic, or tandem HCT, the evidence includes case series. The relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. Due in part to the rarity of this disease, randomized trials on the use of HCT in mantle cell lymphoma have not been conducted. Case series 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. Allogeneic 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 allogeneic HCT, the evidence includes prospective trials and case reports. Relevant outcomes are overall survival, disease-specific survival, change in disease status, morbid events, and treatment-related mortality and morbidity. The role of HCT in PTCL is not well-defined. Few studies have been conducted, and most were performed retrospectively, with a limited number of 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 in which the study addresses. Additionally, studies of this nature often mix of three types of patients: one type of patient has PTCL not otherwise specified, which has a poorer prognosis; another type has anaplastic lymphoma kinase (ALK)-positive anaplastic large-cell lymphomas (ALCL), which has a better prognosis—even with conventional chemotherapy regimens; and a third type has ALK-negative ALCL, which has a worse prognosis than ALK-positive ALCL (but better than patients with PTCL not otherwise specified). There have been no randomized studies comparing chemotherapy regimens solely in patients with PTCL (ie, some randomized studies have included PTCL with aggressive B-cell lymphomas). For front-line therapy, 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. No relevant data for the use of allogeneic HCT in the first-line setting are 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.

Ongoing and Unpublished Clinical Trials

Some currently unpublished phase III trials that might influence this review are listed in National Cancer Institute's Physician Data Query database.

Other currently unpublished trials that might influence this review are listed in **Table 4**.

Table 4. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01811368	Use of Zevalin to Enhance the Efficacy of Non-Myeloablative Allogeneic Transplantation in Patients With Relapsed or Refractory CD20+ Non-Hodgkin's Lymphoma	20	Jun 2020
NCT01908777	A Phase 2 Multicenter Study of High Dose Chemotherapy With Autologous Stem Cell Transplant Followed by Maintenance Therapy With Romidepsin for the Treatment of TCell Non-Hodgkin Lymphoma	34	Jul 2020
NCT02859402	Allogenic Stem Cell Transplantation With 3-days Busulfan Plus Fludarabine as Conditioning in Patients With Relapsed or Refractory T-, NK/T-cell Lymphomas	34	Dec 2021
NCT03583424	A Phase I/II Trial of Venetoclax and BEAM Conditioning Followed by Autologous Stem Cell Transplantation for Patients With Primary Refractory Non-Hodgkin Lymphoma	18	Dec 2021
Unpublished			
NCT00802113	Sequential Myeloablative Stem Cell Transplantation and Reduced Intensity Allogeneic Stem Cell Transplantation in Patients With Refractory or Recurrent Non-Hodgkin's Lymphoma and Hodgkin's Disease	30	Oct 2014 (results posted on clinicaltrials.gov; summarized in Indication 3)
NCT01296256	Bendamustine, Cytarabine, Etoposide and Melphalan as Conditioning for Autologous Stem Cell Transplant in Patients With Aggressive Non-Hodgkin's Lymphoma	60	Nov 2015 (updated Feb 2016)

NCT: national clinical trial.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2011 Input

In response to requests, input was received from three physician specialty societies and three academic medical centers while this policy was under review in 2011. Input was solicited particularly for the use of hematopoietic cell transplantation (HCT) in mantle cell lymphoma (MCL) and peripheral T-cell lymphoma. There was a uniform agreement for the use of autologous HCT to consolidate the first remission in MCL. There was a general agreement for the use of allogeneic HCT as salvage therapy for MCL, with less agreement on the use of autologous HCT in the salvage setting. For peripheral T-cell lymphoma, there was general agreement on the use of autologous HCT to consolidate a complete remission in high-risk patients and the salvage setting. Input was split on the use of allogeneic HCT to consolidate a first complete remission or as salvage therapy, but there was more support to consider it medically necessary in both settings.

2009 Input

In response to requests, input was received from one physician specialty society and one academic medical center while this policy was under review in 2009. There was general agreement with the policy statements. Both reviewers agreed that allogeneic HCT with reduced-intensity conditioning should be considered medically necessary in patients with non-Hodgkin lymphoma who do not qualify for a myeloablative allogeneic HCT. One reviewer responded on the medical necessity of HCT in patients with MCL in the first remission and recently published literature supported this. There was conflicting input on whether HCT should be considered investigational for peripheral T-cell lymphoma. Also, the one reviewer commented that with the increasing use of rituximab and its success in improving patient outcomes, the role of HCT in consolidating first complete response in high-risk patients is coming into question.

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network guidelines on B-cell lymphomas (v.6.2019) include the following recommendations[72]:

- For follicular lymphoma, marginal zone lymphomas, and mantle cell lymphoma, recommend allogeneic HCT as second-line consolidation therapy.
- For DLBCL, "[a]llogenic 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 to achieve a complete or partial response to second-line therapy National Comprehensive Cancer Network guidelines on T-cell lymphomas (v.2.2019) include the following recommendations[73]:

> "Second-line systematic therapy followed by consolidation with HDT [high-dose therapy]/ASCR [autologous stem cell rescue] or allogeneic HSCT 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."

