Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: BMT - Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Description/Background

ACUTE LYMPHOBLASTIC LEUKEMIA

Acute lymphoblastic leukemia (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 an outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse.(1) Two of the most important factors predictive of risk are patient age and white blood cell count at diagnosis.(1) Certain genetic characteristics of leukemic cells strongly influence prognosis. Therapy may include hematopoietic cell transplantation (HCT).

Childhood Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children; it represents nearly 25% of cancer diagnoses in children younger than 15 years.(3) Remission of disease is now typically achieved with pediatric chemotherapy regimens in approximately 95% of children with ALL, with long-term survival rates of up to 85%. 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.(2) 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 to only 10% to 15% for those who relapse less than 3 years after treatment. Thus, hematopoietic cell transplantation (HCT) may be a strong consideration in those with short remissions. At present, comparative outcomes with autologous or allogeneic HCT are unknown.

Adult Acute Lymphoblastic Leukemia

In adults, ALL accounts for 20% of acute leukemias. Between 60% and 80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy; however,

individuals who experience a relapse after remission usually die within 1 year.(4) 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.

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

Myeloablative (Conventional) Conditioning

The myeloablative (conventional) practice of allo-HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total body irradiation. Intense conditioning regimens are limited to individuals whose health status is sufficient to tolerate the administration of cytotoxic agents with total body irradiation at doses sufficient to cause bone marrow ablation in the recipient. The beneficial treatment effect of this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect mediated by non-self-immunologic effector cells. While the slower GVM effect is considered 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 and failure caused by the 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 ability 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 individual before undergoing bone marrow ablation. Therefore, autologous HCT is typically performed as consolidation therapy when the individual’s

disease is in complete remission. Individuals who undergo autologous HCT are also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

Reduced-Intensity or Non-myeloablative Conditioning for Allo-HCT
Reduced-intensity conditioning (RIC), sometimes referred to as non-myeloablative (NMA) conditioning, refers to the pretransplant use of lower doses of cytotoxic drugs with or without less intense regimens of radiotherapy than are used in myeloablative conditioning treatments. Although the definition of RIC/NMA 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/NMA 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. These RIC/NMA regimens range from nearly totally myeloablative to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and individual condition. Individuals who undergo RIC/NMA with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism.

HLA Typing
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 individual, where usually there is sharing of only 3 of the 6 major histocompatibility antigens. Most individuals 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 risks of graft-versus-host disease with haploidentical donors are approaching those similar to HLA-matched donors.

Regulatory Status

The 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 (CFR) Title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Medical Policy Statement

The safety and effectiveness of hematopoietic cell transplantation for acute lymphoblastic leukemia has been established. It may be considered a useful therapeutic option for individuals who meet specific selection criteria.

Inclusionary and Exclusionary Guidelines

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Inclusions:

- *Autologous* or *allogeneic* hematopoietic cell transplantation to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission[a] but at high risk[b] of relapse.
- *Autologous* or *allogeneic* cell transplantation to treat childhood ALL in *second or greater* remission or *refractory* ALL.
- *Allogeneic* hematopoietic cell transplantation to treat relapsing ALL after a prior *autologous* HCT.
- Reduced-intensity conditioning allogeneic hematopoietic cell transplantation as a treatment of ALL in children who are in complete[a] first or second remission, and who, for medical reasons would be unable to tolerate a standard myeloablative conditioning regimen.

[a] Defined by bone marrow biopsy/aspirate demonstrating < 5% blasts

[b] Childhood High Risk Factors for Relapse

Adverse prognostic factors and factors associated with high risk of relapse in children include the following:

- *Age younger than 1 year or older than 9 years,*
- *White blood cell count at presentation above 50,000/µL,*
- *Hypodiploidy (<45 chromosomes),*
- *Translocation involving chromosomes 9 and 22 (t[9;22]) aka BCR-ABL fusion,*
- *Translocation involving chromosomes 4 and 11 (t[4;11]) aka MLL-AF4 fusion,*
- *Pre-B or T-lineage immunophenotype,*
- *Central nervous system involvement,*
- *Poor response to initial therapy including poor response to prednisone prophase,*
- *Poor treatment response to induction therapy at 6 weeks with high-risk having ≥ 0.01% minimal residual disease measured by flow cytometry.*

Exclusions:

- All other conditions not listed above.

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ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

Inclusions:

- *Autologous* hematopoietic cell transplantation to treat adult ALL in first complete remission[a] but at high risk[b] of relapse.
- *Allogeneic* hematopoietic cell transplantation to treat adult ALL in first complete remission[a] for any risk level.
- *Allogeneic* hematopoietic cell transplantation to treat adult ALL in second or greater remissions, or in adults with relapsed or refractory ALL.
- *Allogeneic* hematopoietic cell transplantation to treat relapsing ALL after a prior *autologous* HCT.
- Reduced-intensity conditioning *allogeneic* hematopoietic cell transplantation as a treatment of ALL in adults who are in complete[a] first or second remission, and who, for medical reasons would be unable to tolerate a standard myeloablative conditioning regimen.

[a] Defined by bone marrow biopsy/aspirate demonstrating < 5% blasts

[b] ***Adult High Risk Factors for Relapse***

Individual with any of the following may be considered at high-risk for relapse:

- *Age older than 35 years,*
- *Leukocytosis at presentation of greater than 30,000/µl (B-cell lineage) or greater than 10,000/µl (T-cell lineage),*
- *"Poor prognosis" genetic abnormalities like the Philadelphia chromosome (t[9;22]),*
- *Extramedullary disease*
- *Time to attain complete remission longer than 4 weeks.*

Exclusions:

- *Autologous* hematopoietic cell transplantation to treat adult ALL in second or greater remission or those with refractory disease.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes (if inclusionary criteria are met):

38204	38205	38206	38207	38208	38209
38210	38211	38212	38213	38214	38215
38230	38232	38240	38241	38242	38243
81267	81268	81370	81371	81372	81373
81374	81375	81376	81377	81378	81379
81380	81381	81382	81383	86812	86813
86816	86817	86821	S2140	S2142	S2150

Other codes (investigational, not medically necessary, etc.):

N/A

POTENTIAL CONTRAINDICATIONS FOR TRANSPLANT:

Note: Final patient eligibility for transplant is subject to the judgment and discretion of the requesting transplant center.

