MEDICAL POLICY

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

Effective Date:	5/1/2023

I. 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.

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.

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The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help health care professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital Blue Cross when determining medical necessity according to this policy.

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/µL, 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/µL 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/µL (B cell lineage) or greater than 100,000/µL (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 (eg, graft-versus-host disease) may be higher than with HLA-matched donors; however, as medical treatments improve, the 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

II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross please see additional information below, and subject to benefit variations as discussed in Section VI below.

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

III. DESCRIPTION/BACKGROUND

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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.

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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.

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/μL (B-cell lineage) or greater than 100,000/μL (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 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.

IV. RATIONALE

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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). 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.

Additional Information

2013 Input

Given a scarcity of evidence on this topic - with no substantial trials likely to be forthcoming, that allo-HCT after failed autologous HCT has been shown to be of clinical benefit in other

hematologic malignancies and is potentially curative, that reduced-intensity conditioning allo-HCT is considered medically necessary to treat ALL in second or greater remission or relapsed or refractory ALL, and the support from 2013 clinical input of this use, the policy statements were revised to medical necessity for this indication in children and adults.

V. DEFINITIONS

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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 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

VI. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice, and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. CODING INFORMATION

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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							
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

IX. REFERENCES

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1. *PDQ® Pediatric Treatment Editorial Board. PDQ Childhood Acute Lymphoblastic Leukemia Treatment. Bethesda, MD: National Cancer Institute. Updated October 27, 2022 Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am. Feb 2008; 55(1): 1-20, ix. PMID 18242313*
2. *Carroll WL, Bhojwani D, Min DJ, et al. Pediatric acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2003: 102-31. PMID 14633779*

3. *National Cancer Institute. Adult Acute Lymphoblastic Leukemia Treatment (PDQ)Health Professional Version. 2022;*
4. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). 1987 TEC Evaluations. Page 243.*
5. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). 1990 TEC Evaluations. Page 254.*
6. *Lawson SE, Harrison G, Richards S, et al. The UK experience in treating relapsed childhood acute lymphoblastic leukaemia: a report on the medical research council UKALLR1 study. Br J Haematol. Mar 2000; 108(3): 531-43. PMID 10759711*
7. *Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as postremission treatment for children with very high risk acute lymphoblastic leukemia: PETHEMA ALL-93 Trial. J Clin Oncol. Jan 01 2007; 25(1): 16-24. PMID 17194902*
8. *Oliansky DM, Camitta B, Gaynon P, et al. Role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of pediatric acute lymphoblastic leukemia: update of the 2005 evidence-based review. Biol Blood Marrow Transplant. Apr 2012; 18(4): 505-22. PMID 22209888*
9. *Harrison G, Richards S, Lawson S, et al. Comparison of allogeneic transplant versus chemotherapy for relapsed childhood acute lymphoblastic leukaemia in the MRC UKALL R1 trial. MRC Childhood Leukaemia Working Party. Ann Oncol. Aug 2000; 11(8): 999-1006. PMID 11038037*
10. *Wheeler KA, Richards SM, Bailey CC, et al. Bone marrow transplantation versus chemotherapy in the treatment of very high-risk childhood acute lymphoblastic leukemia in first remission: results from Medical Research Council UKALL X and XI. Blood. Oct 01 2000; 96(7): 2412-8. PMID 11001892*
11. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy with autologous stem-cell support in the treatment of adult acute lymphoblastic leukemia. TEC Assessments. 1997;Volume 12:Tab 25.*
12. *Ribera JM, Oriol A, Bethencourt C, et al. Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia. Results of the PETHEMA ALL-93 trial. Haematologica. Oct 2005; 90(10): 1346-56. PMID 16219571*
13. *Yanada M, Matsuo K, Suzuki T, et al. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a metaanalysis. Cancer. Jun 15 2006; 106(12): 2657-63. PMID 16703597*
14. *Hahn T, Wall D, Camitta B, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of acute lymphoblastic leukemia in adults: an evidence-based review. Biol Blood Marrow Transplant. Jan 2006; 12(1): 1-30. PMID 16399566*
15. *Attal M, Blaise D, Marit G, et al. Consolidation treatment of adult acute lymphoblastic leukemia: a prospective, randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after*

autologous bone marrow transplantation. BGMT Group. Blood. Aug 15 1995; 86(4): 1619-28. PMID 7632972