Medicare National Coverage

Medicare has the following national coverage determination for the use of autologous cell transplantation for Hodgkin and non-Hodgkin lymphomas.[74]

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

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

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

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

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

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

Regulatory Status

The 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.

References

1. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous bone marrow transplantation for the treatment of non-Hodgkin's lymphoma. TEC Evaluations 1987;2:61.
2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Allogeneic bone marrow transplantation (BMT) in the treatment of Hodgkin's disease (lymphoma) and non-Hodgkin's lymphoma. TEC Evaluations 1990;5:178.
3. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy with autologous stem-cell support or allogeneic stem-cell support for follicular non-Hodgkin's lymphoma. TEC Assessments 1995;Volume 10:Tab 28
4. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments 2000;Volume 15:Tab 9.
5. National Cancer Institute. Adult Non-Hodgkin Lymphoma Treatment (PDQ)Health Professional Version. 2019; **http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/healthprofessional** Accessed April 2020.
6. Harris NL, Jaffe ES, Stein H, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. Blood. Sep 1 1994;84(5):1361-1392. PMID 8068936
7. Harris NL, Jaffe ES, Diebold J, et al. The World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues. Report of the Clinical Advisory Committee meeting, Airlie House, Virginia, November 1997. Ann Oncol. Dec 1999;10(12):1419-1432. PMID 10643532
8. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. May 19 2016;127(20):2375-2390. PMID 26980727
9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non- Hodgkin's Lymphomas. Version 2.2015. **https://www2.tri-kobe.org/nccn/guideline/hematologic/nhl/english/nhl.pdf** Accessed April 2020.
10. Laport GG. The role of hematopoietic cell transplantation for follicular non-Hodgkin's lymphoma. Biol Blood Marrow Transplant. Jan 2006;12(1 Suppl 1):59-65. PMID 16399587
11. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med. Sep 30 1993;329(14):987-994. PMID 8141877
12. Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. Sep 1 2004;104(5):1258-1265. PMID 15126323
13. Al Khabori M, de Almeida JR, Guyatt GH, et al. Autologous stem cell transplantation in follicular lymphoma: a systematic review and meta-analysis. J Natl Cancer Inst. Jan 4 2012;104(1):18-28. PMID 22190633
14. Schaaf M, Reiser M, Borchmann P, et al. High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults. Cochrane Database Syst Rev. Jan 18 2012;1:CD007678. PMID 22258971
15. Ladetto M, De Marco F, Benedetti F, et al. Prospective, multicenter randomized GITMO/IIL trial comparing intensive (R-HDS) versus conventional (CHOP-R) chemoimmunotherapy in high-risk follicular lymphoma at diagnosis: the superior disease control of R-HDS does not translate into an overall survival advantage. Blood. Apr 15 2008;111(8):4004-4013. PMID 18239086
16. Sebban C, Mounier N, Brousse N, et al. Standard chemotherapy with interferon compared with CHOP followed by high-dose therapy with autologous stem cell transplantation in untreated patients with advanced follicular lymphoma: the GELF-94 randomized study from the Groupe d'Etude des Lymphomes de l'Adulte (GELA). Blood. Oct 15 2006;108(8):2540-2544. PMID 16835383

17. Deconinck E, Foussard C, Milpied N, et al. High-dose therapy followed by autologous purged stem-cell transplantation and doxorubicin-based chemotherapy in patients with advanced follicular lymphoma: a randomized multicenter study by GOELAMS. Blood. May 15 2005;105(10):3817-3823. PMID 15687232

18. Lenz G, Dreyling M, Schiegnitz E, et al. Myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission prolongs progression-free survival in follicular lymphoma: results of a prospective, randomized trial of the German Low-Grade Lymphoma Study Group. Blood. Nov 1 2004;104(9):2667-2674. PMID 15238420

19. Schouten HC, Qian W, Kvaloy S, et al. High-dose therapy improves progression-free survival and survival in relapsed follicular non-Hodgkin's lymphoma: results from the randomized European CUP trial. J Clin Oncol. Nov 1 2003;21(21):3918-3927. PMID 14517188

20. Bozkaya Y, Uncu D, Dagdas S, et al. Evaluation of lymphoma patients receiving high-dose therapy and autologous stem cell transplantation: experience of a single center. Indian J Hematol Blood Transfus. Sep 2017;33(3):361-369. PMID 28824238

21. Jimenez-Ubieto A, Grande C, Caballero D, et al. Autologous stem cell transplantation may be curative for patients with follicular lymphoma with early therapy failure who reach complete response after rescue treatment. Hematol Oncol. 2018 Dec;36(5). PMID 30129233

22. Greb A, Bohlius J, Schiefer D, et al. High-dose chemotherapy with autologous stem cell transplantation in the first-line treatment of aggressive non-Hodgkin lymphoma (NHL) in adults. Cochrane Database Syst Rev. Jan 23 2008(1): CD004024. PMID 18254036