The selection process for approved tissue transplants is designed to obtain the best result for each patient. Therefore, potential contraindications to HCT may include, but are not limited to:

- Poor cardiac function: Ejection fraction should be greater than 45% with no overt symptoms of congestive heart failure.
- Poor pulmonary function: Pulmonary function tests must be greater than or equal to 50% of predicted value.
- Poor renal function: Renal creatinine clearance should be greater than 40 ml/min or creatinine must be less than or equal to 2mg/dl.
- Poor liver function: There should be no history of severe chronic liver disease
- Presence of HIV or an active form of hepatitis B, hepatitis C or human T-cell lymphotropic virus (HTLV-1).

Clinical documentation supplied to the health plan must demonstrate that ***attending staff at the transplant center have considered all contraindications*** as part of their overall evaluation of potential organ transplant recipient ***and have decided to proceed.***

Rationale

AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

Clinical Context and Therapy Purpose

The purpose of hematopoietic cell transplantation (HCT) is to provide a treatment option that is an alternative to or an improvement on existing therapies in children with acute lymphoblastic leukemia (ALL).

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are children with ALL.

Interventions

The therapy being considered is autologous hematopoietic cell transplantation.

Comparators

Comparators of interest include conventional dose chemotherapy.

Outcomes

The general outcomes of interest are overall survival, disease specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

The evidence review on childhood acute lymphoblastic leukemia (ALL) was initially based on TEC Assessments completed in 1987 and 1990.(5,6) In childhood ALL, conventional chemotherapy is associated with complete remission (CR) rates of approximately 95%, with

long-term durable remissions up to 85%. Therefore, for patients in a first complete remission (CR1), hematopoietic cell transplantation (HCT) is considered necessary only in those with risk factors predictive of relapse.

Randomized Controlled Trials
An RCT comparing outcomes of HCT (both autologous and allogeneic) with conventional-dose chemotherapy in children with ALL was identified subsequent to the TEC Assessments.(7) Patients were eligible for autologous transplantation if they did not have a suitable donor. A total of 256 patients were enrolled, with 123 patients receiving chemotherapy alone and 15 patients receiving autologous transplant. For patients receiving chemotherapy alone, the 5-year event-free survival (EFS) was 48%; for patients receiving autologous HCT the 5-year EFS was 47%. Relapse was the major cause of treatment failure in both the chemotherapy alone and autologous transplant groups (p=.05). Overall outcomes after autologous HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy, and no clear benefit for any 1 treatment was identified.

A 2007 randomized trial, Comparison of Intensive Chemotherapy, Allogeneic, or Autologous Stem-Cell Transplantation as Post remission Treatment for Children with Very High Risk Acute Lymphoblastic Leukemia (PETHEMA ALL-93, n=106) demonstrated no significant differences in disease-free survival (DFS) or overall survival rates (OS) at median follow-up of 78 months in children with very high-risk ALL in CR1 who received autologous (n=38) or allogeneic HCT (allo-HCT; n=24) or standard chemotherapy (n=38) with maintenance treatment.(8) Similar results were observed using intention-to-treat (ITT) or per-protocol analyses. However, several limitations could have affected outcomes: the relatively small numbers of patients, variations across centers in the preparative regimen used before HCT and time elapsed between CR and undertaking of assigned treatment and use of genetic randomization based on donor availability rather than true randomization (i.e., patients in the allo-HCT arm).

Section Summary: Autologous Hematopoietic Cell Transplantation for Childhood Acute Lymphoblastic Leukemia
In some patients (e.g., those at very high risk of relapse or following relapse HCT), autologous HCT remains a therapeutic option to manage childhood ALL despite risks as illustrated by RCT evidence.

Allogeneic Hematopoietic Cell Transplantation for Childhood Acute Lymphoblastic Leukemia

Clinical Context and Therapy Purpose
The purpose of HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in children with ALL.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is children with ALL.

Interventions
The therapy being considered is allo-HCT.

Comparators
Comparators of interest include conventional-dose chemotherapy.

Outcomes
The general outcomes of interest are OS, DSS, TRM, and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence

Systematic Reviews
A 2012 systematic review of the literature and position statement by the American Society for Blood and Marrow Transplantation (ASBMT) evaluated the role of cytotoxic therapy with HCT for pediatric ALL.(9) The systematic review identified 10 studies comparing HCT with chemotherapy for patients in CR1, including the PETHEMA trial. Reviewers identified a subset of patients at high-risk for whom allo-HCT would be indicated. Reviewers also identified 12studies comparing HCT with chemotherapy for patients in second (CR2) or beyond, or relapsed disease.

Randomized Controlled Trials
An RCT comparing outcomes of HCT (both autologous and allogeneic) with conventional-dose chemotherapy in children with ALL was identified subsequent to the aforementioned TEC Assessments.(7) A total of 256patients were enrolled, with 123 patients receiving chemotherapy alone and 63 patients receiving an allo-HCT. For patients receiving chemotherapy alone, the 5-year EFS was 48%; for patients receiving allo-HCT the 5-yearEFS was 45% for related donor transplants and 52% for unrelated donor transplants. Death in second remission was the major cause of treatment failure in the allo-HCT group ($p<.001$). Overall outcomes after allo-HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy, with the improved EFS of allo-HCT being offset by the high TRM.

Another RCT subsequent to the TEC assessments compared the outcome of children with relapsed ALL who received allo-HCT (n=104) to chemotherapy (n=125).(10) There were 15 patients in the chemotherapy group that also received autologous HCT. There was no significant difference in outcomes found between the groups; the 8-year EFS advantage by the allo-HCT group was 8% over the chemotherapy group (95% confidence interval [CI], -9% to -24%). Allo-HCT was not found to be clinically significant over chemotherapy, however, there was a subset of patients (who had short first remissions) that had a moderate EFS benefit related to allo-HCT.

