NC Medicaid Hematopoietic Stem-Cell Transplantation For Non-Hodgkin Lymphomas	Medicaid and Health Choice Clinical Coverage Policy No: 11A-11 Amended Date: January 15, 2020

To all beneficiaries enrolled in a Prepaid Health Plan (PHP): for questions about benefits and services available on or after implementation, please contact your PHP

Table of Contents

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Related Clinical Coverage Policies

Refer to https://medicaid.ncdhhs.gov/ for the related coverage policies listed below:

11A-14, Placental and Umbilical Cord Blood as a Source of Stem Cells

11A-16 Hematopoietic Stem Cell Transplantation for Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

1A-39, Routine Costs in Clinical Trial Services for Life Threatening Conditions

1.0 Description of the Procedure, Product, or Service

1.1 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. Hematopoietic 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 with the exception of umbilical cord blood).

1.2 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 effect (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 rejections and GVHD, which also increases susceptibility of the patient to opportunistic infections.

1.3 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 nonrelapse 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 the Policy, the term "reduced-intensity conditioning" will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (traditional) regimens.

1.4 Non-Hodgkin's 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 (3) major categories of lymphoid malignancies based on morphology and cell lineage: B-cell neoplasms, T-cell/natural killer (NK)-cell neoplasms, and Hodgkin's lymphoma.

The most recent lymphoid neoplasm classification is the 2016 WHO Classification:

Mature B-cell neoplasms

a. Chronic lymphocytic leukemia/small lymphocytic lymphoma
b. Monoclonal B-cell lymphocytosis*

c. B-cell prolymphocytic leukemia
d. Splenic marginal zone lymphoma
e. Hairy cell leukemia
f. *Splenic lymphoma/leukemia, unclassifiable*
    1. Splenic diffuse red pulp small B-cell lymphoma
    2. Hairy cell leukemia-variant
g. Lymphoplasmacytic lymphoma
    1. Waldenstrom macroglobulinemia
h. Monoclonal gammopathy of undetermined significance (MGUS), IgM*
i. Heavy chain diseases
    1. Alpha heavy chain disease
    2. Gamma heavy chain disease
    3. Mu heavy chain disease
j. Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
k. Plasma cell myeloma
l. Solitary plasmacytoma of bone
m. Extraosseous plasmacytoma
n. Monoclonal immunoglobulin deposition diseases*
o. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
p. Nodal marginal zone B-cell lymphoma (MZL)
    1. Pediatric nodal MZL
q. Follicular lymphoma
    1. In situ follicular neoplasia*
    2. Duodenal-type follicular lymphoma*
r. Pediatric type follicular lymphoma*
s. *Large B-cell lymphoma with IRF4 rearrangement**
t. Primary cutaneous follicle center lymphoma
u. Mantle cell lymphoma
    1. In situ mantle cell neoplasia*
v. Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
    *1. Germinal center B-cell type**
    *2. Activated B-cell type**
w. T-cell/histiocyte-rich large B-cell lymphoma
x. Primary DLBCL of the central nervous system (CNS)
y. Primary cutaneous DLBCL, leg type
z. EBV^+ DLBCL, not otherwise specified*
aa. *EBV^+ mucocutaneous ulcer**
bb. DLBCL associated with chronic inflammation
cc. Lymphomatoid granulomatosis
dd. Primary mediastinal (thymic) large B-cell lymphoma
ee. Intravascular large B-cell lymphoma
ff. ALK [anaplastic lymphoma kinase] + large B-cell lymphoma
gg. Plasmablastic lymphoma
hh. Primary effusion lymphoma
ii. *HHV81 DLBCL, not otherwise specified**
jj. Burkitt lymphoma
kk. *Burkitt-like lymphoma with 11q aberration**
ll. High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
mm. High-grade B-cell lymphoma, not otherwise specified*

nn. B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

*Changes from the 2008 classification.
Provisional entities are listed in italics.