23. Haioun C, Lepage E, Gisselbrecht C, et al. Benefit of autologous bone marrow transplantation over sequential chemotherapy in poor-risk aggressive non-Hodgkin's lymphoma: updated results of the prospective study LNH87-2. Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. Mar 1997;15(3):1131-1137. PMID 9060555

24. Kaiser U, Uebelacker I, Abel U, et al. Randomized study to evaluate the use of high-dose therapy as part of primary treatment for aggressive lymphoma. J Clin Oncol. Nov 15 2002;20(22):4413-4419. PMID 12431962

25. Kluin-Nelemans HC, Zagonel V, Anastasopoulou A, et al. Standard chemotherapy with or without high-dose chemotherapy for aggressive non-Hodgkin's lymphoma: randomized phase III EORTC study. J Natl Cancer Inst. Jan 3 2001;93(1):22-30. PMID 11136838

26. Sweetenham JW, Santini G, Qian W, et al. High-dose therapy and autologous stem-cell transplantation versus conventional-dose consolidation/maintenance therapy as postremission therapy for adult patients with lymphoblastic lymphoma: results of a randomized trial of the European Group for Blood and Marrow Transplantation and the United Kingdom Lymphoma Group. J Clin Oncol. Jun 1 2001;19(11):2927-2936. PMID 11387366

27. Fisher RI. Autologous stem-cell transplantation as a component of initial treatment for poor-risk patients with aggressive non-Hodgkin's lymphoma: resolved issues versus remaining opportunity [comment]. J Clin Oncol. Nov 15 2002;20(22):4411-4412. PMID 12431961

28. Haioun C, Lepage E, Gisselbrecht C, et al. Survival benefit of high-dose therapy in poor-risk aggressive non- Hodgkin's lymphoma: final analysis of the prospective LNH87-2 protocol--a groupe d'Etude des lymphomes de l'Adulte study. J Clin Oncol. Aug 2000;18(16):3025-3030. PMID 10944137

29. Fisher RI. Autologous bone marrow transplantation for aggressive non-Hodgkin's lymphoma: lessons learned and challenges remaining. J Natl Cancer Inst. Jan 3 2001;93(1):4-5. PMID 11136829

30. Hahn T, Wolff SN, Czuczman M, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of diffuse large cell B-cell non-Hodgkin's lymphoma: an evidence-based review. Biol Blood Marrow Transplant. Jul 2001;7(6):308-331. PMID 11464975

31. Kimby E, Brandt L, Nygren P, et al. A systematic overview of chemotherapy effects in aggressive non-Hodgkin's lymphoma. Acta Oncol. Jul 2001;40(2-3):198-212. PMID 11441932

32. Philip T, Biron P. High-dose chemotherapy and autologous bone marrow transplantation in diffuse intermediate- and high-grade non-Hodgkin lymphoma. Crit Rev Oncol Hematol. Feb 2002;41(2):213-223. PMID 11856597

33. Betticher DC, Martinelli G, Radford JA, et al. Sequential high dose chemotherapy as initial treatment for aggressive subtypes of non-Hodgkin lymphoma: results of the international randomized phase III trial (MISTRAL). Ann Oncol. Oct 2006;17(10):1546-1552. PMID 16888080

34. Baldissera RC, Nucci M, Vigorito AC, et al. Frontline therapy with early intensification and autologous stem cell transplantation versus conventional chemotherapy in unselected high-risk, aggressive non-Hodgkin's lymphoma patients: a prospective randomized GEMOH report. Acta Haematol. Jan 2006;115(1-2):15-21. PMID 16424644

35. Olivieri A, Santini G, Patti C, et al. Upfront high-dose sequential therapy (HDS) versus VACOP-B with or without HDS in aggressive non-Hodgkin's lymphoma: long-term results by the NHLCSG. Ann Oncol. Dec 2005;16(12):1941-1948. PMID 16157621

36. Stiff PJ, Unger JM, Cook JR, et al. Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma. N Engl J Med. Oct 31 2013;369(18):1681-1690. PMID 24171516

37. Strubmann T, Fritsch K, Baumgarten A, et al. Favourable outcomes of poor prognosis diffuse large B-cell lymphoma patients treated with dose-dense rituximab, high-dose methotrexate and six cycles of CHOP-14 compared to first-line autologous transplantation. Br J Haematol. Sep 2017;178(6):927-935. PMID 28643323

38. Casasnovas RO, Ysebaert L, Thieblemont C, et al. FDG-PET-driven consolidation strategy in diffuse large B-cell lymphoma: final results of a randomized phase 2 study. Blood. Sep 14 2017;130(11):1315-1326. PMID 28701367

39. Qualls D, Sullivan A, Li S, et al. High-dose thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation as upfront consolidation for systemic non-Hodgkin lymphoma with synchronous central nervous system involvement. Clin Lymphoma Myeloma Leuk. Dec 2017;17(12):884-888. PMID 28870642

40. Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program. Dec 2009:523-531. PMID 20008237

41. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. Dec 7 1995;333(23):1540-1545. PMID 7477169