Wheeler et al was a third RCT that was subsequent to the TEC assessments that compared allo-HCT treatment (n= 101)to chemotherapy (n=351) in children with ALL in first remission.(11) The median time to transplantation was 5 months and the median follow-up was 8 years. The 10-year EFS advantage by the allo-HCT group was 6% higher over the chemotherapy group (95% CI, -10.5% to 22.5%). The allo-HCT group also had fewer relapses

compared to the chemotherapy group, 31% compared to 55% respectively; however, the allo-HCT group did have more remission deaths compared to the chemotherapy.

Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation
The use of reduced-intensity conditioning (RIC) regimens have been investigated as a means to extend the substantial graft-versus-leukemia effect of post-remission allo-HCT to patients who could expect to benefit from this approach but who are ineligible or would not tolerate a fully myeloablative procedure.

A multicenter prospective study by Pulsipher et al (2009) involved 47 pediatric patients (median age, 11 years; range, 2 to 20 years) with hematologic cancers, including ALL (n=17), who underwent allo-HCT with a fludarabine-based RIC regimen.(12) Among the 17 ALL cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, which included previous myeloablative allo- or autologous HCT, but these treatments were not individually reported. While most data were aggregated, some survival findings were specified, showing an event-free survival (EFS) rate of 35% and an OS rate of 37% at 2-year follow-up for the ALL patients. Although most patients lived only a few months after relapse or rejection, some were long-term survivors (>3 years after HCT) after further salvage treatment. Neither transplant-related mortality nor HCT-related morbidities were reported by disease. However, this evidence would suggest allo-HCT with RIC can be used in children with high-risk ALL and can facilitate long-term survival in individuals with no therapeutic recourse.

A retrospective cohort study by Trujillo et al (2021) assessed 42 pediatric patients (median age, 11 years; range, 2 to 17 years) with high-risk leukemias, including ALL (n=26).(13) Patients who underwent allo-HCT with a cyclophosphamide-based RIC regimen between 2012 and 2017 in the Colombian study center were included. Overall, 33% of the patients were in CR1, 50% were in CR2, 14% were in CR3, and 3% had refractory disease. Patients with ALL were all previously treated with Berlin-Frankfurt-Munich (BFM)-based chemotherapy. Most of the data were aggregated, however, some survival findings were specified for ALL. The study found that there were no statistically significant differences in OS or EFS between patients with ALL and those with acute myelogenous leukemia (AML). Overall, the study found that between those positive or negative for pre-HCT minimal residual disease, or based on pre-HCT remission status, there was also no statistically significant difference in OS or EFS. Median duration for follow-up was 45 months and OS and EFS for the study group at 36 months were 56% and 46%, respectively.

Section Summary: Allogeneic Hematopoietic Cell Transplantation for Childhood Acute Lymphoblastic Leukemia
While the risks of TRM do not outweigh the OS benefit in all patients, as demonstrated by RCT evidence, in some patients (e.g., those at very high-risk of relapse or following relapse HCT), allo-HCT remains a therapeutic option to manage childhood ALL.

ALLOGENEIC HCT for ADULT ALL

Clinical Context and Therapy Purpose
The purpose of hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in adults with ALL.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are adults with ALL.

Interventions
The therapy being considered is autologous hematopoietic cell transplantation.

Comparators
Comparators of interest include conventional dose chemotherapy.

Outcomes
The general outcomes of interest are overall survival (OS), disease specific survival (DSS), treatment-related mortality (TRM), and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence

This evidence review on adult ALL was informed by a 1997 TEC Assessment of autologous HCT.(12) This Assessment offered the following conclusions:

- For patients in CR1, available evidence suggested survival was equivalent after autologous HCT or conventional-dose chemotherapy. For these patients, the decision between autologous HCT and conventional chemotherapy may reflect a choice between intensive therapy of short duration and longer but less-intensive treatment.
- In other settings, such as in second (CR2) or subsequent remissions, the evidence was inadequate to determine the relative effectiveness of autologous HCT compared with conventional chemotherapy.

Systematic Reviews
The ASBMT (2012) updated its 2005 guidelines for treatment of ALL in adults, covering literature to mid-October 2010.(9) The ASBMT indicated a grade A treatment recommendation for autologous HCT in patients who did not have a suitable allogeneic stem cell donor; ASBMT suggested that although survival outcomes appeared similar between autologous HCT and post-remission chemotherapy, the shorter treatment duration with the former is an advantage.

Randomized Controlled Trials
Ribera et al (2005) reported results from the multicenter (35 Spanish hospitals), randomized PETHEMA ALL-93 trial (n=222 patients), which was published after the ASBMT literature search.(15) Among 183 high-risk adult patients in CR1, those with a human leukocyte antigen (HLA)–identical family donor were assigned to allo-HCT (n=84); the remaining cases were randomly assigned to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to two years in CR (n=48). At a 70-month median follow-up, the trial did not detect a statistically significant difference in outcomes among all three arms by per-protocol or ITT analyses. PETHEMA ALL-93 trial investigators pointed out several factors that could have affected outcomes: relatively small numbers of patients; variations among centers

in the preparative regimen used before HCT; differences in risk group assignment; and use of genetic randomization based on donor availability rather than true randomization (i.e., patients included in the allo-HCT arm).

Section Summary: Autologous HCT for Adult ALL
The evidence indicates post-remission myeloablative autologous HCT is an effective therapeutic option for a large proportion of adults with ALL in CR1. For adults who survive HCT, there is a significant relapse rate. The 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.

Allogeneic Hematopoietic Cell Transplantation for Adult Acute Lymphoblastic Leukemia

Clinical Context and Therapy Purpose
The purpose of HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in adults with ALL.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is adults with ALL.

