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## **1.0 Description of the Procedure, Product, or Service**

### **Hematopoietic Stem-Cell Transplantation**

Hematopoietic stem-cell transplantation (SCT) 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 SCT) or from a donor (i.e., allogeneic SCT). 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 SCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic SCT. Compatibility is established by typing of 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 arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

### **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 SCT 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 that develops 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 SCT**

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 conventional 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 non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

Some patients for whom a conventional myeloablative allogeneic HSCT could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic HSCT. These include those whose age (typically older than 60 years) or comorbidities (e.g, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude the use of a standard myeloablative conditioning regimen.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for non-Hodgkin’s lymphoma indicate autologous or allogeneic SCT is appropriate for treatment of poor-risk patients with Lymphoblastic lymphoma (i.e. when disease is considered systemic).

The ideal allogeneic donors for HLA-identical siblings, matching at the HLA-a, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched unrelated donor identified through the National Marrow donor Registry is typically the next option considered. Recently there has been interest in haploidentical donors, typically a parent or a child of a patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of the recipients will have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with the donors is not as extensive as that with matched donors.

### **Acute Lymphoblastic Leukemia (ALL)**

#### **Childhood ALL**

ALL is the most common cancer diagnosed in children and represents almost 25% of cancers in children younger than 15 years. Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in approximately 95% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large, randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.

ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse. Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis. Certain genetic characteristics of the leukemic cells strongly influence prognosis.

**Clinical and biologic factors predicting clinical outcome can be summarized as follows:**

<b>Factor</b>	<b>Favorable</b>	<b>Unfavorable</b>
Age at diagnosis	1-9 years	Less than 1 or greater than 9 years
Sex	Female	Male
WBC count	Less than 50,000/ $\mu$ L	Greater than 50,000/ $\mu$ L
Genotype	Hyperdiploidy (greater than 50 chromosomes) t(12;21) or TEL/AML 1 fusion	Hypodiploidy (less than 45 chromosomes) t(9;22) or BCR/ABL fusion t(4;11) or MLL/AF4 fusion
Immunophenotype	Common, preB	ProB, T-lineage

### **Adult ALL**

ALL accounts for approximately 20% of acute leukemias in adults. Approximately 60%–80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy; however, only 35%–40% can be expected to survive 2 years. Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, to explain the outcome differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyperdiploidy and t(12;21) are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities like the Philadelphia chromosome t[9;22] are seen in 25%–30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of greater than 30,000/ $\mu$ L (B-cell lineage) and greater than 100,000/ $\mu$ L (T-cell lineage).

### **Related Policies:**

Cord Blood as a Source of Stem Cells

## **2.0 Eligible Recipients**

### **2.1 General Provisions**

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

## **2.2 EPSDT Special Provision: Exception to Policy Limitations for Recipients under 21 Years of Age**

### **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 recipients 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 clinician). This means EPSDT covers most of the medical or remedial care a child needs to improve or maintain his/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 recipient'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 recipient's right to a free choice of providers

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

- a. that is unsafe, ineffective, or experimental/investigational.
- b. 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/or 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 will correct or improve or maintain the recipient's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

### **\*\*EPSDT and Prior Approval Requirements**

- a. If the service, product, or procedure requires prior approval, the fact that the recipient is under 21 years of age does **NOT** eliminate the requirement for prior approval.
- b. **IMPORTANT ADDITIONAL INFORMATION** about EPSDT and prior approval is found in the *Basic Medicaid Billing Guide*, sections 2 and 6, and on the EPSDT provider page. The Web addresses are specified below.

**Basic Medicaid Billing Guide:** <http://www.ncdhhs.gov/dma/basicmed/>

**EPSDT provider page:** <http://www.ncdhhs.gov/dma/epsdt/>

### 3.0 When the Procedure, Product, or Service Is Covered

**IMPORTANT NOTE:** EPSDT allows a recipient less than 21 years of age to receive services in excess of the limitations or restrictions below and without meeting the specific criteria in this section when such services are **medically necessary health care services** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem]; that is, documentation shows how the service, product, or procedure will correct or improve or maintain the recipient's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

**EPSDT DOES NOT ELIMINATE THE REQUIREMENT FOR PRIOR APPROVAL IF PRIOR APPROVAL IS REQUIRED.** For additional information about EPSDT and prior approval requirements, refer to **Subsection 2.2** of this policy.

#### 3.1 General Criteria

Medicaid covers procedures, products, and services related to this policy when they are 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 recipient'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 recipient, the recipient's caretaker, or the provider.

