

## Corporate Medical Policy

# Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia

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### Description of Procedure or Service

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

Hematopoietic stem-cell transplantation (HSCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Bone marrow stem cells may be obtained from the transplant recipient (i.e., autologous HSCT) or from a donor (i.e., allogeneic HSCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a lower incidence of rejection or graft-versus-host disease (GVHD).

Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HSCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HSCT. Compatibility is established by typing 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 HSCT**

The success of autologous HSCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. As a consequence, autologous HSCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HSCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

The conventional (“classical”) practice of allogeneic HSCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect 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

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allogeneic HSCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

## Reduced-Intensity Conditioning for Allogeneic HSCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in 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.

## 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:**

Factor	Favorable	Unfavorable
Age at diagnosis	1-9 years	<1 or >9 years
Sex	Female	Male
WBC count	<50,000/ $\mu$ L	$\geq$ 50,000/ $\mu$ L
Genotype	Hyperdiploidy (>50 chromosomes) t(12;21) or TEL/ <i>AML1</i> fusion	Hypodiploidy (<45 chromosomes) t(9:22) or <i>BCR/ABL</i> fusion t(4;11) or <i>MLL/AF4</i> fusion
Immunophenotype	Common, preB	ProB, T-lineage

### Adult ALL

ALL accounts for approximately 20% of acute leukemias in adults. Approximately 60%–80% of adults

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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 >30,000/μL (B-cell lineage) and >100,000/μL (T-cell lineage).

**Note:** The use of killer (LAK) cells in the treatment of malignancies is addressed in a separate policy, Adoptive Immunotherapy.

**Note:** For the purpose of this policy unless otherwise specified in the text, the term “allogeneic SCT” refers to the use of a myeloablative pretransplant conditioning regimen.

## **Related Policies:**

Cord Blood as a Source of Stem Cells  
Adoptive Immunotherapy  
Donor Leukocyte Infusion

*\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

## **Policy**

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**BCBSNC will provide coverage for Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia (ALL) when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

**Some patients may be eligible for coverage under Clinical Trials. Refer to the policy on Clinical Trial Services for Life-Threatening Conditions.**

## **Benefits Application**

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

**Some health benefit plans may exclude benefits for transplantation.**

**Refer to the Member's Benefit Booklet for prior review requirements.**

## **When Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia is covered**

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### **Children**

- 1) 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. (See Policy

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Guidelines for Relapse Risk Prognostic Factors.)

- 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.

## Adults

- 1) 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. (See Policy Guidelines for Relapse Risk Prognostic Factors.)
- 2) Allogeneic hematopoietic stem cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission for any risk level.
- 3) 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.
- 4) Reduced-intensity conditioning allogeneic hematopoietic SCT may be considered medically necessary as a treatment of ALL 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. (See Policy Guidelines)
- 5) High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment in adults with Progenitor-B cell ALL.

## When Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia is not covered

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### Children

1. Allogeneic hematopoietic SCT is considered investigational to treat relapsing ALL after a prior autologous SCT.

### Adults

1. Autologous hematopoietic SCT is investigational to treat adult ALL in second or greater remission or those with refractory disease.
2. Allogeneic hematopoietic SCT is investigational to treat relapsing ALL after a prior autologous SCT.

## Policy Guidelines

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### Relapse Risk Prognostic Factors

#### Children

Adverse prognostic factors in children include the following: age less than 1 year or more than 9 years, male gender, white blood cell count at presentation above 50,000/ $\mu$ L, hypodiploidy (<45 chromosomes), t(9:22) or BCR/ABL fusion, t(4;11) or MLL/AF4 fusion, and ProB or T-lineage immunophenotype.

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/ $\mu$ L or greater,
- (b) Poor treatment response to induction therapy at 6 weeks with high risk having  $\geq$ 1% minimal residual disease measured by flow cytometry,

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- (c) All children with T-cell phenotype,
- (d) Patients with either the t(9;22) or t(4;11) regardless of early response measures

## Adults

Relapse risk prognostic factors are less well defined in adults. 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 >30,000/ $\mu$ L (B-cell lineage) and >100,000/ $\mu$ L (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.

