Name of Policy:
Hematopoietic Stem-Cell Transplantation for Non-Hodgkin Lymphomas

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Category: Therapy
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Policy Grade: B

Background:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient’s illness, injury or disease.
Description of Procedure or Service: Hematopoietic Stem-Cell Transplantation

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in 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 radiation therapy. Bone-marrow stem cells may be obtained from the transplant recipient (i.e., autologous HSCT) or from a donor (i.e., allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each leg of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

Conventional Preparative Conditioning for Hematopoietic SCT

The success of autologous HSCT is predicated on the ability 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 space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by nonself immunologic effector cells that develop after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.
Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in traditional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allogeneic HSCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells.

For the purposes of this Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

Non-Hodgkin Lymphoma (NHL)

A heterogeneous group of lymphoproliferative malignancies, 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 (WF) was developed to unify different classification systems into one. The WF divided NHL into low-, intermediate-, and high-grade, with subgroups based on histologic cell type. Since 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 WF 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 (WHO) classification. The WHO/REAL classification recognizes three major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin lymphoma.

The most recent lymphoma classification is the 2008 WHO classification:

Updated WHO Classification 2008

*Mature B-Cell Neoplasms*
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- 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
Waldenstrom macroglobulinemia
Heavy chain diseases
Alpha heavy chain disease
Gamma heavy chain disease
Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extravasous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma (MZL)
Pediatric type nodal MZL
Follicular lymphoma
Pediatric type follicular lymphoma
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
T cell/histiocyte-rich large B-cell lymphoma
DLBCL associated with chronic inflammation
Epstein-Barr virus (EBV)+ DLBCL of the elderly
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK [anaplastic lymphoma kinase] + large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

*These represent provisional entities or provisional subtypes of other neoplasms. Diseases shown in italics are newly included in the 2008 WHO classification.

Mature T-cell and NK-cell neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK-cells*
Aggressive NK-cell leukemia
Systemic EBV + T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorder
Lymphomatoid papulosis
Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma*
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium CD4+ T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK+
Anaplastic large cell lymphoma (ALCL), ALK–*

*These represent provisional entities or provisional subtypes of other neoplasms.
Diseases shown in italics are newly included in the 2008 WHO classification.

In the United States, B-cell lymphomas represent 80%–85% of cases of NHL, and T-cell lymphomas represent 15%–20%. NK 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 (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/mucosa-associated lymphoid tissue (MALT) lymphoma 5%. All other subtypes each represent less than 2% of cases 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. Early-stage indolent NHL (Stage 1 or 2) may be effectively treated with radiation alone. Although indolent NHL is responsive to radiation and chemotherapy, a continuous rate of relapse is seen in advanced stages. These patients can often be re-treated, 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 one year or less.

FL (follicular lymphoma) 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 SLL/CLL, lymphoplasmacytoid lymphoma, marginal zone lymphomas, and cutaneous T-cell lymphoma.
Aggressive NHL has a shorter natural history; however, 30%–60% of these patients can be cured with intensive combination chemotherapy regimens. Aggressive lymphomas include DLBCL, MCL, PTCL, anaplastic large cell lymphoma, and Burkitt’s lymphoma.

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). Prior to the development of IPI in 1993, prognosis was predominantly based on disease stage.

Based on the number of risk factors present and adjusted for patient age, the IPI defines four risk groups: low, low intermediate, high intermediate and high risk, based on five significant risk factors prognostic of OS:

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 and overall survival (OS) at five years. Age-adjusted (aaIPI) 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 >2, 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-IV
3. Hemoglobin level less than 12.0 g/dL
4. More than 4 lymph node areas involved
5. Elevated serum lactate dehydrogenase (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 (more than three risk factors).

**Mantle Cell Lymphoma (MCL)**
Mantle cell lymphoma (MCL) comprises approximately 6%–8% of NHL, and has been recognized within the past 15 years as a unique lymphoma subtype with a particularly aggressive course. MCL is characterized by a chromosomal translocation t, and the term mantle cell lymphoma was proposed in 1992 by Banks et al. The number of therapeutic trials are not as numerous for MCL as for other NHL as it was not widely recognized until the REAL classification. MCL shows a strong predilection for elderly men, and the majority of cases (70%) present with disseminated (Stage 4) disease and extranodal involvement is common. Localized MCL is quite rare. MCL has a median survival of approximately two–four years, and although most patients achieve remission with first-line therapy, relapse inevitably occurs, often within 12–18 months. MCL is rarely, if ever, cured with conventional therapy, and no standardized therapeutic approach to MCL is used.

There had been no generally established prognostic index for patients with MCL. Application of the IPI or FLIPI system to patients with MCL showed serious 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. Therefore, a new prognostic index for patients with MCL was developed, and should prove useful in comparing clinical trial results for MCL.

**MCL international prognostic index (MIPI):**
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 count (WBC)
   a) Zero points each are assigned for age younger than 50 years, ECOG performance 0–1, LDH ratio less than 0.67, WBC less than 6,700
   b) One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999.
   c) Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
   d) Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

MIPI allows separation of three groups with significantly different prognoses:
- 0–3 points=low risk, 44% of patients, median OS not reached and a five-year OS rate of 60%
- 4–5 points=intermediate risk, 35% of patients, median OS 51 months
- 6–11 points=high risk, 21% of patients, median OS 29 months
Peripheral T-Cell Lymphoma (PTCL)
Immature T-cell lymphomas are generally treated on leukemia protocols, whereas mature (peripheral) T-cell lymphomas are usually treated with chemotherapy regimens similar to those used in DLBCL. PTCLs are less responsive to standard chemotherapy than DLBCLs and, therefore, carry a worse prognosis than aggressive B-cell counterparts. The poor results with conventional chemotherapy have prompted exploration of the role of HSCT as therapy.

Staging
The Ann Arbor staging classification is commonly used for the staging of lymphomas and is the scheme defined in the AJCC Manual for Staging Cancer. Originally developed for Hodgkin's disease, this staging scheme was later expanded to include non-Hodgkin's lymphoma.

Ann Arbor Classification
Stage I
Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

Stage II
Involvement of two 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).

Stage 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).

Stage IV
Diffuse or disseminated involvement of one or more extralymphatic organs or tissues with or without associated lymph node enlargement.