Interventions
The therapy being considered is allo-HCT.

Comparators
Comparators of interest include conventional-dose chemotherapy.

Outcomes
The general outcomes of interest are OS, DSS, TRM, and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence

Systematic Reviews
A meta-analysis by Yanada et al (2006) pooled evidence from 7 studies of allo-HCT published between 1994 and 2005that included a total of 1274 patients with ALL in CR1.(16) Results showed that, regardless of risk category, allo-HCT was associated with a significantly longer OS (hazard ratio [HR], 1.29; 95% CI, 1.02 to 1.63; p=.037) for all patients who had a suitable donor versus patients without a donor who received chemotherapy or autologous HCT. Pooled evidence from patients who had high-risk disease showed an increased survival advantage for allo-HCT compared with those without a donor (HR=1.42; 95% CI, 1.06 to 1.90; p=.019). However, the individual studies were relatively small, the treatment results were not always comparable, and the definitions of high-risk disease features varied across all studies.

The ASBMT (2012) updated its 2005 guidelines for treatment of ALL in adults, covering literature to mid-October 2010.(9) The evidence then available supported a grade A treatment recommendation (at least 1 meta-analysis, systematic review, or RCT) that myeloablative allo-HCT would be an appropriate treatment for adult ALL in CR1 for all risk groups. The ASBMT recommended allo-HCT over chemotherapy for adults with ALL in CR2 or beyond.

An individual patient data meta-analysis by Gupta et al (2013) included 13 studies (N=2962), several of which are evaluated herein.(17) Results suggested that matched sibling donor myeloablative HCT improved survival only for younger adults (<35 years old) in CR1 compared with chemotherapy, with an absolute benefit of 10% at 5 years. The analysis also suggested a trend toward inferior OS among autologous HCT recipients compared with chemotherapy in CR1 (odds ratio[OR], 1.18; 95% CI, 0.99 to 1.41; p=.06), primarily due to higher transplant-related mortality in the autograft patients than in chemotherapy recipients.

Randomized Controlled Trials

While the utility of allo-HCT for post-remission therapy in patients with high-risk ALL has been established, its role in standard-risk patients has been less clear. This question was addressed by the International ALL Trial, a collaborative effort conducted by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States (MRC UKALL XII/ECOG 2993).(18) The Phase III Randomized Trial of Autologous and Allogeneic Stem Cell Transplantation Versus Intensive Conventional Chemotherapy in Acute Lymphoblastic Leukemia in First Remission (ECOG 2993) trial was a phase 3 randomized study designed to prospectively define the role of myeloablative allo-HCT, autologous HCT, and conventional consolidation and maintenance chemotherapy for adults up to age 60 years with ALL in CR1. This 2008 trial is the largest RCT in which all patients (N=1913) received essentially identical therapy, regardless of their disease risk assignment. After induction treatment that included imatinib mesylate for Philadelphia (Ph) chromosome-positive patients, all patients who had a human leukocyte antigen-matched sibling donor (n=443) were assigned to allo-HCT. Patients with the Ph chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HCT. Patients who did not have a matched sibling donor or were older than 55 years(n=588) were randomized to a single autologous HCT or consolidation and maintenance chemotherapy.

In ECOG 2993, the OS rate at 5-year follow-up of all 1913 patients was 39%; it reached 53% for Ph-negative patients with a donor (n=443) compared with 45% without a donor (n=588) (p=.01).(18) Analysis of Ph-negative patient outcomes by disease risk showed a 5-year OS rate of 41% among patients with high-risk ALL and a sibling donor versus 35% of high-risk patients with no donor (p=.2). In contrast, the OS rate at 5-year follow-up was 62% among standard-risk Ph-negative patients with a donor and 52% among those with no donor, a statistically significant difference (p=.02). Among Ph-negative patients with the standard-risk disease who underwent allo-HCT, the relapse rate was 24% at 10 years compared with 49% among those who did not undergo HCT (p<.001). Among Ph-negative patients with high-risk ALL, the relapse rate at 10-year follow-up was 37% following allo-HCT versus 63% without a transplant (p<.001), demonstrating the potent graft-versus-leukemia effect with allogeneic transplantation. This evidence clearly showed a significant long-term survival benefit associated with post-remission allo-HCT in standard-risk Ph-negative patients, an effect previously not demonstrated in numerous smaller studies. Failure to demonstrate a significant OS benefit in high-risk Ph-negative cases can be attributed to high non-relapse mortality (NRM) rate at 1 and 2 years, mostly due to graft-versus-host-disease(GVHD) and infections. At

2 years, the NRM rate was 36% among high-risk patients with a donor compared with 14% among those who did not have a donor. Among standard-risk cases, the NRM rates at 2 years were 20% in patients who underwent allo-HCT and 7% in those who received autologous HCT or continued chemotherapy.

In a separate 2009 report on the Ph-positive patients in the ECOG 2993 trial, intention-to-treat analysis (n=158) showed 5-year OS rates of 34% (95% CI, 25% to 46%) for those who had a matched sibling donor and 25% (95% CI, 12% to 34%)for those with no donor who received consolidation and maintenance chemotherapy.(19) Although the difference in OS rates was not statistically significant, this analysis demonstrated a moderate superiority of post-remission-matched sibling allo-HCT over chemotherapy in patients with high-risk ALL in CR1, in concordance with this evidence review.