Mature T-cell and NK-cell neoplasms

a. T-cell prolymphocytic leukemia
b. T-cell large granular lymphocytic leukemia
c. *Chronic lymphoproliferative disorder of NK-cells*
d. Aggressive NK-cell leukemia
e. Systemic EBV [Epstein-Bar virus] + T-cell lymphoma of childhood*
f. Hydroa vacciniforme-like lymphoproliferative disorder*
g. Adult T-cell leukemia/lymphoma
h. Extranodal NK/T-cell lymphoma, nasal type
i. Enteropathy-associated T-cell lymphoma
j. Monomorphic epitheliotropic intestinal T-cell lymphoma*
k. *Indolent T-cell lymphoproliferative disorder of the GI tract**
l. Hepatosplenic T-cell lymphoma
m. Subcutaneous panniculitis-like T-cell lymphoma
n. Mycosis fungoides
o. Sézary syndrome
p. Primary cutaneous CD30+ T-cell lymphoproliferative disorders
    1. Lymphomatoid papulosis
    2. Primary cutaneous anaplastic large-cell lymphoma
q. Primary cutaneous gamma-delta T-cell lymphoma
r. *Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma*
s. *Primary cutaneous acral $CD8^+$ T-cell lymphoma**
t. *Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder**
u. Peripheral T-cell lymphoma, not otherwise specified
v. Angioimmunoblastic T-cell lymphoma
w. *Follicular T-cell lymphoma**
x. *Nodal peripheral T-cell lymphoma with TFH phenotype**
y. Anaplastic large cell lymphoma (ALCL), ALK^+
z. Anaplastic large cell lymphoma (ALCL), ALK^-*
aa. *Breast implant–associated anaplastic large-cell lymphoma**

*Changes from the 2008 classification.
Provisional entities are listed in italics.

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.

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 leukemia (SLL/CLL), lymphoplasmacytic 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 diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), peripheral T-cell lymphoma (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 overall survival (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 one 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 greater than 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 four lymph node areas involved
5. Elevated serum lactate dehydrogenase (LDH) level

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

a. 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(11;14), 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.

1. MCL international prognostic index (MIPI):
   A. Age
   B. ECOG performance status
   C. Serum LDH (calculated as a ratio of LDH to a laboratory's upper limit of normal)
   D. White blood cell count (WBC)
      (i) 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
      (ii) One point each for age 50–59 years, LDH ratio 0.67–0.99, WBC 6,700–9,999.
      (iii) Two points each for age 60–69 years, ECOG 2–4, LDH ratio 1.00–1.49, WBC 10,000–14,999
      (iv) Three points each for age 70 years or older, LDH ratio 1.5 or greater, WBC 15,000 or more

2. MIPI allows separation of three groups with significantly different prognoses:
   A. 0 - 3 points=low risk, 44% of patients, median OS not reached and a five-year OS rate of 60%
   B. 4 - 5 points=intermediate risk, 35% of patients, median OS 51 months
   C. 6 - 11 points=high risk, 21% of patients, median OS 29 months

b. Peripheral T-Cell Lymphoma (PTCL)

The majority of peripheral T-cell lymphomas 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 60–70% 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 20-35%.

The poor results with conventional chemotherapy have prompted exploration of the role of HSCT as therapy.

1.5 Staging

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

Staging of Lymphoma: Ann Arbor Classification:

a. Stage I: Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)

b. Stage 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).

c. 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)

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

1.6 Definitions

1.6.1 Donor Lymphocyte Infusion (DLI)

A type of therapy in which lymphocytes from the blood of a donor are given to a beneficiary who has already received a stem cell transplant from the same donor. The donor lymphocytes may kill remaining cancer cells.

2.0 Eligibility Requirements

2.1 Provisions

2.1.1 General

(*The term "General" found throughout this policy applies to all Medicaid and NCHC policies*)

a. An eligible beneficiary shall be enrolled in either:
   1. the NC Medicaid Program *(Medicaid is NC Medicaid program, unless context clearly indicates otherwise*); or
   2. the NC Health Choice (*NCHC is NC Health Choice program, unless context clearly indicates otherwise)* Program on the date of service and shall meet the criteria in **Section 3.0 of this policy**.

b. Provider(s) shall verify each Medicaid or NCHC beneficiary's eligibility each time a service is rendered.

c. The Medicaid beneficiary may have service restrictions due to their eligibility category that would make them ineligible for this service.

d. Following is only one of the eligibility and other requirements for participation in the NCHC Program under GS 108A-70.21(a): Children must be between the ages of 6 through 18.