Policy:
Effective for dates of services on or after August 23, 2011:
For patients with non-Hodgkin lymphoma (NHL) B-cell subtypes considered aggressive (except mantle cell lymphoma), either allogeneic hematopoietic stem cell transplantation (HSCT) using a myeloablative conditioning regimen or autologous HSCT meets Blue Cross and Blue Shied of Alabama’s medical criteria for coverage:

• As salvage therapy for patients who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy;
• To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse; or
• To consolidate a first CR in patients 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 patients with **mantle cell lymphoma**:

- **Autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage **to consolidate a first remission**.
- **Allogeneic HSCT, myeloablative or reduced-intensity conditioning, meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage **as salvage therapy**.
- **Autologous HSCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational as salvage therapy**.
- **Allogeneic HSCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational** to **consolidate a first remission**.

For patients with **NHL B-cell subtypes considered indolent, either allogeneic HSCT using a myeloablative conditioning regimen or autologous HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

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

**Note:** The term **salvage therapy** describes 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.

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

**Reduced-intensity conditioning (RIC) allogeneic HSCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a treatment of NHL in patients who meet criteria for an allogeneic HSCT but who do not qualify for a myeloablative allogeneic HSCT.

Either autologous HSCT or allogeneic HSCT does not meet Blue Cross and Blue Shield of Alabama’s medial criteria for coverage and is considered **investigational**:

- As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
- To consolidate a first CR for patients 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.

**Note:** Reduced-intensity conditioning (RIC) would be considered an option in patients who meet criteria for an allogeneic hematopoietic stem-cell transplant (HSCT) but whose age (typically older than 55 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, and prior intensive chemotherapy) preclude use of a standard conditioning regimen.
In patients who qualify for a myeloablative allogeneic hematopoietic HSCT on the basis of overall health and disease status, allogeneic HSCT using either myeloablative or RIC may be considered. However, a myeloablative conditioning regimen with allogeneic HSCT may benefit younger patients with good performance status and minimal comorbidities more than allogeneic HSCT with RIC.

Tandem transplants do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational to treat patients with any stage, grade, or subtype of NHL.

Note: 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 non-myeloablative immunosuppressive conditioning followed by infusion of allogeneic stem cells.

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

- Autologous HSCT meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to consolidate a first complete remission in high-risk peripheral T-cell lymphoma.
- Autologous or allogeneic HSCT (myeloablative or reduced-intensity conditioning) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as salvage therapy.
- Allogeneic HSCT does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to consolidate a first remission.

Note: High-risk peripheral T-cell lymphoma is defined as one of the histologic subtypes as follows:

- Nodal: peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS), anaplastic lymphoma kinase negative anaplastic large cell lymphoma (ALK- ALCL) or angioimmunoblastic lymphoma (AIL). High-risk patients may also include the rare patient with ALK+ALCL who is refractory to conventional chemotherapy.

Effective for dates of services prior to August 23, 2011:
For patients with non-Hodgkin’s lymphoma (NHL) subtypes considered aggressive, either allogeneic stem-cell transplant (SCT) using a myeloablative conditioning regimen or autologous SCT meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

- As salvage therapy for patients who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy;
- To achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse;

OR
• To consolidate a first CR in patients 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 patients with NHL subtypes considered indolent, either **allogeneic SCT using a myeloablative conditioning regimen or autologous SCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage:

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

*The term salvage therapy describes 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.

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

*** 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.

For patients with mantle cell lymphoma, **autologous SCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage to consolidate a first remission.

**Reduced-intensity conditioning allogeneic SCT meets** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage as a treatment of NHL in patients who meet criteria above for an allogeneic SCT but who do not qualify for a myeloablative allogeneic SCT.

**Either autologous SCT or allogeneic SCT does not meet** Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered **investigational:**

• As initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
• To consolidate a first CR for patients 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 subtypes; **AND**
• For peripheral T-cell lymphoma at any stage of disease.
Tandem transplants to treat patients with any stage, grade, or subtype of NHL do not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and are considered investigational.

Note: Tandem transplants usually are 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 stem cells.

Allogeneic SCT does not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and is considered investigational to treat NHL that progresses or relapses relatively soon after a prior course of high-dose chemotherapy with autologous SCT. (Note: This policy statement is based on a strict evidence-based analysis on outcomes of allotransplants after a failed autotransplant.)

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
The classification of NHL has undergone significant changes, and several new and unique subtypes have emerged (e.g., MCL, PTCL).

Indolent Lymphomas
Stem-Cell Transplant (SCT) as First-Line Treatment for Indolent Non-Hodgkin Lymphoma (NHL)
In 2012, Al Khabori et al performed a systematic review and meta-analysis of the use of autologous HSCT in untreated, advanced follicular lymphoma (FL). Four randomized controlled trials (RCTs) comparing autologous HSCT to conventional chemotherapy in 941 patients, were included. Three trials reported overall survival (OS); moderate quality evidence from these trials did not show an improved OS with the use of HSCT as part of the initial treatment of FL. Adverse outcomes including treatment-related mortality and the development of myelodysplastic syndrome, acute myeloid leukemia, and solid tumors, were not different between the two arms.

In 2012, Schaaf et al performed a systematic review with meta-analysis of RCTs comparing autologous HSCT with chemotherapy or immuno-chemotherapy in patients with previously untreated or relapsed FL with respect to OS, progression-free survival (PFS), treatment-related mortality, adverse events and secondary malignancies. Five RCTs involving 1,093 patients were included; four trials in previously untreated patients and one trial in relapsed patients. The
quality of the five trials was judged to be moderate. There was a statistically significant increase in PFS in previously untreated FL patients in the HSCT arm (HR: 0.42 (95% confidence interval [CI]: 0.33 to 0.54; p<0.00001). However, there was not a statistically significant OS advantage (HR: 0.97; 95% CI: 0.76 to 1.24; p=0.81). In the four trials in previously untreated patients, there were no statistically significant differences between HSCT and the control-arm in terms of treatment-related mortality (RR: 1.28; 95% CI: 0.25 to 6.61; p=0.77), secondary acute myeloid leukemia/myelodysplastic syndromes (RR: 2.87; 95% CI: 0.7 to 11.75; p=0.14) or solid cancers (RR: 1.20; 95% CI: 0.25 to 5.77; p=0.82). Adverse events were rarely reported and were more frequent in patients who underwent HSCT. For patients with relapsed FL, there was some evidence from one trial with 70 patients that HSCT was advantageous in terms of PFS and OS (PFS: HR=0.30; 95% CI: 0.15 to 0.61; OS: HR=0.40; 95% CI: 0.18 to 0.89). No results were reported from this trial for treatment-related mortality, adverse events, or secondary cancers.

