Clinical Policy: Hematopoietic Stem-Cell Transplantation for Leukemia

Reference Number: WNC.CP.238 Coding Implications
Last Review Date: Revision Log

See Important Reminder **at the end of this policy for important regulatory and legal information.**

Note: When state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Description[1]

This policy describes the medical necessity criteria for Hematopoietic Stem-Cell Transplantation (HSCT) for Leukemia.

Policy/Criteria[1]

I. WellCare of North Carolina® shall cover Hematopoietic Stem Cell Transplantation for **Chronic Myeloid Leukemia (CML)** in the following situations:

- **A.** Allogeneic HSCT using a myeloablative conditioning regimen may be considered medically necessary as a treatment of CML; **or**
- **B.** Allogeneic HSCT using a reduced-intensity conditioning (RIC) regimen may be considered medically necessary as a treatment of CML in patients who meet clinical criteria for an allogeneic HSCT but who are not considered candidates for a myeloablative conditioning allogeneic HSCT.
- **C.** Donor lymphocyte infusion (DLI) is considered medically necessary and, therefore, covered following allogeneic hematopoietic stem cell transplantation (HSCT) that is medically necessary for the treatment of CML 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.
- **D.** Some patients for whom a conventional myeloablative allotransplant could be curative may be considered candidates for reduced-intensity conditioning (RIC) allogeneic SCT. 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. For patients who qualify for a myeloablative allogeneic SCT on the basis of clinical status, either a myeloablative or RIC regimen may be considered medically necessary. The National Comprehensive Cancer Network (NCCN) guidelines on Chronic Myelogenous Leukemia recommend allogeneic bone marrow transplant for the treatment of primary CML and CML with disease progression. However, autologous bone marrow transplant for CML is not addressed in these guidelines.

II. WellCare of North Carolina® shall cover Hematopoietic Stem Cell Transplantation for **Acute Myeloid Leukemia (AML)** in the following situations:

- **A.** Allogeneic HSCT using a myeloablative conditioning regimen to treat:
  1. Poor- to intermediate-risk AML in first complete remission;
  2. AML that is refractory to standard induction chemotherapy but can be brought into clinical remission with intensified induction chemotherapy;
  3. AML that relapses following chemotherapy induced first complete remission but can be brought into second complete remission or beyond with intensified induction chemotherapy; **or**
  4. AML in patients who have relapsed following a prior autologous HSCT but can be brought into clinical remission with intensified induction chemotherapy and are medically able to tolerate the procedure.
- **B.** Allogeneic HSCT using a reduced-intensity conditioning regimen as a treatment of AML in patients who are in complete marrow and extramedullary remission, and who for medical reasons would be unable to tolerate a myeloablative conditioning regimen;
- **C.** Autologous HSCT to treat AML in first or second remission or relapsed AML if responsive to intensified induction chemotherapy;
- **D.** Donor lymphocyte infusion is considered medically necessary and, therefore, covered following allogeneic hematopoietic stem cell transplantation (HSCT) that is medically necessary for the treatment of AML 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.

III. WellCare of North Carolina® shall cover Hematopoietic Stem Cell Transplantation for **Acute Lymphoblastic Leukemia (ALL)** in the following situations:

- **A.** Children
  1. Allogeneic or autologous stem cell transplantation 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:
     a. Poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1,000/μL or greater, **or**
     b. 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**
     c. All children with T-cell phenotype, **or**
     d. Patients with either the t(9;22) or t(4;11) regardless of early response measures.
  2. 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;
  3. Allogenic HSCT is considered medically necessary to treat relapsing ALL after a prior autologous HSCT.

B. Adults
1. Autologous HSCT 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:
   a. Age greater than 35 years,
   b. Leukocytosis at presentation of greater than 30,000/μL (B-cell lineage) and greater than 100,000/μL (T-cell lineage),
   c. Extramedullary disease, particularly CNS,
   d. "Poor prognosis" genetic abnormalities like the Philadelphia chromosome t(9;22),
   e. Time to attain complete remission longer than 4 weeks.
2. Allogeneic HSCT may be considered medically necessary as a treatment of adult ALL in first complete remission for any risk level.
3. Allogeneic HSCT may be considered medically necessary as a treatment of adult ALL in second or greater remission, or in patients with relapsed or refractory ALL.
4. Reduced intensity conditioning allogeneic HSCT 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.
5. High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment in adults with Progenitor-B cell ALL.
6. Allogenic HSCT is considered medically necessary to treat relapsing ALL after a prior autologous HSCT.

C. Adult or Child
1. Donor lymphocyte infusion is considered medically necessary and, therefore, covered following allogeneic HSCT that is medically necessary for the treatment of ALL 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.

IV. WellCare of North Carolina® shall cover allogeneic Hematopoietic Stem Cell Transplantation for **Chronic Lymphocytic Leukemia (CLL)** using either a myeloablative or reduced-intensity pretransplant conditioning regimen to treat CLL in members with markers of poor-risk disease.

A. Donor lymphocyte infusion is considered medically necessary and, therefore, covered following allogeneic HSCT that is medically necessary for the treatment of CLL 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.