The 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, Dutch-Belgian HOVON Cooperative Group (2009) reported results combined from 2 successive randomized trials in previously untreated adults with ALL ages 60 years or younger, in whom myeloablative allo-HCT was consistently used for all who achieved CR1 and who had a human leukocyte antigen-matched sibling donor, irrespective of risk category.(20) The 433 eligible patients included 288 who were younger than 55 years, in CR1, and eligible to receive consolidation treatment using autologous HCT or allo-HCT. Allo-HCT was performed in 91 (95%) of 96 with a compatible sibling donor. At 5-year follow-up, OS rates were 61% among all patients with a donor and 47% among those without a donor (p=.08). The cumulative incidences of relapse at 5-year follow-up among all patients were 24% in those with a donor and 55% in those (n=161) without a donor(p<.001). Among patients stratified by disease risk, those in the standard-risk category with a donor (n=50) had a 5-yearOS rate of 69% and a relapse rate at 5 years of 14% compared with 49% and 52%, respectively, among those (n=88)without a donor (p=.05). High-risk patients with a donor (n=46) had a 5-year OS rate of 53% and relapse rate at 5 years of34% versus 41% and 61%, respectively, among those with no donor (n=3; p=.50). NRM rates among standard-risk patients were 16% among those with a donor and 2% among those without a donor; in high-risk patients, Nonrelapse mortality rates were15% and 4%, respectively, among those with and without a donor.

The HOVON data were analyzed from remission evaluation before consolidation whereas the ECOG 2993 data were analyzed from diagnosis, which complicates the direct comparison of their outcomes. The HOVON data were reanalyzed by donor availability from diagnosis to facilitate a meaningful comparison. This reanalysis showed a 5-year OS rate of 60%in standard-risk patients with a donor in the HOVON trial, which is very similar to the 62% OS rate observed in standard-risk patients with a donor in the ECOG 2993 trial. Collectively, these results suggest that patients with standard-risk ALL can expect to benefit from allo-HCT in CR1, provided the NRM risk is less than 20% to 25%.(20)

Observational Studies

Several recent studies have evaluated changes in survival rates over time. A 2017 multicenter clinical trial from Europe reported on 4859 adults with ALL in CR1 treated with allo-HCT from either a matched sibling donor (n=2681) or an unrelated donor (n=2178).(21) Survival rates generally improved over time (i.e., from 1993-2002 to 2008-2012). For the period 2008 to 2012, 2-year OS rates after matched sibling donor HCT were 76% for 18- to 25-year-olds, 69% for 26- to 35-year-olds and 36- to 45-year-olds, and 60% for 46- to 55-year-olds. During that

time, 2-year OS rates after unrelated donor HCT were 66% for 18- to 25-year-olds, 70% for 26- to 35-year-olds, 61% for 36- to 45-year-olds, and 62% for 46- to 55-year-olds. Also, Dinmohamed et al (2016) reviewed survival trends among adults with ALL who underwent HCT between 1989 and 2012.(24) Data were available on 1833 patients. Survival rates increased significantly over time in all age groups (18-24, 25-39, 40-59, 60-69, and ≥70 years old). For the most recent period (2007 to 2012), 5-year relative survival rates by age group were 75%, 57%, 37%, 22%, and 5%, respectively.

Donor Source

A 2011 Cochrane review evaluated the evidence for the efficacy of matched sibling stem cell donor versus no donor status for adults with ALL in CR1.(25) Fourteen trials with treatment assignment based on genetic randomization (N=3157) were included. Matched sibling donor HCT was associated with a statistically significant OS advantage compared with the no-donor group (HR=0.82; 95% CI, 0.77 to 0.97; p=.01). Patients in the donor group had a significantly lower rate of primary disease relapse than those without a donor (relative risk [RR], 0.53; 95% CI, 0.37 to 0.76; p<.001)and significantly increased NRM (RR=2.8; 95% CI, 1.66 to 4.73; p=.001). These results support the conclusions of this evidence review that allo-HCT (matched sibling donor) is an effective post-remission therapy in adults.

A more recent meta-analysis by Owattanapanich et al (2022) compared outcomes of stem cell transplantations in adults with ALL involving high-risk features or relapse using haploidentical donors versus other stem cell sources, including matched sibling donors, matched unrelated donors, and cord blood transplantations.(24) Twenty-eight studies were included (17 retrospective, 11 prospective). Investigators found no significant differences in OS of haploidentical and other stem cell sources. For haploidentical versus matched donors, the pooled OR was 0.94 (95% CI, 0.79 to 1.12), and for haploidentical versus cord blood, the OR was 1.24 (95% CI, 0.78 to 1.96). The incidence of relapse was significantly higher with matched sibling donor compared to haploidentical donor (OR, 0.69; 95% CI, 0.48 to 0.99). In terms of adverse events, both grade II through IV acute and long-term GVHD were significantly higher in those with haploidentical donors compared to matched sibling donors (OR, 1.78; 95% CI, 1.15 to 2.74; OR, 1.33; 95% CI, 1.00 to 1.77, respectively).

REDUCED-INTENSITY CONDITIONING ALLO-HCT

A meta-analysis by Abdul Wahid et al (2014) included data from five studies in which RIC (n=528) was compared with myeloablative conditioning regimens (n=2,489) in adult with ALL who received allogeneic HCT mostly in CR1.(25) This analysis of data from nonrandomized studies suggested progression-free survival at one to six years is significantly lower after RIC (36%) than after myeloablative conditioning (41%; OR=0.76; 95% CI, 0.61 to 0.93; p<0.01). However, this improvement in survival after RIC was offset by the significantly lower NRM in the RIC group than in the myeloablative group (OR=0.76; 95% CI, 0.61 to 0.95), resulting in similar OS (OR=1.03; 95% CI, 0.84 to 1.26; p=0.76). Use of RIC also was associated with lower rates of GVHD, but higher rates of relapse compared with myeloablative conditioning (OR=1.77; 95% CI, 1.45 to 2.71; p<0.000).