## Reduced-Intensity Conditioning

Some patients for whom a conventional myeloablative allogeneic HSCT could be curative may be considered candidates for 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 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 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.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable codes: 38205, 38206, 38230, 38232, 38240, 38241, 38242, S2150*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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## Scientific Background and Reference Sources

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- TEC Assessment, January, 1998; Volume 12, No. 25
- BCBSA Medical Policy Reference Manual, 4/30/2000
- TEC Assessment, August, 2000; Volume 15, No. 9
- BCBSA Medical Policy Reference Manual, 8/18/2000
- Specialty Matched Consultant Advisory Panel - 11/2002
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 12/18/02
- Specialty Matched Consultant Advisory Panel 11/2004
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 9/27/05
- Specialty Matched Consultant Advisory Panel - 3/2006
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 4/17/07
- Specialty Matched Consultant Advisory Panel - 3/2008
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 1/14/2010
- Specialty Matched Consultant Advisory Panel – 5/2010
- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphoma (v.1.2010). Retrieved March 25, 2010 from [http://www.nccn.org/professionals/physician\\_gls/PDF/nhl.pdf](http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf).
- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Non-Hodgkin's Lymphoma (v.2.2011). Retrieved March 14, 2011 from [http://www.nccn.org/professionals/physician\\_gls/PDF/nhl.pdf](http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf).
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 1/13/2011
- Specialty Matched Consultant Advisory Panel – 4/2011
- BCBSA Medical Policy Reference Manual [Electronic Version]. 8.01.32, 1/12/2012
- Specialty Matched Consultant Advisory Panel – 4/2012

## Policy Implementation/Update Information

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- 1/01 Specialty Matched Consultant Advisory Group.
- 2/01 Original policy issued.
- 2/03 Specialty Matched Consultant Advisory Panel review 11/2002. No change in criteria. Codes 86812-86822 removed; codes 38231 and 86915 deleted and codes 38242, 38205 and 38206 added to the Billing/Coding section. System coding changes.
- 1/04 Benefits Application and Billing/Coding sections updated for consistency.

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- 2/04 Individual CPT codes listed for CPT ranges 38240-38242 under Billing/Coding section.
- 7/29/04 Added code S2150 to the Billing/Coding section of the policy.
- 12/9/04 Specialty Matched Consultant Advisory Panel review 11/29/2004. No changes to criteria. Revised Description of Procedure or Service section. Reformatted When Bone Marrow Transplant for Acute Lymphocytic Leukemia is covered section. Wording revised under When Bone Marrow Transplant for acute Lymphocytic Leukemia is not covered. Added policy number to Policy Key Words section. "Hematopoietic" and "Opportunistic" added to Definitions. References added.
- 4/10/06 Specialty Matched Consultant Advisory Panel review 3/15/2006. Added to the "When covered" section an additional indication; "3. High dose chemotherapy with allogeneic stem cell support may be considered medically necessary as a treatment in young adults with Progenitor-B ALL". References added.
- 6/2/08 Specialty Matched Consultant Advisory Panel review 3/17/08. Added reference to the Clinical Trials policy to the "Policy" section. Removed from the "When Not Covered" section; "High dose chemotherapy and allogeneic stem cell support is considered investigational for children and adults, as a treatment of relapsing ALL after a prior course of high-dose chemotherapy and autologous stem cell support." References added. (btw)
- 6/22/10 Policy Number(s) removed. (amw)
- 7/6/10 Specialty Matched Consultant Advisory Panel review 5/24/2010. Policy name changed from Bone Marrow Transplant for Acute lymphocytic Leukemia to Hematopoietic Stem-Cell Transplantation for Lymphoblastic Leukemia. Removed reference to "Bone Marrow Transplant, high dose chemotherapy and stem cell support" and inserted "hematopoietic stem-cell transplantation" throughout policy as appropriate. Description extensively revised. Updated "high risk of relapse" criteria for both children and adults. Added under "When Covered" section; "Adult", "2. Allogeneic hematopoietic stem-cell transplantation may be considered medically necessary as a treatment of adult ALL in first complete remission for any risk level." Added "4. 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." Revised the "When Not Covered" section to indicate; "**Children** 1. Allogeneic hematopoietic SCT is considered investigational to treat relapsing ALL after a prior autologous SCT. "**Adults** 1. Autologous hematopoietic SCT is investigational to treat adult ALL in second or greater remission or those with refractory disease. 2. Allogeneic hematopoietic SCT is investigational to treat relapsing ALL after a prior autologous SCT." "**NOTE:** The use of donor leukocyte infusions to treat relapse after allogeneic SCT for either children or adults is considered separately in the policy entitled, Donor Leukocyte Infusion." "Policy Guidelines" updated. References added. (btw)
- 5/24/11 Specialty Matched Consultant Advisory Panel review 4/27/11. Moved all "Notes" to the "Description" section. Revised the following statement in the "Benefits Application" section for consistency; "Some health benefit plans may exclude benefits for transplantation." Moved the following statement from "Policy Guidelines" to "Benefit Applications"; "Refer to the Member's Benefit Booklet for prior review requirements." Moved information related to Relapse Risk Prognostic Factors and Reduced Intensity Conditioning to the "Policy Guideline" section. "Policy Guidelines" updated. References added. (btw)
- 2/21/12 New 2012 CPT code 38232 added to Billing/Coding section. (btw)

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5/15/12 Specialty Matched Consultant Advisory Panel review 4/18/2012. Description section updated for format consistency. No change to policy intent. References added. (btw)

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