#### 3.2 Specific Criteria

N.C. Medicaid covers hematopoietic stem-cell or bone marrow transplantation for ALL in the following situations :

##### **Children**

- a. Allogeneic or autologous stem cell transplantation may be considered medically necessary as a treatment of childhood ALL in first complete remission but at high risk of relapse. High risk of relapse following initial complete remission is indicated by the presence of at least **one** of the following:
  1. Poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1,000/ $\mu$ L or greater, or
  2. Poor treatment response to induction therapy at 6 weeks with high risk having greater than or equal to 1% minimal residual disease measured by flow cytometry, or
  3. All children with T-cell phenotype, or
  4. Patients with either the t(9;22) or t(4;11) regardless of early response measures
- b. Autologous or allogeneic stem cell transplantation support may be considered medically necessary as a treatment of childhood ALL in second or greater remission or refractory ALL.

**Adults**

- a. Autologous hematopoietic stem cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission but at high risk of relapse. High risk of relapse following initial complete remission is indicated by the presence of at least one of the following:
  1. age greater than 35 years,
  2. leukocytosis at presentation of greater than 30,000/ $\mu$ L (B-cell lineage) and greater than 100,000/ $\mu$ L (T-cell lineage),
  3. Extramedullary disease, particularly CNS,
  4. "Poor prognosis" genetic abnormalities like the Philadelphia chromosome t(9;22),
  5. Time to attain complete remission longer than 4 weeks.
- b. Allogeneic hematopoietic stem cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission for any risk level.
- c. Allogeneic hematopoietic stem cell transplantation may be considered medically necessary as a treatment of adult ALL in second or greater remission, or in patients with relapsed or refractory ALL.
- d. Reduced-intensity conditioning allogeneic hematopoietic SCT may be considered medically necessary as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission, and who, for medical reasons would be unable to tolerate a standard myeloablative conditioning regimen. These include patients whose age (typically older than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.
- e. High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment in adults with Progenitor-B cell ALL.

**3.3 Policy Guidelines**

As noted in **Section 1.0**, there is no clear age cut off that distinguishes adults from children with ALL.

While some HDC protocols can be administered on an outpatient basis, typically the recipient is hospitalized for management of the marrow ablative complications of the therapy. All recipients receiving whole body radiotherapy, typically those receiving an allogeneic transplant (from donor to recipient), will require prolonged hospitalization.

The National Comprehensive Cancer Network (NCCN) clinical practice guidelines for non-Hodgkin's lymphoma indicate autologous or allogeneic SCT is appropriate for treatment of poor-risk patients with lymphoblastic lymphoma (i.e., when disease is considered to be systemic).

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 6). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of graft-versus-host-disease and overall morbidity

of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors

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

**IMPORTANT NOTE:** EPSDT allows a recipient less than 21 years of age to receive services in excess of the limitations or restrictions below and without meeting the specific criteria in this section when such services are **medically necessary health care services** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem]; that is, documentation shows how the service, product, or procedure will correct or improve or maintain the recipient's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

**EPSDT DOES NOT ELIMINATE THE REQUIREMENT FOR PRIOR APPROVAL IF PRIOR APPROVAL IS REQUIRED.** For additional information about EPSDT and prior approval requirements, refer to **Subsection 2.2** of this policy.

### **4.1 General Criteria**

Procedures, products, and services related to this policy are not covered when

- a. the recipient does not meet the eligibility requirements listed in **Section 2.0**;
- b. the recipient does not meet the medical necessity criteria listed in **Section 3.0**;
- c. the procedure, product, or service unnecessarily 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**

N.C. Medicaid does not cover hematopoietic stem-cell or bone marrow transplantation for ALL in the following situations :

#### **Children**

- a. Allogeneic hematopoietic SCT to treat relapsing ALL after a prior autologous SCT;

#### **Adults**

- a. Autologous hematopoietic SCT to treat adult ALL in second or greater remission or those with refractory disease; and
- b. Allogeneic hematopoietic SCT to treat relapsing ALL after a prior autologous SCT.

#### **Adult or Child**

- a. when the recipient's psychosocial history limits the recipient's ability to comply with pre- and post-transplant medical care.
- b. when current recipient or caretaker non-compliance would make compliance with a disciplined medical regime improbable

## 5.0 Requirements for and Limitations on Coverage

**IMPORTANT NOTE:** EPSDT allows a recipient less than 21 years of age to receive services in excess of the limitations or restrictions below and without meeting the specific criteria in this section when such services are **medically necessary health care services** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem]; that is, documentation shows how the service, product, or procedure will correct or improve or maintain the recipient's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

**EPSDT DOES NOT ELIMINATE THE REQUIREMENT FOR PRIOR APPROVAL IF PRIOR APPROVAL IS REQUIRED.** For additional information about EPSDT and prior approval requirements, refer to **Subsection 2.2** of this policy.

### 5.1 Prior Approval

Prior Approval is required for all transplants, including bone marrow transplant for ALL.

If prior approval has been given for stem cell transplants, actual donor expenses (**procuring, harvesting, short-term storing and all associated laboratory costs**) are covered.

