

MEDICAL POLICY

POLICY TITLE	HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA
POLICY NUMBER	MP 9.041

CLINICAL BENEFIT	<input type="checkbox"/> MINIMIZE SAFETY RISK OR CONCERN. <input type="checkbox"/> MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. <input type="checkbox"/> ASSURE APPROPRIATE LEVEL OF CARE. <input type="checkbox"/> ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. <input checked="" type="checkbox"/> ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. <input type="checkbox"/> ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective date:	5/1/2026

POLICY

Childhood Acute Lymphoblastic Leukemia

Autologous or allogeneic hematopoietic cell transplantation (HCT) may be considered **medically necessary** to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse (for definition of high-risk factors, see Policy Guidelines).

Autologous or allogeneic HCT may be considered **medically necessary** to treat childhood ALL in second or greater remission or refractory ALL.

Allogeneic HCT may be considered **medically necessary** to treat relapsing ALL after a prior autologous HCT in children.

Adult Acute Lymphoblastic Leukemia

Autologous HCT may be considered **medically necessary** to treat adult ALL in first complete remission but at high risk of relapse (for definition of high-risk factors, see Policy Guidelines).

Allogeneic HCT may be considered **medically necessary** to treat adult ALL in first complete remission for any risk level (for definition of risk factors, see Policy Guidelines).

Allogeneic HCT may be considered **medically necessary** to treat adult ALL in second or greater remission, or in adults with relapsed or refractory ALL.

Autologous HCT is **investigational** to treat adult ALL in second or greater remission or those with refractory disease. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Allogeneic HCT may be considered **medically necessary** to treat relapsing ALL after a prior autologous HCT.

Reduced intensity conditioning allogeneic HCT 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 (see Policy Guidelines), would be unable to tolerate a standard myeloablative conditioning regimen.

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Note: The use of donor leukocyte infusions to treat relapse after allogeneic HCT for either children or adults is considered separately in **MP 2.004 Donor Lymphocyte Infusion for Hematologic Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant.**

POLICY GUIDELINES

Relapse Risk Prognostic Factors

Childhood Acute Lymphoblastic Leukemia

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/ μ L, hypodiploidy (less than 45 chromosomes), translocation involving chromosomes 9 and 22 (t [9; 22]) or BCR/ABL fusion, translocation involving chromosomes 4 and 11 (t [4; 11]) or MLL/AF4 fusion, and ProB or T-lineage immunophenotype. Several risk stratification schema exist but, in general, the following findings help define children at high risk of relapse: 1) poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/ μ L or greater, or poor treatment response to induction therapy at 6 weeks with high risk having 1% or higher minimal residual disease measured by flow cytometry, 2) all children with T-cell phenotype, and 3) patients with either the t(9;22) or t(4;11) regardless of early response measures.

Adult Acute Lymphoblastic Leukemia

Risk factors for relapse are less well-defined in adults, but a patient with any of the following may be considered at high risk for relapse: age greater than 35 years, leukocytosis at presentation of greater than 30,000/ μ L (B cell lineage) or greater than 100,000/ μ L (T-cell lineage), "poor prognosis" genetic abnormalities like the Philadelphia chromosome (t [9; 22]), extramedullary disease, and time to attain complete remission longer than four (4) weeks.

Reduced-Intensity Conditioning

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

The ideal allogeneic donors are human leukocyte antigen (HLA) identical siblings, matched at the HLA-A, -B, and DR (antigen-D related) loci on each arm of chromosome 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 three (3) of the six (6) major histocompatibility antigens. Most will have such a donor. The risk of morbidity (e.g., graft-versus-host disease) may be higher than with HLA-matched donors; however, as medical treatments improve, the

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risks of graft-versus-host disease with haploidentical donors are approaching those similar to HLA-matched donors.

Cross-Reference:

MP 2.317 BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

PRODUCT VARIATIONS

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations. Please see additional information below.

FEP PPO - Refer to FEP medical policy manual. The FEP medical policy manual can be found at: fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies.

DESCRIPTION/BACKGROUND

ALL is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified to risk-adapted therapy according to certain clinical and genetic risk factors that predict an outcome. Therapy may include HCT.

Acute Lymphoblastic Leukemia

Childhood Acute Lymphoblastic Leukemia

ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years. Remission of disease is now typically achieved with pediatric chemotherapy regimens in 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. The prognosis after first relapse is related to the length of the original remission. For example, leukemia-free survival is 40% to 50% for children whose first remission was longer than 3 years compared with 10% to 15% for those who relapse less than 3 years after treatment. Thus, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allogeneic HCT are unknown.

ALL is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified by 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 at diagnosis. Certain genetic characteristics of leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized in the Policy Guidelines section.

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Adult ALL

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy; however, only 35% to 40% can be expected to survive two years. Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, explain differences in outcomes between the two groups. For example, the “good prognosis” genetic abnormalities, such as hyperdiploidy and translocation of chromosomes 12 and 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 such as the Philadelphia chromosome (translocation of chromosomes 9 and 22) are seen in 25% to 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/ μ L (B-cell lineage) or greater than 100,000/ μ L (T-cell lineage).