2.1.2 Specific

(***The term "Specific" found throughout this policy only applies to this policy***)

a. Medicaid
None Apply.

b. NCHC
None Apply.

2.2 Special Provisions

2.2.1 EPSDT Special Provision: Exception to Policy Limitations for a Medicaid Beneficiary under 21 Years of Age

a. **42 U.S.C. § 1396d(r) [1905(r) of the Social Security Act]**

Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) is a federal Medicaid requirement that requires the state Medicaid agency to cover services, products, or procedures for Medicaid beneficiary under 21 years of age **if** the service is **medically necessary health care** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem] identified through a screening examination (includes any evaluation by a physician or other licensed practitioner).

This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his or her health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

Medically necessary services will be provided in the most economic mode, as long as the treatment made available is similarly efficacious to the service requested by the beneficiary's physician, therapist, or other licensed practitioner; the determination process does not delay the delivery of the needed service; and the determination does not limit the beneficiary's right to a free choice of providers.

EPSDT does not require the state Medicaid agency to provide any service, product or procedure:

1. that is unsafe, ineffective, or experimental or investigational.
2. that is not medical in nature or not generally recognized as an accepted method of medical practice or treatment.

Service limitations on scope, amount, duration, frequency, location of service, and other specific criteria described in clinical coverage policies may be exceeded or may not apply as long as the provider's documentation shows that the requested service is medically necessary "to correct or ameliorate a defect, physical or mental illness, or a condition" [health problem]; that is, provider documentation shows how the service, product, or procedure meets all EPSDT criteria, including to correct or improve or maintain the beneficiary's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

b. **EPSDT and Prior Approval Requirements**

1. If the service, product, or procedure requires prior approval, the fact that the beneficiary is under 21 years of age does **NOT** eliminate the requirement for prior approval.
2. **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *NCTracks Provider Claims and Billing Assistance Guide,* and on the EPSDT provider page. The Web addresses are specified below.

   NCTracks Provider Claims and Billing Assistance Guide: https://www.nctracks.nc.gov/content/public/providers/provider-manuals.html

   EPSDT provider page: https://medicaid.ncdhhs.gov/

2.2.2 EPSDT does not apply to NCHC beneficiaries

2.2.3 Health Choice Special Provision for a Health Choice Beneficiary age 6 through 18 years of age

NC Medicaid shall deny the claim for coverage for an NCHC beneficiary who does not meet the criteria within **Section 3.0** of this policy. Only services included under the NCHC State Plan and the NC Medicaid clinical coverage policies, service definitions, or billing codes are covered for an NCHC beneficiary.

3.0 When the Procedure, Product, or Service Is Covered

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for Medicaid Beneficiaries under 21 Years of Age.

3.1 General Criteria Covered

Medicaid and NCHC shall cover the procedure, product, or service related to this policy when medically necessary, and:

a. the procedure, product, or service is individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the beneficiary's needs;
b. the procedure, product, or service can be safely furnished, and no equally effective and more conservative or less costly treatment is available statewide; and
c. the procedure, product, or service is furnished in a manner not primarily intended for the convenience of the beneficiary, the beneficiary's caretaker, or the provider.

3.2 Specific Criteria Covered

3.2.1 Specific criteria covered by both Medicaid and NCHC

Medicaid and NCHC shall cover hematopoietic stem cell transplantation for non-Hodgkin lymphoma in the following situations:

a. For beneficiaries 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:

1. as salvage therapy for beneficiaries who do not achieve a complete remission (CR) after first-line treatment (induction) with a full course of standard-dose chemotherapy;
2. to achieve or consolidate a CR for those in a chemosensitive first or subsequent relapse; or
3. to consolidate a first CR in beneficiaries with diffuse large B-cell lymphoma, with an age adjusted International Prognostic Index score that predicts a high- or high-intermediate risk of relapse.

b. For patients with mantle cell lymphoma:
   1. Autologous HSCT to consolidate a first remission; or
   2. Allogeneic HSCT, myeloablative or reduced-intensity conditioning as salvage therapy.