In 2008, Ladetto et al reported the results of a Phase III, randomized, multicenter trial of patients with high-risk follicular lymphoma, treated at diagnosis. A total of 134 patients were enrolled to receive either rituximab-supplemented high-dose chemotherapy (HDC) and autologous SCS (R-HDC) or six courses of cyclophosphamide, doxorubicin (or Adriamycin), vincristine (Oncovin), and prednisolone (CHOP) followed by rituximab (CHOP-R). Of these patients 79% completed R-HDC and 71% completed CHOP-R. Complete remission was 85% with R-HDC and 62% with CHOP-R. At a median follow-up of 51 months, the four-year event-free survival (EFS) was 61% and 28% (R-HDC vs. CHOP-R), with no difference in overall survival (OS). Molecular remission (defined as negative results by polymerase chain reaction on two or more consecutive bone marrow samples spaced six months apart in patients who reached complete remission [CR]) was achieved in 80% of R-HDC and 44% of CHOP-R patients, and was the strongest independent outcome predictor. In 71% of the CHOP-R patients who had a relapse, salvage R-HDC was performed and achieved an 85% CR rate and a 68% three-year EFS.

In 2006, Sebban et al reported the results of a randomized, multicenter study. A total of 209 patients received CHVP plus interferon (CHVP-I arm) and 131 patients received CHOP followed by HDC with total body irradiation and autologous SCT (CHOP-HDT arm). Response rates were similar in both groups (79% and 78% after induction therapy, respectively). After a median follow-up of 7.5 years, intent-to-treat analysis showed no difference between the two arms for OS (p=0.53) or EFS (p=0.11). The authors concluded that there was no statistically significant benefit to first-line, high-dose therapy in patients with follicular lymphoma, and that high-dose therapy should be reserved for relapsing patients.

Deconinck et al investigated the role of autotransplants as initial therapy in 172 patients with follicular lymphoma considered at high risk due to the presence of either B symptoms (i.e., weight loss, fever, or night sweats), a single lymph node larger than 7cm, more than three involved nodal sites, massive splenomegaly, or a variety of other indicators of high tumor burden. The patients were randomized to receive either an immunochemotherapy regimen or a high-dose therapy followed by purged autotransplant. While the autotransplant group had a higher response rate and longer median EFS, there was no significant improvement in OS rate due to an excess of secondary malignancies.
In 2004, Lenz et al reported on the results of a trial of 307 patients with advanced stage lymphoma in first remission, including follicular lymphoma, mantle cell lymphoma, or lymphoplasmacytoid lymphoma. Patients were randomized to receive either consolidative therapy with autotransplant or interferon therapy. The five-year progression-free survival (PFS) rate was considerably higher in the autotransplant arm (64.7%) compared to the interferon arm (33.3%). However, the median follow-up of patients is still too short to allow any comparison of OS.

**HSCT for Relapsed, Indolent NHL**

The majority of patients with follicular lymphoma relapse, and with relapsed disease, cure is very unlikely, with a median survival of 4.5 years after recurrence. In the European CUP trial, 89 patients with relapsed, non-transformed follicular lymphoma with partial or complete response after standard induction chemotherapy were randomized to one of three arms: three additional cycles of conventional chemotherapy (n=24), HDC and unpurged autologous SCS (n=33), or HDC with purged autologous SCS (n=32). OS at four years for the chemotherapy versus unpurged versus purged arms was 46%, 71%, and 77%, respectively. Two-year PFS was 26%, 58%, and 55%, respectively. No difference was found between the two autotransplant arms. Although several studies have consistently shown improved disease-free survival (DFS) with autoSCT for relapsed follicular lymphoma, this study was the first to show a difference in OS benefit.

**Section Summary**

Randomized trials have shown no survival advantage to HSCT as first-line therapy for indolent B-cell lymphomas; however, randomized studies have shown a survival benefit for relapsed disease.

**Aggressive Lymphomas**

**HSCT for First-Line Therapy for Aggressive NHL**

Several randomized trials reported on between 1997 and 2002 compared outcomes of autotransplants used to consolidate a first CR in patients with intermediate or aggressive non-Hodgkin’s lymphoma (NHL), with outcomes of an alternative strategy that delayed transplants until relapse. As summarized in an editorial, the preponderance of evidence showed that consolidating first CRs with SCT did not improve OS for the full population of enrolled patients. However, a subgroup analysis at eight years’ median follow-up focused on 236 patients at high or high-intermediate risk of relapse (based on age-adjusted International Prognostic Index [IPI] scores) who were enrolled in the largest of these trials (the LNH87-2 protocol). The subgroup analysis reported superior overall (64% vs. 49%; relative risk 1.51, p=0.04) and DFS (55% vs. 39%; relative risk 1.56, p=0.02) for patients at elevated risk of relapse who were consolidated with an autologous HSCT.

A large, multi-group, prospective, randomized Phase III comparison of these strategies (the S9704 trial) is ongoing to confirm results of the subgroup analysis in a larger population with diffuse large B-cell lymphoma at high- and high-intermediate risk of relapse. Nevertheless, many clinicians view the LNH87-2 subgroup analysis as sufficient evidence to support use of autotransplants to consolidate a first CR when risk of relapse is high. In contrast, editorials and
recent reviews agree that available evidence shows no survival benefit from autotransplants to consolidate first CR in patients with intermediate or aggressive NHL at low- or low-intermediate risk of relapse (using age-adjusted IPI score).

Between 2005 and 2008, several reports of randomized trials have shown no survival benefit to HSCT as first-line therapy for aggressive lymphomas, as summarized next.

Greb et al undertook a systematic review and meta-analysis to determine whether HDC with SCS as first-line treatment in patients with aggressive NHL improves survival compared to patients treated with conventional chemotherapy. Fifteen randomized controlled trials (RCTs) including 3,079 patients were eligible for the meta-analysis. Thirteen studies with 2,018 patients showed significantly higher CR rates in the HDC/SCS group (p=0.004). However, HDC did not have an effect on OS when compared to conventional chemotherapy. According to the IPI, subgroup analysis of prognostic groups showed no survival differences between HDC and conventional chemotherapy in 12 trials, and EFS also was not significantly different between the two groups. The authors concluded that despite higher CR rates, there is no benefit for HDC with SCS as first-line treatment in aggressive NHL.