42. Fujita N, Kobayashi R, Atsuta Y et al. Hematopoietic stem cell transplantation in children and adolescents with relapsed or refractory B-cell non-Hodgkin lymphoma. Int. J. Hematol. 2019 Apr;109(4). PMID 30701466

43. Monjanel H, Deconinck E, Perrodeau E, et al. Long-term follow-up of tandem high-dose therapy with autologous stem cell support for adults with high-risk age-adjusted international prognostic index aggressive non-Hodgkin Lymphomas: a GOELAMS pilot study. Biol Blood Marrow Transplant. Jun 2011;17(6):935-940. PMID 21109011

44. Papadopoulos KP, Noguera-Irizarry W, Wiebe L, et al. Pilot study of tandem high-dose chemotherapy and autologous stem cell transplantation with a novel combination of regimens in patients with poor risk lymphoma. Bone Marrow Transplant. Sep 2005;36(6):491-497. PMID 16044139

45. Tarella C, Zanni M, Di Nicola M, et al. Prolonged survival in poor-risk diffuse large B-cell lymphoma following front-line treatment with rituximab-supplemented, early-intensified chemotherapy with multiple autologous hematopoietic stem cell support: a multicenter study by GITIL (Gruppo Italiano Terapie Innovative nei Linfomi). Leukemia. Aug 2007;21(8):1802-1811. PMID 17554382

46. Banks PM, Chan J, Cleary ML, et al. Mantle cell lymphoma. A proposal for unification of morphologic, immunologic, and molecular data. Am J Surg Pathol. Jul 1992;16(7):637-640. PMID 1530105

47. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. Jan 15 2008;111(2):558-565. PMID 17962512

48. Dreyling M, Lenz G, Hoster E, et al. Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle- cell lymphoma: results of a prospective randomized trial of the European MCL Network. Blood. Apr 1 2005;105(7):2677-2684. PMID 15591112

49. Till BG, Gooley TA, Crawford N, et al. Effect of remission status and induction chemotherapy regimen on outcome of autologous stem cell transplantation for mantle cell lymphoma. Leuk Lymphoma. Jun 2008;49(6):1062-1073. PMID 18452065

50. Geisler CH, Kolstad A, Laurell A, et al. Long-term progression-free survival of mantle cell lymphoma after intensive front-line immunochemotherapy with in vivo-purged stem cell rescue: a nonrandomized phase 2 multicenter study by the Nordic Lymphoma Group. Blood. Oct 1 2008;112(7):2687-2693. PMID 18625886

51. Evens AM, Winter JN, Hou N, et al. A phase II clinical trial of intensive chemotherapy followed by consolidative stem cell transplant: long-term follow-up in newly diagnosed mantle cell lymphoma. Br J Haematol. Feb 2008;140(4):385-393. PMID 18162124

52. Garcia-Noblejas A, Cannata-Ortiz J, Conde E, et al. Autologous stem cell transplantation (ASCT) in patients with mantle cell lymphoma: a retrospective study of the Spanish lymphoma group (GELTAMO). Ann Hematol. Aug 2017;96(8):1323-1330. PMID 28536895

53. Villanueva ML, Vose JM. The role of hematopoietic stem cell transplantation in non-Hodgkin lymphoma. Clin Adv Hematol Oncol. Jul 2006;4(7):521-530. PMID 17147239

54. Khouri IF, Lee MS, Saliba RM, et al. Nonablative allogeneic stem-cell transplantation for advanced/recurrent mantle-cell lymphoma. J Clin Oncol. Dec 1 2003;21(23):4407-4412. PMID 14645431

55. Maris MB, Sandmaier BM, Storer BE, et al. Allogeneic hematopoietic cell transplantation after fludarabine and 2 Gy total body irradiation for relapsed and refractory mantle cell lymphoma. Blood. Dec 1 2004;104(12):3535- 3542. PMID 15304387

56. Tam CS, Bassett R, Ledesma C, et al. Mature results of the M. D. Anderson Cancer Center risk-adapted transplantation strategy in mantle cell lymphoma. Blood. Apr 30 2009;113(18):4144-4152. PMID 19168784

57. Geisler C. Mantle cell lymphoma: are current therapies changing the course of disease? Curr Oncol Rep. Sep 2009;11(5):371-377. PMID 19679012

58. Reimer P. Impact of autologous and allogeneic stem cell transplantation in peripheral T-cell lymphomas. Adv Hematol. 2010;2010:320624. PMID 21253465

59. Corradini P, Tarella C, Zallio F, et al. Long-term follow-up of patients with peripheral T-cell lymphomas treated up-front with high-dose chemotherapy followed by autologous stem cell transplantation. Leukemia. Sep 2006;20(9):1533-1538. PMID 16871285

60. Mercadal S, Briones J, Xicoy B, et al. Intensive chemotherapy (high-dose CHOP/ESHAP regimen) followed by autologous stem-cell transplantation in previously untreated patients with peripheral T-cell lymphoma. Ann Oncol. May 2008;19(5):958-963. PMID 18303032