c. For patients with NHL B-cell subtypes considered indolent, either allogeneic HSCT using a myeloablative conditioning regimen or autologous HSCT:
   1. as salvage therapy for beneficiaries who do not achieve CR after first-line treatment (induction) with a full course of standard-dose chemotherapy; or
   2. 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.

d. Reduced-intensity conditioning allogeneic HSCT may be considered medically necessary as a treatment of NHL in beneficiaries who meet criteria for an allogeneic HSCT but who do not qualify for a myeloablative allogeneic HSCT (refer to **Subsection 3.2.4 Policy Guidelines**).

e. For beneficiaries with mature T-cell or NK-cell (peripheral T-cell) neoplasms:
   1. Autologous HSCT to consolidate a first complete remission in high-risk subtypes (refer to **Subsection 3.2.4 Policy Guidelines**); or
   2. Autologous or allogeneic HSCT (myeloablative or reduced-intensity conditioning) as salvage therapy.

f. Donor lymphocyte infusion (DLI) (refer to **Section 1.6**) is considered medically necessary and, therefore, covered following allogeneic hematopoietic stem cell transplantation (HSCT) that is medically necessary for the treatment of NHL that has relapsed or is refractory, to prevent relapse in the setting of a high risk of relapse, or to convert an individual from mixed to full donor chimerism.
   Note: Small lymphocytic lymphoma (SLL) may be considered a node-based variant of chronic lymphocytic leukemia (CLL) and is considered separately in clinical coverage policy **11A-16** Hematopoietic Stem-Cell Transplantation for CLL and SLL.

3.2.2 Medicaid Additional Criteria Covered

None Apply.

3.2.3 NCHC Additional Criteria Covered

None Apply.

3.2.4 Policy Guidelines

a. Reduced-intensity conditioning (RIC) would be considered an option in beneficiaries 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, or prior intensive chemotherapy) preclude use of a standard conditioning regimen.

b. In beneficiaries who qualify for a myeloablative allogeneic 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 beneficiaries with good performance status and minimal comorbidities more than allogeneic HSCT with RIC.
c. The term **salvage therapy** describes chemotherapy given to beneficiaries who have either: 1) failed to achieve complete remission after initial treatment for newly diagnosed lymphoma; or 2) relapsed after an initial complete remission.
d. A **chemosensitive relapse** is defined as relapsed non-Hodgkin's lymphoma that does not progress during or immediately after standard-dose induction chemotherapy (i.e., achieves stable disease or a partial response.)
e. **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.
f. **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.
g. 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:
    1. T-cell large granulocyte leukemia (T-LGL);
    2. chronic lymphoproliferative disorder of NK cells;
    3. early stage mycosis fungoides;
    4. primary cutaneous ALCL; and
    5. ALK+ ALCL

4.0 When the Procedure, Product, or Service Is Not Covered

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for Medicaid Beneficiaries under 21 Years of Age.

4.1 General Criteria Not Covered

Medicaid and NCHC shall not cover the procedure, product, or service related to this policy when:

a. the beneficiary does not meet the eligibility requirements listed in **Section 2.0;**
b. the beneficiary does not meet the criteria listed in **Section 3.0;**
c. the procedure, product, or service duplicates another provider's procedure, product, or service; or

d. the procedure, product, or service is experimental, investigational, or part of a clinical trial.

4.2 Specific Criteria Not Covered

4.2.1 Specific Criteria Not Covered by both Medicaid and NCHC

Medicaid and NCHC shall not cover hematopoietic stem-cell transplantation for non-Hodgkin lymphoma in the following situations:

a. For beneficiaries with mantle cell lymphoma:
   1. Autologous HSCT as salvage therapy; or
   2. Allogeneic HSCT to consolidate a first remission.
b. Either autologous HSCT or allogeneic HSCT:
   1. as initial therapy (i.e., without a full course of standard-dose induction chemotherapy) for any NHL;
   2. to consolidate a first complete remission (CR) for beneficiaries with diffuse large B-cell lymphoma and an International Prognostic Index score that predicts a low- or low-intermediate risk of relapse; or
   3. to consolidate a first complete remission (CR) for those with indolent NHL B-cell subtypes.
c. Tandem transplants to treat beneficiaries with any stage, grade, or subtype of NHL.
d. For beneficiaries with mature T-cell or NK-cell (peripheral T-cell) neoplasms, allogeneic HSCT to consolidate a first remission.