Betticher et al reported the results of a Phase 3 multicenter, randomized trial comparing sequential HDC with SCS (SHiDo) to standard CHOP as first-line therapy in 129 patients with aggressive NHL. Remission rates were similar in the two groups, and after a median observation time of 48 months, there was no difference in OS with 46% in the SHiDo group and 53% in the group that received CHOP (p=0.48). The authors concluded that SHiDo did not confer any survival benefit as initial therapy in patients with aggressive NHL.

Baldissera et al reported on the results of a prospective RCT comparing HDC and auto SCS to conventional chemotherapy as frontline therapy in 56 patients with high-risk aggressive NHL. The five-year actuarial OS and PFS were not statistically different between the two study groups; only DFS was statistically different (97% vs. 47%, for the HDC/SCS and conventional groups, respectively; p=0.02.)

Olivieri et al reported on a randomized study of 223 patients with aggressive NHL using upfront HDC with autologous SCS versus conventional chemotherapy (plus HDC/SCS in cases of failure). In the conventional group, 29 patients achieved a partial response or no response, and went on to receive HDC and SCS. With a median follow-up of 62 months, there was no difference in seven-year probability of survival (60% and 57.8%; p=0.5), DFS (62% and 71%; p=0.2), and PFS (44.9% and 40.9%; p=0.7) between the two groups. The authors concluded that patients with aggressive NHL do not benefit from upfront HSCT.

Results of a Phase III multicenter randomized trial (SWOG-9704) of autologous HSCT as consolidation for aggressive (high-intermediate or high-risk) diffuse B-cell NHL were published in October 2013. In this trial, 253 patients received five cycles of induction chemotherapy (CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone with [n=156, 47%] or without rituximab). Those who had at least a partial response to five cycles of induction therapy were randomly assigned to receive three additional cycles of CHOP (n=128) or one additional cycle of CHOP followed by autologous HSCT (n=125). The primary efficacy
end points of the trial were two-year PFS and OS. Two-year PFS rates were 69% and 55% in the HSCT and control group, respectively (HR control vs HSCT=1.72, 95% CI, 1.18 to 2.51, p=0.005). The two-year OS rates in the HSCT and control group were 74% and 71%, respectively (HR=1.26, 95% CI, 0.82 to 1.94, p=0.30). Unplanned exploratory analyses showed a differential treatment effect according to disease risk level. Among high-risk patients, the two-year OS rate was 82% in the HSCT group and 64% in the control group (log-rank test p=0.01). The main results of this trial comport with earlier study results in not discerning a significant effect of early autologous HSCT on OS among a group of patients with high-intermediate- and high-risk diffuse B-cell NHL. However, it appears that the survival curve shows a plateau among the high-risk HSCT patients out to perhaps ten years after study registration. Although this evidence was from exploratory subset analysis, it further supports the medical necessity of this approach in such cases compared with non-transplant strategies.

**HSCT for Relapsed, Aggressive NHL**

Autologous HSCT is the treatment of choice for relapsed or refractory aggressive NHL for patients who achieve a CR or partial response (PR) with second-line therapy. The pivotal trial establishing the superiority of autologous HSCT for relapsed DLBCL was the PARMA trial, a prospective randomized study in which 215 patients with chemosensitive disease in first or second relapse of aggressive lymphoma were given two courses of conventional chemotherapy. One hundred and nine patients responded and were randomized to receive four courses of chemotherapy plus radiation (n=54) or radiotherapy plus intensive chemotherapy and autologous HSCT (n=55). The two groups did not differ in baseline characteristics. Median follow-up was 63 months. Response rate was 84% in the HSCT group, versus 44% in the non-transplant group. EFS for the transplant group was 46% versus 12% in the non-transplant group (p=0.001), and OS was 53% in the transplant group versus 32% in the non-transplant group (p=0.038).

**Section Summary**

Data from randomized trials have shown conflicting results, but some have shown an overall survival benefit with HSCT to consolidate a first CR in patients with aggressive B-cell lymphomas at high or high-intermediate risk of relapse.

Randomized studies of HSCT for relapsed aggressive B-cell lymphomas have shown an overall survival benefit with this approach.

**Tandem Transplants**

No prospective controlled studies comparing tandem with single transplants have been identified in the published literature.

A pilot Phase II trial evaluated tandem high-dose therapy with stem-cell support between 1994 and 1999 in 45 patients with age adjusted-IPI equal to three untreated aggressive non-Hodgkin’s lymphoma. After induction, responders underwent tandem autologous transplantation; 31 out of 41 evaluable patients completed the program. There were four toxic deaths. The primary end point of the study was complete response rate, which was 49%. With a median follow-up of 114 months for surviving patients, the OS was 51%, and 19 of the 22
patients (86%) who reached a CR were alive and relapse-free. Prospective evaluation of quality of life and comorbidities of surviving patients did not reveal long-term toxicities.

A pilot study in 2005 included 41 patients with poor-risk NHL and Hodgkin disease who were given tandem high-dose chemotherapy and autologous HSCT. Thirty-one patients (76%) completed both transplants. Overall toxic death rate was 12%. The study evaluated the maximum tolerated dose of the chemotherapeutic regimen and did not compare tandem versus single transplants for NHL.

Tarella et al reported on a multicenter, nonrandomized, prospective trial consisting of 112 patients with previously untreated DLBCL and age-adjusted IPI Score of 2-3. All patients received rituximab-supplemented, early-intensified high-dose chemotherapy with multiple autologous HSCT. Although the study concluded the treatment regimen improved patients’ life expectancy, the comparisons were made with historic controls that had received conventional chemotherapy.

A retrospective analysis of 34 high-risk NHL patients who underwent autologous HSCT followed closely by reduced-intensity allogeneic HSCT (“tandem auto-allo”) included patients treated from January 2002 to November 2010. In this study, researchers began to identify appropriate allogeneic donors at the initiation of the salvage regimen. The patients' median age was 47 years. Histologic subtypes were: diffuse large B-cell (n=5), follicular (n=14), transformed follicular (n=4), mantle-cell (n=5), plasmacytoid lymphoma (n=1), anaplastic large T-cell (n=2), and peripheral T-cell (n=3). HLA-identical sibling donors were located for 29 patients, and 10/10-matched unrelated individuals were identified for five cases. The median interval between autologous HSCT and allogeneic HSCT was 77 days (range 36–197 days). At a median follow-up of 46 months since allogeneic HSCT, the five-year OS was 77% and PFS was 68%. Six patients experienced disease relapse or progression, the 100-day TRM was 0%, and two-year TRM incidence was 6%. These results suggest tandem autologous-allogeneic transplantation appears feasible in high-risk NHL patients having a HLA-identical donor, but further study is necessary to establish its role in this setting.