61. Rodriguez J, Conde E, Gutierrez A, et al. Frontline autologous stem cell transplantation in high-risk peripheral T- cell lymphoma: a prospective study from The Gel-Tamo Study Group. Eur J Haematol. Jul 2007;79(1):32-38. PMID 17598836

62. Wang J, Wei L, Ye J, et al. Autologous hematopoietic stem cell transplantation may improve long-term outcomes in patients with newly diagnosed extranodal natural killer/T-cell lymphoma, nasal type: a retrospective controlled study in a single center. Int J Hematol. Jan 2018;107(1):98-104. PMID 28856590

63. Kewalramani T, Zelenetz AD, Teruya-Feldstein J, et al. Autologous transplantation for relapsed or primary refractory peripheral T-cell lymphoma. Br J Haematol. Jul 2006;134(2):202-207. PMID 16759221

64. Song KW, Mollee P, Keating A, et al. Autologous stem cell transplant for relapsed and refractory peripheral T-cell lymphoma: variable outcome according to pathological subtype. Br J Haematol. Mar 2003;120(6):978-985. PMID 12648067

65. Rodriguez J, Conde E, Gutierrez A, et al. The adjusted International Prognostic Index and beta-2-microglobulin predict the outcome after autologous stem cell transplantation in relapsing/refractory peripheral T-cell lymphoma. Haematologica. Aug 2007;92(8):1067-1074. PMID 17640855

66. Jacobsen ED, Kim HT, Ho VT, et al. A large single-center experience with allogeneic stem-cell transplantation for peripheral T-cell non-Hodgkin lymphoma and advanced mycosis fungoides/Sezary syndrome. Ann Oncol. Jul 2011;22(7):1608-1613. PMID 21252059

67. Kyriakou C, Canals C, Finke J, et al. Allogeneic stem cell transplantation is able to induce long-term remissions in angioimmunoblastic T-cell lymphoma: a retrospective study from the lymphoma working party of the European group for blood and marrow transplantation. J Clin Oncol. Aug 20 2009;27(24):3951-3958. PMID 19620487

68. Corradini P, Dodero A, Zallio F, et al. Graft-versus-lymphoma effect in relapsed peripheral T-cell non-Hodgkin's lymphomas after reduced-intensity conditioning followed by allogeneic transplantation of hematopoietic cells. J Clin Oncol. Jun 1 2004;22(11):2172-2176. PMID 15169805

69. Le Gouill S, Milpied N, Buzyn A, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. J Clin Oncol. May 10 2008;26(14):2264-2271. PMID 18390969

70. Hosing C, Champlin RE. Stem-cell transplantation in T-cell non-Hodgkin's lymphomas. Ann Oncol. Jul 2011;22(7):1471-1477. PMID 21551006

71. Rodriguez J, Gutierrez A, Martinez-Delgado B, et al. Current and future aggressive peripheral T-cell lymphoma treatment paradigms, biological features and therapeutic molecular targets. Crit Rev Oncol Hematol. Sep 2009;71(3):181-198. PMID 19056295

72. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: B-Cell Lymphomas. Version 6.2019. **https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf** Accessed April 2020.

73. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: T-Cell Lymphomas. Version 2.2019. **https://www.nccn.org/professionals/physician_gls/pdf/t-cell.pdf** Accessed April 2020.

74. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation (Formerly 110.8.1) (110.23). 2016; **https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=366&ncdver=1&DocID=110.23&list_type=ncd&bc=gAAAAAgAAAAAAA%3d%3d&** Accessed April 2020.

History

Date	Comments
04/14/14	New PR policy; replaces 8.01.20. Policy updated with literature search through December 23, 2013. Policy section reworded and reformatted. Policy statements changed as follows: NHL B-cell – RIC is now medically necessary; B-cell Indolent – RIC is now investigational (previously medically necessary); Mature T-cell or NK – RIC is now investigational to consolidate CR (previously medically necessary). References 37 and 42 added; reference 66 updated.
06/24/14	Update Related Policies. Remove 8.01.35, 8.01.42 and 8.01.54, then add 8.01.532
12/03/14	Update Related Policies. Remove 8.01.17 and 8.01.26.
04/24/15	Annual Review. Policy updated with literature review; no change in policy statements.
08/09/16	Update Related Policies. Remove 8.01.27 as it was archived.
11/04/16	Coding update. Removed codes that are transplant benefit related.
12/01/16	Annual review, approved November 8, 2016. Added references 68 and 69. No changes to policy statement.

Date	Comments
04/01/17	Updated titles in Related Policies.
08/01/17	Updated title of Related Policy 8.01.511.
12/01/17	Annual Review, approved November 9, 2017. Updated WHO classifications and Summary of Evidence section. No changes to policy statement.
05/01/18	Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017. Policy statements unchanged.
09/01/18	Minor update. Re-adding Consideration of Age information which was inadvertently removed during a previous update.
04/01/19	Minor update, added Documentation Requirements section.
05/01/19	Annual Review, approved April 18, 2019. Policy updated with literature review through November 2018; reference 60 added. Policy statements unchanged.
05/01/20	Annual Review, approved April 23, 2020. Policy updated with literature review through November 2019; references added. Policy statements unchanged.
05/06/20	Delete policy, approved May 5, 2020. This policy will be deleted effective July 2, 2020, and replaced with InterQual criteria for dates of service on or after July 2, 2020.
06/10/20	Interim Review, approved June 9, 2020, effective June 10, 2020. This policy is reinstated immediately and will no longer be deleted or replaced with InterQual criteria on July 2, 2020.