A multicenter, single-arm study (Gutierrez-Aguirre et al, 2007) of patients (n=43; median age 19 years; range: 1 to 55 years) in CR2 reported, a 3-year OS rate of 30% with 100-day mortality and NRM rates of 15% and 21%, respectively.(26) Despite achievement of complete donor chimerism in 100% of the patients, 28 (65%) had leukemic relapse, with 67% ultimately dying. A registry-based study by Mohty et al (2008) included 97 adults (median age 38 years,

range 17–65 years) who underwent RIC and allogeneic HCT to treat ALL in CR1 (n=28), beyond CR1 (CR2/CR3, n=26/5) and advanced or refractory disease (n=39).(27) With median follow-up of approximately 3 years, in the overall population 2-year OS was 31%, with NRM of 28% and relapse rate of 51%. In patients transplanted in CR1, the OS rate was 52%; in CR2/CR3, it was 27%; in patients with advanced or refractory ALL, OS was 20%. These data suggest RIC and allo-HCT have some efficacy as salvage therapy in high-risk ALL.

Reduced-intensity conditioning (RIC) for allo-HCT was investigated in a prospective phase II study (Cho et al, 2009) of 37 consecutive adults (median age, 45 years; range, 15 to 63 years) with high-risk ALL (43% Ph-positive, 43% high white blood cell) in CR1 (81%) or CR2 (19%) who were ineligible for myeloablative allo-HCT because of age, organ dysfunction, low Karnofsky Performance Status score (<50%), or the presence of infection.(28) Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Post-remission RIC consisted of fludarabine and melphalan, with GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib before HCT. The three-year cumulative incidence of relapse was 19.7%; the NRM rate was 17.7%. The three-year cumulative OS rate was 64.1%, with a disease-free survival rate of 62.6% at the same point. After a median follow-up of 36 months (range, 121 to 96 months), 25 (67.6%) patients were alive, 24 (96%) of whom remained in CR.

Rosko et al (2017) used Center for International Blood and Marrow Transplant Research registry data to examine the effectiveness of RIC HCT in adults 55 years or older with B-cell ALL and explored prognostic factors associated with long-term outcomes.(32) The authors evaluated 273 participants with B-cell ALL with disease status in CR1 (71%), CR2 or beyond (17%), and primary induction failure/relapse (11%) who underwent RIC HCT between 2001 and 2012. Among patients with available cytogenetic data, 50% were Ph-positive. The 3-year OS rate was 38% (95% CI, 33% to 44%). The 3-year cumulative incidences of non-relapse mortality and relapse were 25% (95% CI, 20% to 31%) and 47% (95% CI, 41% to 53%), respectively.

Section Summary: Allogeneic Hematopoietic Cell Transplantation for Adult Acute Lymphoblastic Leukemia

The evidence indicates post-remission myeloablative allo-HCT is an effective therapeutic option for a large proportion of adults with ALL in CR1. However, the increased mortality and morbidity from GVHD limit the use of allo-HCT, particularly for older patients. For adults who survive HCT, there is a significant relapse rate. The 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. Based on currently available evidence RIC allo-HCT may benefit patients who demonstrate complete marrow and extramedullary CR1 or CR2, could be expected to benefit from myeloablative allo-HCT, and who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allo-HCT.

ALLOGENEIC TRANSPLANT AFTER FAILED AUTOLOGOUS TRANSPLANT

Clinical Context and Test Purpose

The purpose of allogeneic hematopoietic cell transplantation is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with ALL who relapse after a prior autologous hematopoietic cell transplant.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are adult patients with ALL who relapse after a prior autologous hematopoietic cell transplant.

Interventions
The therapy being considered is allogeneic hematopoietic cell transplantation.

Comparators
Comparators of interest include conventional dose chemotherapy.

Outcomes
The general outcomes of interest are overall survival, disease specific survival, treatment-related mortality, and treatment-related morbidity.

Follow-up over months to years is of interest for relevant outcomes.

Study Selection Criteria
Methodologically credible studies were selected using principles described above.

Review of Evidence

A 2000 TEC Assessment focused on allo-HCT after a prior failed autologous HCT, in the treatment of a variety of malignancies, including ALL.(33) The TEC Assessment found the evidence inadequate to permit conclusions about outcomes of this treatment strategy. Published evidence was limited to small, uncontrolled clinical series with short follow-up. Subsequent literature searches have not identified strong evidence to permit conclusions on this use of HCT.

Section Summary: Allogeneic Transplant After Failed Autologous Transplant
Small uncontrolled case series with short-term follow-up are inadequate to draw conclusions on the effect of all-HCT after a failed HCT on health outcomes in patients with ALL.

SUMMARY OF EVIDENCE
For individuals who have childhood acute lymphoblastic leukemia (ALL) in first complete remission at high risk of relapse, subsequent remission, or refractory ALL who receive autologous or allogeneic hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (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 first complete remission (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. 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 American Society for Blood and Marrow Transplantation. 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 first complete remission, subsequent remission, or refractory ALL who receive allo- HCT, the evidence includes RCTs, 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 (RIC) 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 relapse after a prior autologous HCT for adult or childhood ALL who receive allo-HCT, the evidence includes case series. 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 that the technology results in an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2013 Input

Blue Cross Blue Shield Association received input 1 medical society, 2 academic medical centers, and 3 physicians from Blue Distinction Centers while this policy was under review in 2013. In general, clinical input supported most existing policy statements. However, most reviewers disagreed that allogeneic hematopoietic cell transplantation (allo-HCT) is considered investigational to treat relapsing acute lymphoblastic leukemia (ALL) after a prior autologous HCT in either children or adults. 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, and that reduced-intensity conditioning allo-HCT is considered medically necessary to treat ALL in second or greater remission or relapsed or refractory ALL, the policy statements were revised to medical necessity for this indication in children and adults.

PRACTICE GUIDELINES AND POSITION STATEMENTS

The American Society for Transplantation and Cellular Therapy

The 2020 guidelines from the American Society for Transplantation and Cellular Therapy (previously known as the American Society for Blood and Marrow Transplantation) were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on use of HCT in and out of the clinical trial setting.(31) Recommendations on ALL are listed in Table 1.