4.2.2 Medicaid Additional Criteria Not Covered

None Apply.

4.2.3 NCHC Additional Criteria Not Covered

a. NCGS § 108A-70.21(b) "Except as otherwise provided for eligibility, fees, deductibles, copayments, and other cost sharing charges, health benefits coverage provided to children eligible under the Program shall be equivalent to coverage provided for dependents under North Carolina Medicaid Program except for the following:
   1. No services for long-term care.
   2. No nonemergency medical transportation.
   3. No EPSDT.
   4. Dental services shall be provided on a restricted basis in accordance with criteria adopted by the Department to implement this subsection."

5.0 Requirements for and Limitations on Coverage

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for Medicaid Beneficiaries under 21 Years of Age.

5.1 Prior Approval

Medicaid and NCHC shall require prior approval for Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphoma. The provider shall obtain prior approval before rendering Hematopoietic Stem Cell Transplantation for Non-Hodgkin lymphoma

If prior approval has been given for Hematopoietic Stem Cell Transplantation for Non-Hodgkin Lymphoma, actual donor transplant-related medical expenses **(procuring, harvesting, short-term storing and all associated laboratory costs)** are covered.

If prior approval has been given for allogeneic HSCT for Non-Hodgkin Lymphoma and a donor lymphocyte infusion (DLI) is later indicated (refer to **Section 3.2**), separate prior approval shall not be required for the DLI procedure.

5.2 Prior Approval Requirements

5.2.1 General

The provider(s) shall submit to the Department of Health and Human Services (DHHS) Utilization Review Contractor the following:

a. the prior approval request; and
b. all health records and any other records that support the beneficiary has met the specific criteria in **Subsection 3.2** of this policy.

5.2.2 Specific

None Apply.

5.3 Specific Transplant Prior Approval Requirements

The provider(s) shall submit the following to the NC Medicaid transplant nurse consultant:

a. Letter of medical necessity **signed by the attending transplant physician,** which documents indications for transplant, regimens and dates, the social history and the transplant evaluation;
b. All health care records and any other records that support the beneficiary has met the specific criteria in **Subsection 3.2** of this policy including:
    1. Lab results (less than three months old) to include Complete Blood Count (CBC), complete electrolytes, liver enzymes, Prothrombin Time (PT), International Normalized Ratio (INR), glucose and A1C (Glycated Hemoglobin if Type I or Type II diabetic), and blood type;
    2. Serologies: to include Human Immunodeficiency Virus (HIV), Hepatitis, panel, Rapid Plasma Reagin (RPR), Epstein-Barr Virus (EBV), Cytomegalovirus (CMV), Varicella, Rubella, Herpes Simplex Virus (HSV) I/II, and toxoplasmosis. (*Positive* serology results may be reported that are greater than three months old);
    3. Diagnostic studies (less than six months old) required in a complete packet include:
        A. Cardiac: Echocardiogram, Electrocardiogram (ECG), and/or cardiac catheterization as appropriate for beneficiary's clinical status;
        B. Pulmonary: Pulmonary Function Test if beneficiary has cardiac or pulmonary issues, or a history of smoking; and
        C. Chest x-ray for all transplant candidates;
    4. Other diagnostic tests may be requested as appropriate;
    5. Beneficiary's height and weight
    6. All diagnostic and procedure results, including bone marrow aspiration (not more than six months old)
c. Complete psychological and social evaluation to include:

1. beneficiary's medical compliance;
2. beneficiary's support network;
3. post-transplant care plan, with identification of primary and secondary care providers; and
4. history of mental health issues/substance use/legal issues

d. Beneficiaries with a psychiatric history are required to have an evaluation by a psychiatrist with expertise in evaluating the specific psychiatric issues that relate to transplant candidates.