Section Summary
No randomized studies have been conducted on the use of tandem HSCT for the treatment of non-Hodgkin lymphomas, and the published data consist of small numbers of patients. Therefore, the data on tandem transplants is insufficient to determine outcomes with this type of treatment.

NHL Subtypes
Several subtypes have emerged with unique clinical and biologic features that will be addressed separately in the policy (specifically MCL and PTCL).

Mantle Cell Lymphoma
In an attempt to improve the outcome of mantle cell lymphoma (MCL), several Phase II trials investigated the efficacy of autologous HSCT, with published results differing substantially. Some studies found no benefit to HSCT, and others suggested an EFS advantage, at least in a
subset of patients. The differing results in these studies were likely due to different time points of transplant (first vs. second remission) and other patient selection criteria.

In 2005, the results of the first randomized trial were reported by Dreyling et al of the European MCL Network. A total of 122 patients with MCL received either autologous HSCT or interferon as consolidation therapy in first CR or PR. Among these patients, 43% had a low-risk, 11% had a high-intermediate risk, and 6% had a high-risk profile. Autologous HSCT resulted in a PR rate of 17% and a CR rate of 81% (versus PR of 62% and CR of 37% with interferon). Survival curves for time to treatment failure (TTF) after randomization showed that autologous HSCT was superior to interferon (p=0.0023). There also was significant improvement in the three-year PFS demonstrated in the autologous HSCT versus interferon arm (54% and 25%, respectively; p=0.01). At the time of the reporting, no advantage was seen in OS, with a three-year OS of 83% versus 77%. The trial also suggested that the impact of autologous HSCT could depend on the patient’s remission status prior to the transplant, with a median PFS of 46 months in patients in CR versus 33 months in patients in PR.

Till et al reported the results of the outcomes of 56 patients with MCL treated with induction chemotherapy with cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyperCVAD) with or without rituximab followed by autologous HSCT in first CR or PR (n=21), CHOP with or without rituximab followed by autologous HSCT in first CR or PR (n=15), or autologous HSCT following disease progression (n=20). OS and PFS at three years among patients transplanted in CR or PR were 93% and 63% compared with 46% and 36%, all respectively for patients transplanted with relapsed/refractory disease. The hazard of mortality among patients transplanted with relapsed or refractory disease was 6.1 times that of patients transplanted in first CR or PR (p=0.0006).

Geisler et al reported on 160 previously untreated patients with MCL with dose-intensified induction immunochemistry. Responders received high-dose chemotherapy with in vivo purged autologous HSCT. Overall and CR was achieved in 96% and 54%, respectively. The six-year OS, EFS, and PFS were 70%, 56%, and 66%, respectively, with no relapses occurring after five years.

Evens et al reported on 25 untreated patients with MCL who received induction chemotherapy, with an overall response rate of 74%. Seventeen patients received a consolidative autologous (n=13) or allogeneic (n=4) HSCT. Five-year EFS and OS for all patients was 35% and 50%, respectively. After a median follow-up of 66 months, the five-year EFS and OS for patients who received autologous HSCT was 54% and 75%, respectively.

There have been several studies regarding reduced-intensity chemotherapy (RIC) and allogeneic HSCT. Khouri et al reported on results of RIC allogeneic HSCT in 18 patients with relapsed MCL, and after a median follow-up of 26 months, the actuarial probability of EFS was 82% at three years. Maris et al. evaluated allogeneic HSCT in 33 patients with relapsed and recurrent MCL. At two years, the relapse and non-relapse mortality rates were 9% and 24%, respectively, and the OS and DFS were 65% and 60%, respectively.
Tam et al reported a retrospective study which included all patients with MCL who had undergone HSCT in sequential Phase 2 protocols (autologous or nonmyeloablative allogeneic) at the University of Texas M.D. Anderson Cancer Center between February 1990 and June 2007. The approach to transplantation was risk-adapted and based primarily on the patient’s treatment status. Autologous HSCT was performed as consolidation therapy for patients in first remission after chemotherapy (1990-2001). From 2001 onward, because of the favorable clinical outcomes found with rituximab (R)-hyperCVAD chemotherapy, autologous HSCT was performed only in patients not in CR after R-hyperCVAD and in patients who had received less-intensive induction chemotherapy (e.g., R-CHOP). For patients with relapsed or primary refractory MCL, autologous HSCT was performed before the use of nonmyeloablative allogeneic in 1997. After 1997, nonmyeloablative allogeneic was performed whenever a histocompatible donor was available. Patients generally underwent autologous HSCT up to the age of 70 and RIC-allogeneic up to the age of 65 years. Since 2004, patients up to the age of 75 years could receive an autologous transplant. The study included 121 patients with MCL: 50 who underwent autologous HSCT in first CR (46%) or PR (54%) (AUTO1); 36 who underwent autologous HSCT for relapsed or refractory disease (AUTO2); and 35 who underwent nonmyeloablative allogeneic for relapsed or refractory disease (NST). The ages at transplantation were similar in all three groups (median, 57 years [range: 38–73 years] for AUTO1; median, 59 years [range: 42–76 years] for AUTO2; and median, 58 years [range: 43–68 years] for NST).

For the AUTO1 group, at a median follow-up of six years, the actuarial PFS and OS were 39% and 61%, respectively, with median PFS and OS durations of 42 months and 93 months. Of the AUTO2 patients, 31% did not experience a response to initial chemotherapy but did experience a PR or better to salvage therapy with hyperCVAD (n=6), R-hyperCVAD (n=4), or methotrexate and ara-C (n=1). Seventeen patients (47%) were in their second remission, three (8%) were in their third or subsequent remission, and five (14%) had chemorefractory relapse and were transplanted in less than partial remission. The actuarial six-year PFS and OS rates were 10% and 35%, respectively (p=0.01 and 0.02 compared with AUTO1), and the median PFS and OS durations were 27 and 52 months, respectively. These inferior results for both PFS and OS compared with AUTO1 patients were maintained in a multivariate analysis that accounted for differences in baseline factors.