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

PREMERA | BLUE CROSS

An Independent Licensee of the Blue Cross Blue Shield Association

Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:

- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:
Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html.

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

አማሪኛ (Amharic):
ይህ ማስታወቂያ አስፈላጊ መረጃ ይዟል። ይህ ማስታወቂያ ስለ ማመልከቻዎ ወይም የ Premera Blue Cross ሽፋን አስፈላጊ መረጃ ሊኖረው ይችላል። በዚህ ማስታወቂያ ውስጥ ቁልፍ ቀኖች ሊኖሩ ይችላሉ። የጤናን ሽፋንዎን ለመጠበቅና በአከፋፈል እርዳታ ለማግኘት በተውሰኑ የጊዜ ገደቦች እርምጃ መውሰድ ይገባዎት ይሆናል። ይህን መረጃ እንዲያገኙ እና ያለምንም ክፍያ በቋንቋዎ እርዳታ እንዲያገኙ መብት አለዎት።በስልክ ቁጥር 800-722-1471 (TTY: 800-842-5357) ይደውሉ።

العربية (Arabic):
يحوي هذا الإشعار معلومات هامة. قد يحوي هذا الإشعار معلومات مهمة بخصوص طلبك أو التغطية التي تريد الحصول عليها من خلال Premera Blue Cross. قد تكون هناك تواريخ مهمة في هذا الإشعار. وقد تحتاج لاتخاذ إجراء في تواريخ معينة للحفاظ على تغطيتك الصحية أو للمساعدة في دفع التكاليف. يحق لك الحصول على هذه المعلومات والمساعدة بلغتك دون تكبد أية تكلفة. اتصل بـ800-722-1471 (TTY: 800-842-5357)

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或者費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357)。

Oromoo (Cushite):
Beeksisni kun odeeffannoo barbaachisaa qaba. Beeksisti kun sagantaa yookan karaa Premera Blue Cross tiin tajaajila keessan ilaalchisee odeeffannoo barbaachisaa qabaachuu danda'a. Guyyaawwan murteessaa ta'an beeksisa kana keessatti ilaalaa. Tarii kaffaltiidhaan deeggaramuuf yookan tajaajila fayyaa keessaniif guyyaa dhumaa irratti wanti raawwattan jiraachuu danda'a. Kaffaltii irraa bilisa haala ta'een afaan keessaniin odeeffannoo argachuu fi deeggarsa argachuuf mirga ni qabaattu. Lakkoofsa bilbilaa 800-722-1471 (TTY: 800-842-5357) tii bilbilaa.

Français (French):
Cet avis a d'importantes informations. Cet avis peut avoir d'importantes informations sur votre demande ou la couverture par l'intermédiaire de Premera Blue Cross. Le présent avis peut contenir des dates clés. Vous devrez peut-être prendre des mesures par certains délais pour maintenir votre couverture de santé ou d'aide avec les coûts. Vous avez le droit d'obtenir cette information et de l'aide dans votre langue à aucun coût. Appelez le 800-722-1471 (TTY: 800-842-5357).

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan ladann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kèk aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resevwa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou peye pou sa. Rele nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):
Diese Benachrichtigung enthält wichtige Informationen. Diese Benachrichtigung enthält unter Umständen wichtige Informationen bezüglich Ihres Antrags auf Krankenversicherungsschutz durch Premera Blue Cross. Suchen Sie nach eventuellen wichtigen Terminen in dieser Benachrichtigung. Sie könnten bis zu bestimmten Stichtagen handeln müssen, um Ihren Krankenversicherungsschutz oder Hilfe mit den Kosten zu behalten. Sie haben das Recht, kostenlose Hilfe und Informationen in Ihrer Sprache zu erhalten. Rufen Sie an unter 800-722-1471 (TTY: 800-842-5357).

Hmoob (Hmong):
Tsab ntawv tshaj xo no muaj cov ntshiab lus tseem ceeb. Tej zaum tsab ntawv tshaj xo no muaj cov ntsiab lus tseem ceeb txog koj daim ntawv thov kev pab los yog koj qhov kev pab cuam los ntawm Premera Blue Cross. Tej zaum muaj cov hnub tseem ceeb uas sau rau hauv daim ntawv no. Tej zaum koj kuj yuav tau ua qee yam uas peb kom koj ua tsis pub dhau cov caij nyoog uas teev tseg rau hauv daim ntawv no mas koj thiaj yuav tau txais kev pab cuam kho mob los yog kev pab them tej nqi kho mob ntawd. Koj muaj cai kom lawv muab cov ntshiab lus no uas tau muab sau ua koj hom lus pub dawb rau koj. Hu rau 800-722-1471 (TTY: 800-842-5357).