6.0 Provider(s) Eligible to Bill for the Procedure, Product, or Service

To be eligible to bill for the procedure, product, or service related to this policy, the provider(s) shall:

a. meet Medicaid or NCHC qualifications for participation;
b. have a current and signed Department of Health and Human Services (DHHS) Provider Administrative Participation Agreement; and
c. bill only for procedures, products, and services that are within the scope of their clinical practice, as defined by the appropriate licensing entity.

6.1 Provider Qualifications and Occupational Licensing Entity Regulations

None Apply.

6.2 Provider Certifications

None Apply.

7.0 Additional Requirements

Note: Refer to Subsection 2.2.1 regarding EPSDT Exception to Policy Limitations for Medicaid Beneficiaries under 21 Years of Age.

7.1 Compliance

Provider(s) shall comply with the following in effect at the time the service is rendered:

a. All applicable agreements, federal, state and local laws and regulations including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements; and
b. All NC Medicaid's clinical (medical) coverage policies, guidelines, policies, provider manuals, implementation updates, and bulletins published by the Centers for Medicare and Medicaid Services (CMS), DHHS, DHHS division(s) or fiscal contractor(s)

8.0 Policy Implementation/Revision Information

Original Effective Date: January 1, 1994

Revision Information:

Date	Section Revised	Change
07/01/2005	Throughout	Medicaid Policy was updated to include coverage criteria effective with approved date of State Plan amendment 4/1/05.
09/01/2005	Section 2.2	Medicaid: The special provision related to EPSDT was revised.
12/01/2005	Section 2.2	Medicaid The web address for DMA's EDPST policy instructions was added to this section.
12/01/2006	Sections 2.2	Medicaid: The special provision related to EPSDT was revised.
12/01/2006	Sections 3.0 and 4.0	Medicaid: A note regarding EPSDT was added to these sections.
05/01/2007	Sections 2 through 4	Medicaid: EPSDT information was revised to clarify exceptions to policy limitations for recipients under 21 years of age.
05/01/2007	Attachment A	Medicaid: Added the UB-04 as an accepted claims form.
07/01/2010	Throughout	NCHC: Session Law 2009-451, Section 10.31(a) Transition of NC Health Choice Program administrative oversight from the State Health Plan to the Division of Medical Assistance (DMA) in the NC Department of Health and Human Services.
03/01/2012	Throughout	NCHC: To be equivalent where applicable to NC DMA's Clinical Coverage Policy # 11A-11 under Session Law 2011-145, § 10.41.(b)
03/01/2012	Throughout	Policy updated to reflect current community standards and changing transplant protocols
03/01/2012	Throughout	Technical changes to merge Medicaid and NCHC current coverage into one policy.
10/01/2015	All Sections and Attachments	Updated policy template language and added ICD-10 codes to comply with federally mandated 10/1/2015 implementation where applicable.
03/01/2017	Attachment A, Section B	ICD-10 diagnosis codes updated.
03/15/2019	Table of Contents	Added, "To all beneficiaries enrolled in a Prepaid Health Plan (PHP): for questions about benefits and services available on or after November 1, 2019, please contact your PHP."
03/15/2019	All Sections and Attachments	Updated policy template language.
10/01/2019	Throughout	Removed "& Bone Marrow" from title.
10/01/2019	Section 1.4	Updated to the 2016 WHO classifications for lymphoid neoplasms.

Date	Section Revised	Change
10/01/2019	Section 1.6	Added definition for donor lymphocyte infusion.
10/01/2019	Section 3.2.1	Changed verbiage from "peripheral T-cell lymphoma" to "mature T-cell or NK-cell neoplasms." Note added referencing clinical coverage policy **11A-16** Hematopoietic Stem-Cell Transplantation for CLL and SLL. Criteria added for DLI coverage.
10/01/2019	Section 3.2.4	Text added discussing T-cell and NK-cell neoplasm subtypes.
10/01/2019	Section 4.2.1	Changed verbiage from "peripheral T-cell lymphoma" to "mature T-cell or NK-cell neoplasms."
10/01/2019	Section 5.1	Added text that if PA has been given for allogeneic HSCT and DLI is later indicated, separate PA is not required for the DLI procedure.
10/01/2019	Section 5.3	"Indications for transplant" added to letter of medical necessity requirements. Added "panel" to Hepatitis panel to reflect verbiage in the State Plan.
10/01/2019	Section 7.0	Removed the following statements: FDA approved procedures, products, and devices for implantation must be utilized. A statement signed by the surgeon certifying all FDA requirements for the implants, products, and devices must be retained in the beneficiary's medical record and made available for review upon request. This text is not applicable to this policy.
10/01/2019	Attachment A	Added the UB-04 as an accepted claims form. Removed all CPT, HCPCS, and ICD-10 codes.
01/15/2020	Table of Contents	Updated policy template language, "To all beneficiaries enrolled in a Prepaid Health Plan (PHP): for questions about benefits and services available on or after implementation, please contact your PHP."
01/15/2020	Attachment A	Added, "Unless directed otherwise, Institutional Claims must be billed according to the National Uniform Billing Guidelines. All claims must comply with National Coding Guidelines".