Of the patients who underwent nonmyeloablative allogeneic HSCT for relapsed or refractory MCL, 20% did not experience a response to initial chemotherapy but experienced a PR or better to salvage therapy with R-hyperCVAD. Thirty-one percent were in their second remission, 31% were in their third or subsequent remission, and 17% had refractory relapse and received a transplant in less than partial remission. With a median follow-up of 56 months (range, 19-110 months), the median PFS duration was 60 months, and the median OS had not yet been reached. The six-year actuarial PFS rate was 46%, and the six-year actuarial OS rate was 53%. Plateaus in the survival curves were observed for both PFS and OS, with no relapses or deaths occurring in nine patients followed between 63 and 110 months. These outcomes were significantly superior to that of AUTO2 patients, whereby relapses and deaths occurred in a continuous fashion (p=0.01 for PFS; p=0.005 for OS [four-year landmark for OS]). Compared with AUTO1 patients, the RIC-allogeneic HSCT patients had an initially lower OS; however,
this reversed at eight years because of the lack of late deaths among nonmyeloablative allogeneic patients.

This study provides evidence that MCL may be curable in both the frontline and salvage settings. In chemotherapy-naïve patients, their results showed that rituximab-containing autologous HSCT in first remission may result in long-term disease control, with only one relapse occurring among 11 patients followed between two and eight years, in contrast to that of autologous transplantation without rituximab, in which relapses occurred in a continuous fashion. In contrast to frontline transplantation, the outcomes of autologous transplantation in patients with relapsed or refractory MCL remain unsatisfactory, with no evidence of a cured fraction on survival curves. The results of autologous and nonmyeloablative allogeneic HSCT in patients with relapsed or refractory MCL were also markedly different. Patients receiving a nonmyeloablative allogeneic transplant showed significantly superior disease control and a disease-free plateau, extending between five and nine years, whereas patients who received an autologous transplant had a median remission of two years and experienced a continuous pattern of relapse. Therefore, nonmyeloablative allogeneic HSCT may be capable of salvaging a cure in patients no longer curable with maximum cytotoxic strategies.

Two recent major therapeutic advances have substantially altered the outlook of patients with MCL: 1) the introduction of rituximab, which in combination with chemotherapy, has improved the results of both frontline and salvage treatments for MCL, and 2) the combination of rituximab and hyperCVAD is capable of achieving CR rates of up to 90% in the frontline setting, with a prolonged five-year failure-free survival of 60% in younger patients.

As noted in the Tam et al study, recent review articles on high-dose therapy for MCL reiterate the finding in several studies of a superior result of transplantation in first CR (autologous or allogeneic) rather than in the relapsed setting, and that intensive immunochemotherapy as induction therapy preceding high-dose therapy plus autologous HSCT is indicated. Also noted are the results of the use of reduced-intensity allogeneic HSCT in the relapsed setting, showing survival plateaus and suggesting curative potential and suggesting benefit in the use of this approach in younger, fit patients with relapsed MCL.

Section Summary
Due in part to the relative rarity of the disease, randomized studies on the use of HSCT in MCL have not been conducted. Case series have shown long-term disease control of this aggressive lymphoma with the use of autologous HSCT (with rituximab) to consolidate a first remission; however, the use of autologous HSCT in the relapsed setting has not shown improved outcomes. Allogeneic HSCT has shown prolonged disease control in the relapsed/refractory setting.

Peripheral T-Cell Lymphoma
Frontline autologous HSCT
Only a few prospective studies with small numbers of patients have investigated autologous HSCT in patients with aggressive PTCL.
Reimer et al conducted the largest prospective study of 83 patients with PTCL from multiple centers to undergo autologous HSCT as first-line therapy. Patients had various histologies, including PTCL-NOS (n=32), angioimmunoblastic (n=27), ALK– ALCL (n=13), and the remainder extranodal subtypes. Sixty-six percent of the patients received the transplant, with the main reason for not receiving the transplant being progression of disease. Of the patients who proceeded to transplant, 32 were in CR and 33 in PR. Treatment-related mortality was 3.6%. Median follow-up was 33 months, and the estimated three-year OS and PFS rates were 48% and 36%, respectively.

Corradini et al reported the results of two Phase II studies involving 62 patients with advanced stage PTCL at diagnosis. In an ITT analysis, 46 of the 62 (74%) completed the whole program. The 16 patients failed to undergo transplant due to early disease progression and/or toxicity. Pretransplant, 56% of patients were in CR, and 16% in PR. Median follow-up was 76 months, with an estimated 12-year OS, DFS and EFS of 34%, 55%, and 30% respectively. Five-year EFS and OS were 40 and 50%, respectively. A multivariate analysis showed that patients who achieved CR before HSCT had a statistically significant benefit in OS and EFS (p=0.0001).

Mercadal et al reported results of a Phase II trial involving 41 patients consecutively diagnosed with PTCL (median age: 47 years). Patients who responded to induction chemotherapy (CR or PR) went on to autologous HSCT. Twenty-four patients responded (CR n=20 and PR n=4). Seventeen of these 24 underwent HSCT (the remaining patients did not due to various reasons including lack of stem-cell mobilization, toxicity, and early relapse). For patients who completed the entire procedure, CR was 51% and PR 7%. Median follow-up was 3.2 years (range: 0.6–8.1), and five of 21 CR patients relapsed and two died in CR due to a secondary malignancy. Four-year PFS was 30% (95% confidence interval [CI]: 15–45%) and OS was 39% (95% CI: 22–56%). No difference in OS was noted among the 24 patients who were eligible for transplant, of which 17 underwent transplant and seven did not.

A prospective Phase II trial by Rodriguez et al showed that autologous HSCT as first-line consolidation therapy improved treatment outcome in patients responding to induction therapy. Nineteen of 26 patients who showed CR or PR to induction therapy received an autologous HSCT. At two years’ post-transplant, OS, PFS, and DFS were 84%, 56%, and 63%, respectively.

_Salvage (relapsed or refractory) autologous HSCT_

Kewalramani et al retrospectively compared a review of 24 consecutive patients with PTCL who underwent autologous HSCT for relapsed or refractory disease after responding to second-line therapy and compared the results with those of 86 consecutive patients with chemosensitive relapsed or primary refractory DLBCL. Patients with less aggressive histologies (e.g., ALCL expressing the ALK protein) were excluded. Median follow-up time was six years, and the five-year PFS rates for PTCL and DLBCL were 24% and 34%, respectively (p=0.14). OS rates were 33% and 39%, respectively. Disease progression occurred in 83% of patients with PTCL and 65% of patients with DLBCL (p=0.13). In a univariate analysis of survival for patients with PTCL, response to second-line therapy and the second-line age-adjusted international prognostic index (sAAIPI) were prognostic for both PFS and OS. The outcomes for PTCL and DLBCL patients were similar when stratified by the sAAIPI, in contrast to patients undergoing
first-line chemotherapy, where T-cell histology consistently confers a poorer prognosis across IPI subgroups.