Table 1. Guidelines for Autologous and Allogeneic HCT in ALL

Indication	Children (Age <18 Years)		Adults (Age ≥18 Years)	
	Allogeneic HCT	Autologous HCT	Allogeneic HCT	Autologous HCT
First complete response, standard-risk	N	N	S	C
First complete response, high-risk	S	N	S	N
Second complete response	S	N	S	C
At least third complete response	C	N	C	N
Not in remission	C	N	C	N

ALL: acute lymphoblastic leukemia; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

National Comprehensive Cancer Network

Current National Comprehensive Cancer Network (NCCN) guidelines for acute lymphoblastic leukemia (ALL) indicate allogeneic hematopoietic cell transplantation (allo-HCT) is appropriate for consolidation treatment of most poor risk (e.g., the Philadelphia chromosome positive, relapsed or refractory) patients with ALL.(4) The guidelines state that for appropriately fit older adults with ALL who are achieving remission, “consideration of autologous or reduced-intensity allogeneic stem cell transplantation may be appropriate.” In addition, the guidelines note that chronologic age is not a good surrogate for fitness for therapy and that patient should be evaluated on an individual basis.

Current National Comprehensive Cancer Network guidelines for pediatric ALL say that "Allogeneic HSCT has demonstrated improved clinical outcomes in pediatric ALL patients with evidence of certain high-risk features and/or persistent disease. In addition, survival rates appear to be comparable regardless of the stem cell source (matched related, matched unrelated, cord blood, or haploidentical donor)." The guidelines state that the benefit of allo-HCT in infants is still controversial.(3)

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

Not applicable.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03314974	Myeloablative Allogeneic Hematopoietic Cell Transplantation Using a Related or Unrelated Donor for the Treatment of Hematological Diseases	300	Nov 2025
NCT01949129	Allogeneic Stem Cell Transplantation for Children and Adolescents With Acute Lymphoblastic Leukaemia	1000	Apr 2026
NCT04232241	Matched Unrelated vs Haploidentical Donor for Allogenic Stem Cell Transplantation in Patients With Acute Leukemia With Identical GVHD Prophylaxis - A Randomized Prospective European Trial	440	Nov 2024
NCT05031897	A 2 Step Approach to Haploidentical Transplant Using Radiation-Based Reduced-Intensity Conditioning	67	Oct 2024

NCT: national clinical trial.

Government Regulations
National:

Medicare National Coverage Determinations Manual 100-3, Chapter 1, Part 2, Section 110.23, "Stem Cell Transplantation." Effective date: 1/27/16; Implementation Date: 10/3/16

General

Stem cell transplantation is a process in which stem cells are harvested from either a patient's (autologous) or donor's (allogeneic) bone marrow or peripheral blood for intravenous infusion. Autologous stem cell transplantation (AuSCT) is a technique for restoring stem cells using the patient's own previously stored cells. AuSCT must be used to effect hematopoietic reconstitution following severely myelotoxic doses of chemotherapy (HDCT) and/or radiotherapy used to treat various malignancies. Allogeneic hematopoietic stem cell transplantation (HSCT) is a procedure in which a portion of a healthy donor's stem cell or bone marrow is obtained and prepared for intravenous infusion. Allogeneic HSCT may be used to restore function in recipients having an inherited or acquired deficiency or defect. Hematopoietic stem cells are multi-potent stem cells that give rise to all the blood cell types; these stem cells form blood and immune cells. A hematopoietic stem cell is a cell isolated from blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, can mobilize out of the bone marrow into circulating blood, and can undergo programmed cell death, called apoptosis - a process by which cells that are unneeded or detrimental will self-destruct.

The Centers for Medicare & Medicaid Services (CMS) is clarifying that bone marrow and peripheral blood stem cell transplantation is a process which includes mobilization, harvesting, and transplant of bone marrow or peripheral blood stem cells and the administration of high

dose chemotherapy or radiotherapy prior to the actual transplant. When bone marrow or peripheral blood stem cell transplantation is covered, all necessary steps are included in coverage. When bone marrow or peripheral blood stem cell transplantation is non-covered, none of the steps are covered.

Indications and Limitations of Coverage

A. Nationally Covered Indications

I. Allogeneic Hematopoietic STEM CELL Transplantation (HSCT)
   a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary

II. Autologous STEM CELL transplantation (AuSCT)
   a) Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §I862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:
      1. Acute leukemia in remission who have a high probability of relapse and who have no human leukocyte antigens (HLA)-matched

B. Nationally Non-Covered Indications

I. Autologous STEM CELL transplantation (AuSCT)
   a) Insufficient data exist to establish definite conclusions regarding the efficacy of AuSCT for the following conditions:
      1. Acute leukemia not in remission

In these cases, AuSCT is not considered reasonable and necessary within the meaning of §I862(a)(1)(A) of the Act and is not covered under Medicare.

Other

All other indications for STEM CELL TRANSPLANTATION not otherwise noted above as covered or non-covered remain at local Medicare Administrative Contractor discretion.

(This NCD last reviewed January 2016.)

Local:

There is no local coverage determination on this topic. Refer to NCD.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- BMT – Hematopoietic Cell Transplantation for Acute Myeloid Leukemia

- BMT – Hematopoietic Cell Transplantation for Autoimmune Diseases
- BMT – Hematopoietic Cell Transplantation for Chronic Lymphocytic Leukemia and Small Cell Lymphocytic Lymphoma – Autologous or Allogeneic
- BMT – Hematopoietic Cell Transplantation for Chronic Myeloid Leukemia
- BMT – Hematopoietic Cell Transplantation for CNS Embryonal Tumors and Ependymoma
- BMT – Hematopoietic Cell Transplantation for Epithelial Ovarian Cancer
- BMT – Hematopoietic Cell Transplantation for Genetic Diseases and Acquired Anemias (Allogeneic)
- BMT – Hematopoietic Cell Transplantation for Germ-Cell Tumors
- BMT – Hematopoietic Cell Transplantation for Hodgkin Lymphoma
- BMT – Hematopoietic Cell Transplantation for Miscellaneous Solid Tumors in Adults
- BMT – Hematopoietic Cell Transplantation for Myelodysplastic Syndromes and Myeloproliferative Neoplasms
- BMT – Hematopoietic Cell Transplantation for Non-Hodgkin Lymphomas
- BMT – Hematopoietic Cell Transplantation for Plasma Cell Dyscrasias, Including Multiple Myeloma and POEMS Syndrome
- BMT – Hematopoietic Cell Transplantation for Primary Amyloidosis
- BMT – Hematopoietic Cell Transplantation for Solid Tumors of Childhood
- BMT – Hematopoietic Cell Transplantation for Waldenström's Macroglobulinemia
- BMT – Malignant Astrocytomas and Gliomas (Autologous)
- Donor Lymphocyte Infusion for Malignancies Treated with an Allogeneic Hematopoietic Cell Transplant
- Orthopedic Applications of Stem-Cell Therapy (Including Allografts and Bone Substitutes used with Autologous Bone Marrow)