Attachment A: Claims-Related Information

Provider(s) shall comply with the, *NCTracks Provider Claims and Billing Assistance Guide*, Medicaid bulletins, fee schedules, NC Medicaid's clinical coverage policies and any other relevant documents for specific coverage and reimbursement for Medicaid and NCHC:

A. Claim Type

Professional (CMS-1500/837P transaction)

Institutional (UB-04/83711)

Unless directed otherwise, Institutional Claims must be billed according to the National Uniform Billing Guidelines. All claims must comply with National Coding Guidelines.

B. International Classification of Diseases and Related Health Problems, Tenth Revisions, Clinical Modification (ICD-10-CM) and Procedural Coding System (PCS)

Provider(s) shall report the ICD-10-CM and Procedural Coding System (PCS) to the highest level of specificity that supports medical necessity. Provider(s) shall use the current ICD-10 edition and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for code description, as it is no longer documented in the policy.

C. Code(s)

Providers Provider(s) shall report the most specific billing code that accurately and completely describes the procedure, product or service provided. Provider(s) shall use the Current Procedural Terminology (CPT), Health Care Procedure Coding System (HCPCS), and UB-04 Data Specifications Manual (for a complete listing of valid revenue codes) and any subsequent editions in effect at the time of service. Provider(s) shall refer to the applicable edition for the code description, as it is no longer documented in the policy.

If no such specific CPT or HCPCS code exists, then the provider(s) shall report the procedure, product or service using the appropriate unlisted procedure or service code.

Unlisted Procedure or Service
CPT: The provider(s) shall refer to and comply with the Instructions for Use of the CPT Codebook, Unlisted Procedure or Service, and Special Report as documented in the current CPT in effect at the time of service.

HCPCS: The provider(s) shall refer to and comply with the Instructions For Use of HCPCS National Level II codes, Unlisted Procedure or Service and Special Report as documented in the current HCPCS edition in effect at the time of service.

D. Modifiers

Providers shall follow applicable modifier guidelines.

E. Billing Units

Provider(s) shall report the appropriate code(s) used which determines the billing unit unit(s).

F. Place of Service

Inpatient hospital, Outpatient hospital

G. Co-payments

For Medicaid refer to Medicaid State Plan:
https://medicaid.ncdhhs.gov/get-involved/nc-health-choice-state-plan

For NCHC refer to NCHC State Plan:
https://medicaid.ncdhhs.gov/get-involved/nc-health-choice-state-plan

H. Reimbursement

Provider(s) shall bill their usual and customary charges.
For a schedule of rates, refer to: https://medicaid.ncdhhs.gov/

I. Billing for Donor Expenses

1. **Billing for Donor Expenses for Medicaid Beneficiaries**
   Donor transplant-related medical expenses are billed on the Medicaid beneficiary's transplant claim using the beneficiary's Medicaid identification number.

   Medicaid reimburses only for the actual donor's transplant-related medical expenses. Medicaid does not reimburse for unsuccessful donor searches.

2. **Billing for Donor Expenses for NCHC Beneficiaries**
   Donor transplant-related medical expenses donors are billed on the NCHC beneficiary's transplant claim.

   NCHC reimburses only for the actual donor's transplant-related medical expenses. NCHC does not reimburse for unsuccessful donor searches.