Iloko (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabalin nga adda ket naglaon iti napateg nga impormasion maipanggep iti apliksayonyo wenno coverage babaen iti Premera Blue Cross. Daytoy ket mabalin dagiti importante a petsa iti daytoy a pakdaar. Mabalin nga adda rumbeng nga aramidenyo nga addang sakbay dagiti partikular a naituding nga aldaw tapno mapagtalinaedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagsasao nga awan ti bayadanyo. Tumawag iti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiama 800-722-1471 (TTY: 800-842-5357).

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Cross の申請または補償範囲に関する重要な情報が含まれている場合があります。この通知に記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期日までに行動を取らなければならない場合があります。ご希望の言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관하여 그리고 Premera Blue Cross 를 통한 커버리지에 관한 정보를 포함하고 있을 수 있습니다. 본 통지서에는 핵심이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하는 이러한 정보와 도움을 귀하의 언어로 비용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357) 로 전화하십시오.

ລາວ (Lao):
ແຈ້ງການນີ້ມີຂໍ້ມູນສຳຄັນ. ແຈ້ງການນີ້ອາດຈະມີຂໍ້ມູນສຳຄັນກ່ຽວກັບຄຳຮ້ອງສະໝັກ ຫຼື ຄວາມຄຸ້ມຄອງປະກັນໄພຂອງທ່ານຜ່ານ Premera Blue Cross. ອາດຈະມີວັນທີສຳຄັນໃນແຈ້ງການນີ້. ທ່ານອາດຈະຈຳເປັນຕ້ອງດຳເນີນການຕາມກຳນົດເວລາສະເພາະເພື່ອຮັກສາຄວາມຄຸ້ມຄອງປະກັນສຸຂະພາບ ຫຼື ຄວາມຊ່ວຍເຫຼືອເລື່ອງຄ່າໃຊ້ຈ່າຍຂອງທ່ານໄວ້. ທ່ານມີສິດໄດ້ຮັບຂໍ້ມູນນີ້ ແລະ ຄວາມຊ່ວຍເຫຼືອເປັນພາສາຂອງທ່ານໂດຍບໍ່ເສຍຄ່າ. ໃຫ້ໂທຫາ 800-722-1471 (TTY: 800-842-5357).

ភាសាខ្មែរ (Khmer):
សេចក្តីជូនដំណឹងនេះមានព័ត៌មានយ៉ាងសំខាន់។ សេចក្តីជូនដំណឹងនេះប្រហែលជាមានព័ត៌មានយ៉ាងសំខាន់អំពីទម្រង់បែបបទ ឬការរ៉ាប់រងរបស់អ្នកតាមរយៈ Premera Blue Cross ។ ប្រហែលជាមាន កាលបរិច្ឆេទសំខាន់នៅក្នុងសេចក្តីជូនដំណឹងនេះ។ អ្នកប្រហែលជាត្រូវការបញ្ចេញសមត្ថភាព ដល់កំណត់ថ្ងៃជាក់ច្បាស់នានា ដើម្បីនឹងរក្សាទុកការជានាវ៉ាប់រងសុខភាពរបស់អ្នក ឬប្រាក់ជំនួយចេញផ្លែ។ អ្នកមានសិទ្ធិទទួលព័ត៌មាននេះ និងជំនួយនៅក្នុងភាសារបស់អ្នកដោយមិនអស់លុយឡើយ។ សូមទូរស័ព្ទ 800-722-1471 (TTY: 800-842-5357)។

ਪੰਜਾਬੀ (Punjabi):
ਇਸ ਨੋਟਿਸ ਵਿਚ ਖਾਸ ਜਾਣਕਾਰੀ ਹੈ. ਇਸ ਨੋਟਿਸ ਵਿਚ Premera Blue Cross ਵਲੋਂ ਤੁਹਾਡੀ ਕਵਰੇਜ ਅਤੇ ਅਰਜੀ ਬਾਰੇ ਮਹੱਤਵਪੂਰਨ ਜਾਣਕਾਰੀ ਹੋ ਸਕਦੀ ਹੈ . ਇਸ ਨੋਜਿਸ ਜਵਚ ਖਾਸ ਤਾਰੀਖਾ ਹੋ ਸਕਦੀਆਂ ਹਨ. ਜੇਕਰ ਤੁਸੀ ਜਸਹਤ ਕਵਰੇਜ ਰਿੱਖਣੀ ਹੋਵੇ ਜਾ ਓਸ ਦੀ ਲਾਗਤ ਜਵਿੱਚ ਮਦਦ ਦੇ ਇਛੁੱਕ ਹੋ ਤਾਂ ਤੁਹਾਨੂੰ ਅੰਤਮ ਤਾਰੀਖ਼ ਤੋਂ ਪਹਿਲਾਂ ਕੁੱਝ ਖਾਸ ਕਦਮ ਚੁੱਕਣ ਦੀ ਲੋੜ ਹੋ ਸਕਦੀ ਹੈ ,ਤੁਹਾਨੂੰ ਮੁਫ਼ਤ ਵਿੱਚ ਤੇ ਆਪਣੀ ਭਾਸ਼ਾ ਵਿੱਚ ਜਾਣਕਾਰੀ ਅਤੇ ਮਦਦ ਪ੍ਰਾਪਤ ਕਰਨ ਦਾ ਅਧਿਕਾਰ ਹੈ ,ਕਾਲ 800-722-1471 (TTY: 800-842-5357).