Song et al compared the outcomes of 36 patients with PTCL who underwent autologous HSCT with 97 patients with relapsed DLBCL. Of the patients with PTCL, 27 were at first relapse, two at greater than one relapse and seven had primary refractory disease. Twenty patients had PTCL-unspecified (PTCL-u); nine had ALCL, and the remainder a mixture of rarer subtypes. Baseline patient characteristics were similar between the PTCL and DLBCL groups. Three-year OS and EFS were 48% and 37%, respectively for PTCL and 53% and 42% for DLBCL (p=0.41 and 0.29, respectively). The patients with PTCL-u had an inferior EFS when compared to the DLBCL patients (23%, p=0.028) and the patients with ALCL had a nonsignificant trend for improved EFS (67%, p=0.41).

Rodriguez et al reported the largest series of patients with refractory or relapsed PTCL who received an autologous HSCT. One-hundred twenty-three patients were derived from registry data between 1990 and 2004. Response to transplantation was as follows: in patients in whom response could be assessed (119 of 123), 73% achieved a CR, 11% a PR and transplant failed to produce benefit in 16% of patients who had stable or progressive disease. Median follow-up was 61 months (range: 0–182). Five-year PFS was 34% (95% CI: 25–44%) and five-year OS was 45% (95% CI: 36–55%). DFS at five years for complete responders was 47% (95% CI: 35–58%).

Allogeneic HSCT

A recent review article on the impact of HSCT in peripheral T-cell lymphomas states that no relevant data for the use of allogeneic HSCT in the front-line setting are available. To further investigate the role of HSCT in previously untreated PTCL, the DSHNHL (German High-grade NHL Study Group) will initiate a prospective randomized multicenter trial comparing upfront autologous versus allogeneic HSCT following induction chemotherapy.

For relapsing and refractory PTCL, data on the use of allogeneic HSCT consist of case reports and approximately five retrospective series with at least ten patients.

Jacobsen et al reported a single-center experience over 12 years using allogeneic HSCT in 52 patients with PTCL or advanced mycosis fungoides/Sezary syndrome. Patients had a variety of disease subtypes, including nodal and extranodal histologies. Eleven patients had undergone a prior autologous HSCT. At the time of the allogeneic HSCT, 23 patients (44%) were in first or subsequent CR and 16 (31%) had a PR. Thirty-one (60%) patients underwent myeloablative conditioning and 21 (40%) underwent RIC. The median follow-up was 49 months. Three-year PFS was 30% (45% in patients with nodal histologies and 6% in patients with extranodal histologies). Overall survival at three years was 41% for all patients. The authors concluded that allogeneic HSCT can produce long-term remissions in relapsed/refractory T-cell lymphoma and that plateaus in both OS and PFS curves suggest that allogeneic HSCT may be curative in a select group of patients.

Kyriakou et al reported the outcomes of 45 patients with angioimmunoblastic lymphoma who were in the European Group for Blood and Marrow Transplantation database and had
undergone an allogeneic HSCT between 1998 and 2005. Eleven patients had failed a prior autologous transplant. Twenty-five patients underwent myeloablative and 20 reduced-intensity conditioning (RIC). Non-relapse mortality was 18%, 22%, and 25% at three, six, and 12 months, respectively. The median follow-up time for the surviving patients was 29 months (range 6-76 months). The estimated OS rate at one and three years was 66% and 64%, respectively. OS for chemotherapy-sensitive patients was significantly better at 81% at 3 years. (For survival comparison, the authors state that angioimmunoblastic lymphoma is characterized by an aggressive clinical course and carries a poor prognosis and that with chemotherapy, OS is less than 30% at five years).

Corradini et al reported outcomes of 17 patients with relapsed or refractory PTCL who underwent a reduced intensity allogeneic HSCT. Median age of the patients was 41 years (range: 23-60 years). Two of the patients had primary chemo-refractory disease, 15 had relapsed disease, and eight had disease relapse after a prior autologous HSCT. After a median follow-up of 28 months from the day of study entry (range: 3-57 months), 14 patients were alive. PFS and OS at three years were 64% (95% CI: 39–89%) and 81% (95% CI: 62–100%), respectively. In this initial series, 15 of the 17 patients had chemotherapy-sensitive disease before transplant. In an update of their experience in 35 patients with a median follow-up of 44 months, PFS and OS were 49% and 54%, respectively.

Le Gouill et al retrospectively reported a large series of patients with several different aggressive histologic subtypes of peripheral T-cell lymphoma who underwent allogeneic HSCT. Seventy-seven patients from 20 French centers who underwent transplant between 1988 and 2006 were included. Median age at diagnosis was 36 years (range: 12–61 years). Median follow-up was 43 months (range: 3.5 to 195 months). Fifty-seven patients received a myeloablative conditioning regimen. All of the patients had received at least one line of therapy before the allogeneic HSCT, including an autologous HSCT in 25% of cases. Five-year toxicity-related mortality incidence was 33% (95% CI: 24–46%). Overall five-year OS and EFS rates were 57% (95% CI: 45–68%) and 53% (95% CI: 41–64%), respectively. There was a large variation in OS and EFS rates by the histopathologic subtypes: five-year OS and EFS rates were 80% (95% CI: 39–94%) and 80% (95% CI: 39–94%) for patients with angioimmunoblastic T-cell lymphoma, 63% (95% CI: 41 to 79%) and 58% (95% CI: 35–75%) for PTCLNOS, and 55% (95% CI: 35–72%), and 48% (95% CI: 28–65%) for ALCL patients, respectively. The five-year OS for other histopathologic subtypes (n=12) was 33% (95% CI: 8–58%), and four of these patients were still alive in CR. All of the patients who could not achieve CR after allogeneic HSCT died within ten months as a result of disease progression. In a multivariate analysis, the strongest predictors of OS were chemotherapy-resistant disease at the time of the allogeneic transplant and the occurrence of severe (grade 3 or 4) acute graft-versus-host disease.