16. *Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia--results of the prospective multicenter LALA-94 trial. Blood. Oct 01 2002; 100(7): 2357-66. PMID 12239143*
17. *Hunault M, Harousseau JL, Delain M, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. Blood. Nov 15 2004; 104(10): 3028-37. PMID 15256423*
18. *Gupta V, Richards S, Rowe J, et al. Allogeneic, but not autologous, hematopoietic cell transplantation improves survival only among younger adults with acute lymphoblastic leukemia in first remission: an individual patient data meta-analysis. Blood. Jan 10 2013; 121(2): 339-50. PMID 23165481*
19. *Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). Blood. Feb 15 2008; 111(4): 1827-33. PMID 18048644*
20. *Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. Blood. May 07 2009; 113(19): 4489-96. PMID 19244158*
21. *Cornelissen JJ, van der Holt B, Verhoef GE, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. Blood. Feb 05 2009; 113(6): 1375-82. PMID 18988865*
22. *Giebel S, Labopin M, Socie G, et al. Improving results of allogeneic hematopoietic cell transplantation for adults with acute lymphoblastic leukemia in first complete remission: an analysis from the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation. Haematologica. Jan 2017; 102(1): 139-149. PMID 27686376*
23. *Dinmohamed AG, Szabo A, van der Mark M, et al. Improved survival in adult patients with acute lymphoblastic leukemia in the Netherlands: a population-based study on treatment, trial participation, and survival. Leukemia. Feb 2016; 30(2): 310-7. PMID 26286115*
24. *Pidala J, Djulbegovic B, Anasetti C, et al. Allogeneic hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first complete remission. Cochrane Database Syst Rev. Oct 05, 2011; (10): CD008818. PMID 21975786*
25. *Abdul Wahid SF, Ismail NA, Mohd-Idris MR, et al. Comparison of reduced-intensity and myeloablative conditioning regimens for allogeneic hematopoietic stem cell transplantation in patients with acute myeloid leukemia and acute lymphoblastic*

leukemia: a meta-analysis. Stem Cells Dev. Nov 01 2014; 23(21): 2535-52. PMID 25072307

26. *Gutierrez-Aguirre CH, Gomez-Almaguer D, Cantu-Rodriguez OG, et al. Non-myeloablative stem cell transplantation in patients with relapsed acute lymphoblastic leukemia: results of a multicenter study. Bone Marrow Transplant. Sep 2007; 40(6): 535-9. PMID 17618317*
27. *Mohty M, Labopin M, Tabrizzi R, et al. Reduced intensity conditioning allogeneic stem cell transplantation for adult patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. Haematologica. Feb 2008; 93(2): 303-6. PMID 18245655*
28. *Cho BS, Lee S, Kim YJ, et al. Reduced-intensity conditioning allogeneic stem cell transplantation is a potential therapeutic approach for adults with high-risk acute lymphoblastic leukemia in remission: results of a prospective phase 2 study. Leukemia. Oct 2009; 23(10): 1763-70. PMID 19440217*
29. *Pulsipher MA, Boucher KM, Wall D, et al. Reduced-intensity allogeneic transplantation in pediatric patients ineligible for myeloablative therapy: results of the Pediatric Blood and Marrow Transplant Consortium Study ONC0313. Blood. Aug 13 2009; 114(7): 1429-36. PMID 19528536*
30. *Trujillo AM, Karduss AJ, Suarez G, et al. Haploidentical Hematopoietic Stem Cell Transplantation with Post-Transplantation Cyclophosphamide in Children with High-Risk Leukemia Using a Reduced-Intensity Conditioning Regimen and Peripheral Blood as the Stem Cell Source. Transplant Cell Ther. May 2021; 27(5): 427.e1-427.e7. PMID 33965184*
31. *Rosko A, Wang HL, de Lima M, et al. Reduced intensity conditioned allograft yields favorable survival for older adults with B-cell acute lymphoblastic leukemia. Am J Hematol. Jan 2017; 92(1): 42-49. PMID 27712033*
32. *Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments. 2000;Volume 15:Tab 9.*
33. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute lymphoblastic leukemia. Version 2.2022.*
34. *National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia. Version 1.2023.*
35. *Kanate AS, Majhail NS, Savani BN, et al. Indications for Hematopoietic Cell Transplantation and Immune Effector Cell Therapy: Guidelines from the American Society for Transplantation and Cellular Therapy. Biol Blood Marrow Transplant. Jul 2020; 26(7): 1247-1256. PMID 32165328*
36. *Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23). 2016*
37. *DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy. Biol Blood*

Marrow Transplant. 2019;25(11):2113-2123. doi:10.1016/j.bbmt.2019.08.014 PMID 31446198

38. *Larson, Richard A. Hematopoietic cell transplantation (HCT) for acute lymphoblastic leukemia/lymphoblastic lymphoma (ALL/LBL) in adult. UpToDate, Last updated August 03, 2022.*
39. *Blue Cross Blue Shield Association Medical Policy Reference Manual. 8.01.32, Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia, February 2023.*

***Other**:*

1. *Mosby's Medical, Nursing & Allied Health Dictionary 6th edition*
2. *Taber's Cyclopedic Medical Dictionary 21st edition*

X. POLICY HISTORY

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MP 9.041	**1/1/18 Admin update.** Medicare variations removed from Commercial Policies.
	2/9/18 Consensus review. No change to policy statements. References and rationale updated.
	2/20/19 Consensus review. No change to policy statements. References and rationale condensed.
	4/6/20 Consensus review. No change to policy statements. References updated, coding reviewed
	3/1/21 Consensus review. No change to policy statement. Policy guidelines, background, rationale, and references updated. NCCN language added.
	2/8/22 Consensus review. No change to policy statement. References added.
	2/13/23 Consensus review. No change to policy statement. New definitions and references.

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