فارسی (Farsi):
این اعلامیه حاوی اطلاعات مهم میباشد .این اعلامیه ممکن است حاوی اطلاعات مهم درباره فرم تقاضا و یا پوشش بیمه ای شما از طریق Premera Blue Cross باشد. به تاریخ های مهم در این اعلامیه توجه نمایید .شما ممکن است برای حفظ پوشش بیمه تان یا کمک در پرداخت هزینه های درمانی تان، به تاریخ های مشخصی برای انجام کارهای خاصی احتیاج داشته باشید .شما حق این را دارید که این اطلاعات و کمک را به زبان خود به طور رایگان دریافت نمایید. برای کسب اطلاعات با شماره 800-722-1471 (کاربران TTY تماس باشماره 800-842-5357) تماس برقرار نمایید.

Polskie (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Państwa wniosku lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócic uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utrzymania polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie Państwo prawo do bezpłatnej informacji we własnym języku. Zadzwońcie pod 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):
Prezenta notificare conține informații importante. Această notificare poate conține informații importante privind cererea sau acoperirea asigurării dumneavoastre de sănătate prin Premera Blue Cross. Pot exista date cheie în această notificare. Este posibil să fie nevoie să acționați până la anumite termene limită pentru a vă menține acoperirea asigurării de sănătate sau asistența privitoare la costuri. Aveți dreptul de a obține gratuit aceste informații și ajutor în limba dumneavoastră. Sunați la 800-722-1471 (TTY: 800-842-5357).

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Fa'asamoa (Samoan):
Atonu ua iai i lenei fa'asilasilaga ni fa'amatalaga e sili ona taua e tatau ona e malamalama i ai. O lenei fa'asilasilaga o se fesoasoani e fa'amatala atili i ai i le tulaga o le polokalame, Premera Blue Cross, ua e tau fia maua atu i ai. Fa'amolemole, ia e iloilo fa'alelei i aso fa'apitoa olo'o iai i lenei fa'asilasilaga taua. Masalo o le'a iai ni feau e tatau ona e faia ao le'i aulia le aso ua ta'ua i lenei fa'asilasilaga ina ia e iai pea ma maua fesoasoani mai ai i le polokalame a le Malo olo'o e iai i ai. Olo'o iai iate oe le aia tatau e maua atu i lenei fa'asilasilaga ma lenei fa'amatalaga i legagana e te malamalama i ai aunoa ma se togiga tupe. Vili atu i le telefoni 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):
Ang Paunawa na ito ay naglalaman ng mahalagang impormasyon. Ang paunawa na ito ay maaaring naglalaman ng mahalagang impormasyon tungkol sa iyong aplikasyon o pagsakop sa pamamagitan ng Premera Blue Cross. Maaaring may mga mahalagang petsa dito sa paunawa. Maaring mangailangan ka na magsagawa ng hakbang sa ilang mga itinakdang panahon upang mapanatili ang iyong pagsakop sa kalusugan o tulong na walang gastos. May karapatan ka na makakuha ng ganitong impormasyon at tulong sa iyong wika ng walang gastos. Tumawag sa 800-722-1471 (TTY: 800-842-5357).

ไทย (Thai):
ประกาศนี้มีข้อมูลสำคัญ ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการการสมัครหรือขอบเขตประกันสุขภาพของคุณผ่าน Premera Blue Cross และอาจมีกำหนดการในประกาศนี้ คุณอาจจะต้องดำเนินการภายในกำหนดระยะเวลาที่แน่นอนเพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย คุณมีสิทธิที่จะได้รับข้อมูลและความช่วยเหลือนี้ในภาษาของคุณโดยไม่มีค่าใช้จ่าย โทร 800-722-1471 (TTY: 800-842-5357)

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про Ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретні кінцеві строки для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дзвоніть за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):
Thông báo này cung cấp thông tin quan trọng. Thông báo này có thông tin quan trọng về đơn xin tham gia hoặc hợp đồng bảo hiểm của quý vị qua chương trình Premera Blue Cross. Xin xem ngày quan trọng trong thông báo này. Quý vị có thể phải thực hiện theo thông báo đúng trong thời hạn để duy trì bảo hiểm sức khỏe hoặc được trợ giúp thêm về chi phí. Quý vị có quyền được biết thông tin này và được trợ giúp bằng ngôn ngữ của mình miễn phí. Xin gọi số 800-722-1471 (TTY: 800-842-5357).