References

1. Carroll WL, Bhojwani D, Min DJ et al. Pediatric acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program 2003:102-31. PMID 14633779
2. Pieters R, Carroll WL. Biology and treatment of acute lymphoblastic leukemia. Pediatr Clin North Am 2008; 55(1):1-20, ix. PMID 18242313
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pediatric Acute Lymphoblastic Leukemia. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf. Accessed March 26, 2024.
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute lymphoblastic leukemia. Version 4.2023; https://www.nccn.org/professionals/physician_gls/pdf/all.pdf. Accessed March 26, 2024.
5. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Autologous bone marrow transplantation in acute lymphocytic and nonlymphocytic leukemias. 1987 TEC Evaluations; page 243.
6. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). High-dose chemotherapy with autologous bone marrow transplantation for acute lymphocytic and nonlymphocytic leukemia in first remission. 1990 TEC Evaluations; page 254.
7. 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 2000; 108(3):531-43. PMID 10759711

8. Ribera JM, Ortega JJ, Oriol A et al. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as post-remission treatment for children with very high risk acute lymphoblastic leukemia: PETHEMA ALL-93 Trial. J Clin Oncol 2007; 25(1):16-24. PMID 17194902
9. 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 2012; 18(4):505-22. PMID 22209888
10. 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 2000; 11(8):999-1006. PMID 11038037
11. 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 2000; 96(7):2412-8. PMID 11001892
12. 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 2009; 114(7):1429-36. PMID 19528536
13. 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
14. 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.
15. 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
16. Yanada M, Matsuo K, Suzuki T, et al. Allogeneic hematopoietic stem cell transplantation as part of post remission therapy improves survival for adult patients with high-risk acute lymphoblastic leukemia: a meta-analysis. *Cancer.* Jun 15 2006;106(12):2657-2663. PMID 16703597
17. 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 2013; 121(2):339-50. PMID 23165481
18. 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 2008; 111(4):1827-33. PMID 18048644
19. 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 2009; 113(19):4489-96. PMID 19244158
20. 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 2009; 113(6):1375-82. PMID 18988865
21. 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
22. 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):310-317. PMID 26286115
23. 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. 2011(10):CD008818. PMID 21975786
24. Owattanapanich W, Leelakanok N, Sanpakit K, et al. A Comparison of the Clinical Outcomes of Haploidentical Transplantation and Other Graft Sources in Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis. Clin Lymphoma Myeloma Leuk. Mar 2022; 22(3): 174-191. PMID 34802994
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 1 2014;23(21):2535-2552. 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 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 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 2009; 23(10):1763-70. PMID 19440217
29. 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
30. 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.
31. 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
32. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for Stem Cell Transplantation Formerly 110.8.1 (110.23). 2016; https://www.cms.gov/medicare-coverage-

database/details/ncddetails.aspx?NCDId=366&ncdver=1&DocID=110.23&list_type=ncd&bc=gAAAAAgAAAAAAA%3d%3d&. Accessed March 26, 2024.
33. American Cancer Society. Acute Lymphocytic Leukemia (ALL) Subtypes and Prognostic Factors. Last revised 2018. https://www.cancer.org/cancer/acute-lymphocytic-leukemia/detection-diagnosis-staging/how-classified.html#:~:text=A%20remission%20(complete%20remission)%20is,or%20symptoms%20of%20the%20disease. Accessed March 26, 2024.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through March 26, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/13	10/16/12	10/16/12	• Topic split out from former combined BMT policies. • Policy formatted to mirror BCBSA. • Added “relative contraindications” to inclusionary/exclusionary section.
1/1/14	10/17/13	10/25/13	Routine maintenance
9/1/15	6/19/15	7/16/15	Routine maintenance. Added references and updated rationale.
9/1/16	6/21/16	6/21/16	Routine maintenance
9/1/17	6/20/17	6/20/17	Routine maintenance References, rationale and Medicare NCD updated
9/1/18	6/19/18	6/19/18	Routine maintenance
9/1/19	6/18/19		Routine maintenance
9/1/20	6/16/20		Routine maintenance
9/1/21	6/15/21		Routine maintenance
9/1/22	6/21/22		Routine maintenance
9/1/23	6/13/23		Routine maintenance (slp) Vendor Managed: N/A Formatting of criteria adjusted
9/1/24	6/11/24		Routine maintenance (slp) Vendor Managed: N/A

Next Review Date: 2nd Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: BMT - HEMATOPOIETIC CELL TRANSPLANTATION FOR ACUTE LYMPHOBLASTIC LEUKEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply. For an approved, preauthorized transplant, BCN will cover the necessary hospital, surgical, lab and X-ray services for a non-member donor, including charges for donating the bone marrow, under the BCN member's certificate, unless the non-member donor has coverage for such services. This also includes solid organ donor procurement fees. Donor travel, meals and lodging expenses are *not* covered unless the BCN member has a rider that covers such services. BCN does NOT cover expenses incurred by a BCN member for donating bone marrow, stem cells or a solid organ (e.g., kidney, liver lobe, lung lobe) to a non-BCN member. The donor services would be considered not medically necessary for the BCN member.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.