Hematopoietic Cell Transplantation

HCT is a procedure in which hematopoietic stem cells are intravenously infused to restore bone marrow and immune function in cancer patients who receive bone marrow-toxic doses of cytotoxic drugs with or without whole-body radiotherapy. Hematopoietic stem cells may be obtained from the transplant recipient (autologous HCT) or a donor (allo-HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood shortly after delivery of neonates. Cord blood transplantation is discussed in detail in evidence review 9.001.

Immunologic compatibility between infused hematopoietic stem cells and the recipient is not an issue in autologous HCT. In allogeneic stem cell transplantation, immunologic compatibility between donor and patient is a critical factor for achieving a successful outcome. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the gene complex expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. An acceptable donor will match the patient at all or most of the HLA loci.

Conditioning for HCT

Conventional Conditioning for HCT

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without existing disease in the absence of pretransplant conditioning. Intense conditioning regimens are limited to patients whose health status is sufficient to tolerate the procedure of body irradiation at doses sufficient to cause bone marrow ablation 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 mediated by non-self-immunologic effector cells. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by substantial adverse effects. These include opportunistic infections secondary to loss of endogenous bone marrow function and organ damage or failure caused by cytotoxic drugs. Subsequent to graft infusion in allo-HCT, immunosuppressant drugs are required to

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minimize graft rejection and graft-versus-host disease, which increases susceptibility to opportunistic infections.

The success of autologous HCT is predicated on the potential of cytotoxic chemotherapy, with or without radiotherapy, to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment but not graft-versus-host disease.

Reduced-Intensity Conditioning for Allo-HCT

RIC allo- HCT refers to the pretransplant use of lower doses of cytotoxic drugs or less intense regimens of radiotherapy than are used in traditional full-dose myeloablative conditioning treatments. Although the definition of RIC is variable, with numerous versions employed, all regimens seek to balance the competing effects of relapse due to residual disease and non-relapse mortality. The goal of RIC is to reduce disease burden and to minimize associated treatment-related morbidity and non-relapse mortality in the period during which the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. RIC regimens range from nearly total myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full donor chimerism. In this review, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

Regulatory Status

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

RATIONALE

Summary of Evidence

For individuals who have childhood ALL in first complete remission (CR1) at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, autologous HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation (ASMBT).

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The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have childhood ALL in CR1 at high-risk of relapse, remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the ASMBT. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, subsequent remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1 or subsequent remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews, and observational studies. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which were considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

DEFINITIONS

ALLOGENIC refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor; after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA). Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor

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effect. Their disadvantage is the risk of graft-versus host disease (GVHD), which increases with great HLA disparity and recipient age.

AUTOLOGOUS refers to originating within an individual, (i.e., self-donation). These stem cells are harvested from patients prior to myeloablative therapy.

KARNOFSKY INDEX is a tool to estimate clinically a patient's physical state, performance, and prognosis. The scale is from 100%, perfectly well and active, to 0%, completely inactive, or dead. It has been used in studying cancer and chronic illness. Lower Karnofsky scores are generally associated with poorer treatment response and prognosis.

REDUCED-INTENSITY ALLOGENIC STEM CELL TRANSPLANTATION uses lower doses of chemotherapy than standard allogenic transplant, it does not completely inactivate the patient's immune system or treat the ALL as aggressively. Older, sicker patients may be helped with this type of treatment.

RELAPSED refers to patients who have achieved remission but later have decreased numbers of normal blood cells and a return of leukemia in their bone marrow.

REFRACTORY refers to patients who have residual leukemia cells in their bone marrow even after they receive intensive treatment.

DISCLAIMER

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as permitted by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

CODING INFORMATION

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

Covered when medically necessary:

Procedure Codes

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S2140	S2142	S2150	38204	38205	38206	38207	38208
38209	38210	38211	38212	38213	38214	38215	38230
38232	38240	38241					

ICD-10-CM Diagnosis Codes	Description
C91.00	Acute lymphoblastic leukemia not having achieved remission
C91.01	Acute lymphoblastic leukemia, in remission
C91.02	Acute lymphoblastic leukemia, in relapse

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POLICY HISTORY

MP 9.041	04/06/2020 Consensus Review. No change to policy statements. References updated; coding reviewed
	03/01/2021 Consensus Review. No change to policy statement. Policy guidelines, background, rationale, and references updated. NCCN language added.
	02/08/2022 Consensus Review. No change to policy statement. References added.
	02/13/2023 Consensus Review. No change to policy statement. New definitions and references.
	04/03/2024 Consensus Review. No change to policy statement. New references.
	11/20/2024 Administrative Update. Removed NCCN statement.
	01/21/2025 Consensus Review. No change to policy stance. Updated rationale, and references.
	01/21/2026 Consensus Review. No change to policy intent. Updated references and disclaimer.

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