## 6.0 Providers Eligible to Bill for the Procedure, Product, or Service

To be eligible to bill for procedures, products, and services related to this policy, providers shall

- a. meet Medicaid's qualifications for participation;
- b. be currently enrolled with N.C. Medicaid; 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.

## 7.0 Additional Requirements

**IMPORTANT NOTE:** EPSDT allows a recipient less than 21 years of age to receive services in excess of the limitations or restrictions below and without meeting the specific criteria in this section when such services are **medically necessary health care services** to correct or ameliorate a defect, physical or mental illness, or a condition [health problem]; that is, documentation shows how the service, product, or procedure will correct or improve or maintain the recipient's health in the best condition possible, compensate for a health problem, prevent it from worsening, or prevent the development of additional health problems.

**EPSDT DOES NOT ELIMINATE THE REQUIREMENT FOR PRIOR APPROVAL IF PRIOR APPROVAL IS REQUIRED.** For additional information about EPSDT and prior approval requirements, refer to **Subsection 2.2** of this policy.

### 7.1 Compliance

Providers shall comply with all applicable federal, state, and local laws and regulations, including the Health Insurance Portability and Accountability Act (HIPAA) and record retention requirements.

**Division of Medical Assistance**  
**High-dose chemotherapy +/- Total Body Irradiation**  
**Including Autologous and Allogeneic Stem Cell Support**  
**for Acute Lymphocytic Leukemia**

**Clinical Coverage Policy No.: 11A-1**  
**Original Effective Date: July 1, 1987**  
**Revised Date: January 1, 2012**

## **8.0 Policy Implementation/Revision Information**

**Original Effective Date:** July 1, 1987

### **Revision Information:**

<b>Date</b>	<b>Section Revised</b>	<b>Change</b>
7/1/05	Entire Policy	Policy was updated to include coverage criteria effective with approved date of State Plan amendment 4/1/05.
9/1/05	Section 2.2	The special provision related to EPSDT was revised.
12/1/05	Section 2.2	The web address for DMA's EDPST policy instructions was added to this section.
12/1/06	Sections 2.2	The special provision related to EPSDT was revised.
12/1/06	Sections 3.0 and 4.0	A note regarding EPSDT was added to these sections.
5/1/07	Sections 2 through 4	EPSDT information was revised to clarify exceptions to policy limitations for recipients under 21 years of age.
5/1/07	Attachment A	Added the UB-04 as an accepted claims form.
1/1/12	Throughout	Policy updated to reflect current community standards and changing transplant protocols.

## **Attachment A: Claims-Related Information**

Reimbursement requires compliance with all Medicaid guidelines, including obtaining appropriate referrals for recipients enrolled in the Medicaid managed care programs.

### **A. Claim Type**

Professional (CMS-1500/837P transaction)

### **B. Diagnosis Codes**

Providers shall bill the ICD-9-CM diagnosis codes(s) to the highest level of specificity that supports medical necessity.

### **C. Procedure Code(s)**

<b>CPT Code(s)</b>	<b>Description</b>
38205	Blood derived Hemopoietic progenitor cell harvesting for transplantation, per collection; allogeneic
38206	Blood derived Hemopoietic progenitor cell harvesting for transplantation, per collection; Autologous
38230	Bone Marrow harvesting for transplantation
38240	Bone marrow or peripheral stem cell transplantation; allogeneic
38241	Bone marrow or peripheral stem cell transplantation; Autologous
38242	Allogeneic donor lymphocyte infusions

<b>ICD-9 Procedure Code(s)</b>	<b>Description</b>
41.00	Bone marrow transplant
41.01	Autologous bone marrow transplant
41.03	Allogeneic bone marrow transplant
41.04	Autologous (hematopoietic) stem cell transplant
41.05	Allogeneic (hematopoietic) stem cell transplant

<b>HCPCS Code(s)</b>	<b>Description</b>
S2150	Bone Marrow or blood derived stem cell (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications including pheresis and cell preparation, /storage; marrow ablative therapy; drugs; supplies; hospitalization with outpatient follow-up; medical/surgical; and the number of days of pre and post transplant care in the global definition.

**D. Modifiers**

Providers are required to follow applicable modifier guidelines.

**E. Billing Units**

The appropriate procedure code(s) used determines the billing unit(s).

**F. Place of Service**

Inpatient Hospital, Outpatient Hospital

**G. Co-payments**

Co-payment(s) are not required for HSCT for ALL.

**H. Reimbursement**

Providers shall bill their usual and customary charges.

**I. Billing for Donor Expenses**

Donor expenses for non-Medicaid donors are billed on the Medicaid recipient's transplant claim using the recipient's Medicaid identification number. Donor expenses for Medicaid donors are billed on the Medicaid donor's claim using the donor's Medicaid identification number.

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