V. WellCare of North Carolina® **shall not** cover Hematopoietic Stem Cell Transplantation for **CML, AML, ALL and/or CLL** in the following situations:
- **A.** Autologous HSCT as a treatment of **CML or CLL**;
- **B.** Autologous HSCT to treat adult ALL in second or greater remission or those with refractory disease.
- **C.** Allogeneic HSCT to treat **CLL except** as noted in Subsection IV of this policy;
- **D.** When the member's psychosocial history limits the member's ability to comply with pre- and post-transplant medical care; **or**
- **E.** When current member or caretaker non-compliance would make compliance with a disciplined medical regimen improbable.

Background[1]

A. Hematopoietic stem-cell transplantation 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 (autologous HSCT) or from a donor (allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Although cord blood is an allogeneic source, the 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 hematopoietic 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 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.

B. **CML** is a hematopoietic stem cell disorder that is characterized by the presence of a chromosomal abnormality called the Philadelphia chromosome, which results from reciprocal translocation between the long arms of chromosomes 9 and 22. This cytogenetic change results in constitutive activation of BCR-ABL, a tyrosine kinase (TK) that stimulates unregulated cell proliferation, inhibition of apoptosis, genetic instability, and perturbation of the interactions between CML cells and the bone marrow stroma only in malignant cells. CML accounts for about 15% of newly diagnosed cases of leukemia in adults and occurs in about 1 to 2 cases per 100,000 adults.

C. **AML** (sometimes called "acute nonlymphocytic leukemia" [ANLL]) refers to a set of leukemias that arise from a myeloid precursor in the bone marrow. AML is characterized by proliferation of myeloblasts, coupled with low production of mature red blood cells, platelets, and often non-lymphocytic white blood cells (granulocytes, monocytes). Clinical signs and symptoms are associated with neutropenia,

thrombocytopenia, and anemia. The incidence of AML increases with age, with a median of 67 years. About 13,000 new cases are diagnosed annually.
The pathogenesis of AML is unclear. It can be subdivided according to resemblance to different subtypes of normal myeloid precursors using the French American-British (FAB) classification. This system classifies leukemias from M0–M7, based on morphology and cytochemical staining, with immunophenotypic data in some instances. The World Health Organization (WHO) subsequently incorporated clinical, immunophenotypic and a wide variety of cytogenetic abnormalities that occur in 50% to 60% of AML cases into a classification system that can be used to guide treatment according to prognostic risk categories.

D. **Childhood 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 pre-symptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.

E. 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.

F. **Adult 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 to explain the outcome differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyper-diploidy 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/μL (B-cell lineage) and greater than 100,000/μL (T-cell lineage).

G. **CLL** is a neoplasm of hematopoietic origin characterized by the accumulation of lymphocytes with a mature, generally well-differentiated morphology; these cells accumulate in blood, bone marrow, lymph nodes, and spleen.

H. Donor Lymphocyte Infusion (DLI) is a type of therapy in which lymphocytes from the blood of a donor are given to a member who has already received a stem cell transplant from the same donor. The donor lymphocytes may kill remaining cancer cells.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024 American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Reviewed Date	Approval Date
Original approval date	04/21	05/21
Reviewed CPT codes.	12/21	02/22
Annual Review. Section V. Added verbiage: "Autologous HSCT to treat adult ALL in second or greater remission or those with refractory disease" CPT codes reviewed.	11/22	11/22
NCHC verbiage removed from NC Guidance Verbiage.	04/23	04/23
Annual Review. CPT codes removed.	11/23	11/23
Annual Review. Removed "Medicaid and health choice" verbiage from References.		

References

1. State of North Carolina Medicaid Clinical Coverage Policy No: 11A-1 Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia (ALL). Program Specific Clinical Coverage Policies | NC Medicaid (ncdhhs.gov). Published August 15, 2023. Accessed July 12, 2024.
2. State of North Carolina Medicaid Clinical Coverage Policy No: 11A-2 Hematopoietic Stem-Cell Transplant for Acute Myeloid Leukemia. Program. Published August 15, 2023. Accessed July 12, 2024.
3. State of North Carolina Medicaid Clinical Coverage Policy No: 11A-3 Hematopoietic Stem-Cell Transplantation for Chronic Myelogenous Leukemia. Program. Published August 15, 2023. Accessed July 12, 2024].
4. State of North Carolina Medicaid Clinical Coverage Policy No: 11A-16 Hematopoietic Stem-Cell Transplantation for Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL).Program Specific Clinical Coverage Policies | NC Medicaid (ncdhhs.gov). Published August 15, 2023. Accessed July 12, 2024.

North Carolina Guidance

Eligibility Requirements

a. An eligible beneficiary shall be enrolled in the NC Medicaid Program (Medicaid is NC Medicaid program, unless context clearly indicates otherwise);
b. Provider(s) shall verify each Medicaid 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.

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.

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/

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 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.

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).

Claims-Related Information
Provider(s) shall comply with the NC Tracks 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:

a. Claim Type - as applicable to the service provided:
   Professional (CMS-1500/837P transaction)
   Institutional (UB-04/837I transaction)
   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) - 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(s).
f. Co-payments -
   For Medicaid refer to Medicaid State Plan:
   https://medicaid.ncdhhs.gov/get-involved/nc-health-choice-state-plan

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

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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