Section Summary
The role of HSCT in peripheral T-cell lymphoma (PTCL) is not well-defined. Few studies have been conducted, many of these retrospectively, with small numbers of patients and heterogeneous patient populations including good- and poor-risk patients in the same study. This is partly due to the rarity and heterogeneity of this group of lymphomas. In particular, studies often mix patients with PTCL-NOS (which has a poorer prognosis) with patients with ALK +
ALCL which has a better prognosis (even with conventional chemotherapy regimens), and ALK-ALCL patients who have a worse prognosis than ALK+ ALCL but better than PTCL-NOS patients.

There have been no randomized studies comparing chemotherapy regimens solely in patients with peripheral T-cell lymphoma (i.e., some randomized studies have included peripheral T-cell lymphoma with aggressive B-cell lymphomas).

Reviews summarize the most recent and largest studies on the use of HSCT as frontline and salvage therapy for PTCL. For frontline therapy, results from recent Phase II studies with autologous HSCT 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 HSCT in the front-line setting are available.

Approximately 30–60% of these patients do not reach transplantation due to early disease progression or toxicity, and 20–30% relapse after transplantation. Patients with relapsed or refractory disease are generally considered incurable with chemotherapy alone. In the salvage setting, the data show that the use of HSCT may improve survival outcomes similar to the results seen in corresponding aggressive B-cell lymphomas in the same treatment setting.

**National Comprehensive Cancer Network (NCCN) guidelines**

**Follicular lymphoma/Indolent lymphomas**
- Autologous HSCT as consolidative therapy for patients in second or third remission (category 2A)
- Allogeneic (fully myeloablative or nonmyeloablative) in highly selected patients

**Diffuse large B-cell lymphoma**
- Autologous HSCT as first-line consolidation in high-risk patients (category 2B)
- Autologous HSCT for relapsed or refractory disease (category 2A)

**Mantle cell lymphoma**
- Autologous HSCT as consolidative therapy in first remission. (category 2A)
- Autologous HSCT for patients with relapsed disease following CR to induction therapy, those patients who obtain only a PR to induction therapy, or those with progressive disease. (category 2A)
- Allogeneic (fully myeloablative or nonmyeloablative) for second-line consolidation. (category 2A)

**Peripheral T-cell lymphoma**
- Autologous HSCT as first-line consolidation therapy in patients (except those considered low-risk, e.g., ALCL ALK-positive) showing a good response to induction therapy. (category 2A)
- Autologous or allogeneic (fully myeloablative or nonmyeloablative) HSCT as second-line consolidation in patients with relapsed or refractory disease with PR or CR to second-line therapy. (category 2A)
Cutaneous T-cell lymphoma (Mycosis Fungoides/Sézary Syndrome)
- For relapsed, refractory, or progressive disease, consider allogeneic HSCT.

Adult T-cell leukemia/lymphoma
- After CR or for persistent or progressive disease, consider allogeneic HSCT. (category 2A)

Clinical Input Received Through Physician Specialty Society and Academic Medical Center
In response to requests from the Blue Cross and Blue Shield Association, input was received from one physician specialty society and one academic medical center while this policy was under review for March 2009. 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. There was general agreement with the policy statements. Both reviewers agreed that RIC allogeneic HSCT should be considered medically necessary in patients with NHL who do not qualify for a myeloablative allogeneic HSCT. One reviewer responded on the medical necessity of HSCT in patients with MCL in first remission and recently published literature supports this. There was conflicting input on whether HSCT should be considered investigational for peripheral T-cell lymphoma. Also, one reviewer commented that with the increasing use of rituximab and its success in improving patient outcomes, the role of HSCT in consolidating first CR in high-risk patients is coming into question.

In response to requests from the Blue Cross and Blue Shield Association, input was received from three physician specialty societies and three academic medical centers while this policy was under review for February 2011. 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. Reviewer input was solicited particularly for the use of HSCT in MCL and PTCL. There was uniform agreement for the use of autologous HSCT to consolidate a 1st remission in MCL. There was general agreement for the use of allogeneic HSCT as salvage therapy for MCL, with less agreement on the use of autologous HSCT in the salvage setting. For PTCL, there was general agreement on the use of autologous HSCT to consolidate a CR in high-risk patients and in the salvage setting. Input was split on the use of allogeneic HSCT to consolidate a first CR or as salvage therapy, but there was more support to consider it medically necessary in both settings.

Key Words:
High-Dose Chemotherapy, Non-Hodgkin’s Lymphoma, Lymphoma, Stem-Cell Transplant,
Benefit Application:
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Coding:
CPT Codes:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>Management of recipient hematopoietic cell donor search and cell acquisition</td>
</tr>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection, autologous</td>
</tr>
<tr>
<td>38208</td>
<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing; per donor</td>
</tr>
<tr>
<td>38209</td>
<td>;thawing of previously frozen harvest with washing; per donor</td>
</tr>
<tr>
<td>38210</td>
<td>;specific cell depletion with harvest, T cell depletion</td>
</tr>
<tr>
<td>38211</td>
<td>;tumor cell depletion</td>
</tr>
<tr>
<td>38212</td>
<td>;red blood cell removal</td>
</tr>
<tr>
<td>38213</td>
<td>;platelet depletion</td>
</tr>
<tr>
<td>38214</td>
<td>;plasma (volume) depletion</td>
</tr>
<tr>
<td>38215</td>
<td>;cell concentration in plasma, mononuclear, or buffy coat layer</td>
</tr>
<tr>
<td>38220</td>
<td>Bone marrow; aspiration only</td>
</tr>
<tr>
<td>38221</td>
<td>Bone marrow; biopsy, needle or trocar</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>; autologous (Effective for dates of service on or after January 1, 2012)</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
</tr>
</tbody>
</table>

HCPCS:

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>G0267</td>
<td>Bone marrow or peripheral stem-cell harvest, modification or treatment to eliminate cell type(s) (e.g., T cells, metastatic carcinoma)</td>
</tr>
</tbody>
</table>
S2150

Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)

References:
8. 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.
9. 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.


Policy History:
Medical Policy Group, September 2009 (3)
Medical Policy Administration Committee, September 2009
Available for comment September 18-November 2, 2009
Medical Policy Panel, February 2011
Medical Policy Group, June 2011 (2): Policy, Key Points, References updated
Medical Policy Administration Committee, July 2011
Available for comment, July 6 through August 22, 2011
Medical Policy Group, February 2012 (3): 2012 Updates – Policy, Key Points, References
Medical Policy Group, February 2013
Medical Policy Group, February 2013 (2): 2013 Updates – Description, Key Points and References; no change in policy statement
Medical Policy Panel, February 2014
Medical Policy Group, February 2014 (3): 2014 Updates to Description, Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.