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## Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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Related Policies (if applicable)
None

### Disclaimer

#### Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

### Coverage

#### 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 section).*

*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 (ALL)

*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 section).*

*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 section).

*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 considered experimental, investigational and/or unproven** to treat adult ALL in second or greater remission or those with refractory disease.

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

## Policy Guidelines

### Relapse Risk Prognostic Factors

#### Childhood Acute Lymphoblastic Leukemia

Adverse prognostic factors in children include the following: age younger than 1 year or older than 9 years, male sex, white blood cell count at presentation above 50,000/ $\mu$ L, hypodiploidy (<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:

- Poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/ $\mu$ L or greater, or poor treatment response to induction therapy at 6 weeks with high-risk having 1% or higher minimal residual disease measured by flow cytometry;
- All children with T-cell phenotype; and
- Individuals 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 an 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/ $\mu$ L (B-cell lineage) or greater than 100,000/ $\mu$ L (T-cell lineage);
- “Poor prognosis” genetic abnormalities like the Philadelphia chromosome (t[9;22]);
- Extramedullary disease; and
- Time to attain complete remission longer than 4 weeks.

## Description

### **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. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized in the Policy Guidelines section. (2)

### **Childhood Acute Lymphoblastic Leukemia**

Acute lymphoblastic leukemia 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 98% 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 the 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, hematopoietic cell transplantation (HCT) may be a strong consideration in those with short remissions. At present, comparative outcomes with autologous or allogeneic HCT (allo-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 a complete response after induction chemotherapy; however, patients 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, to explain differences in outcomes between the 2 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/ $\mu$ L (B-cell lineage) or greater than 100,000/ $\mu$ L (T-cell lineage).

### **Hematopoietic Cell Transplantation**

Hematopoietic cell transplantation 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 Hematopoietic Cell Transplantation

#### *Conventional Conditioning*

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 of this procedure is due to a combination of the 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 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 (GVHD), 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 the 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 also susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not GVHD.

#### *Reduced-Intensity Conditioning Allogeneic Hematopoietic Cell Transplantation*

Reduced-intensity conditioning (RIC) allogeneic 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. These 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 policy, the term reduced-intensity conditioning will refer to all conditioning regimens intended to be nonmyeloablative.

### **Regulatory Status**

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

## **Rationale**

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized control trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **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 policy.

### *Populations*

The relevant population of interest is children with ALL.

### *Interventions*

The therapy being considered is autologous HCT.

### *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 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 long-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.

### Randomized Controlled Trials

An RCT comparing outcomes of HCT (both autologous and allogeneic) with conventional-dose chemotherapy in children with ALL was identified. (5) 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 Postremission 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 OS rates at a median follow-up of 78 months in children with very high-risk ALL in first complete remission (CR1) who received autologous (n=38) or allogeneic

HCT (allo-HCT; n=24) or standard chemotherapy (n=38) with maintenance treatment. (6) Similar results were observed using intention-to-treat 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., for 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 policy.

#### *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 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 long-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.

### 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. (7) 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 12 studies 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. (5) A total of 256 patients 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-year EFS 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 compared the outcome of children with relapsed ALL who received allo-HCT ( $n=104$ ) to chemotherapy ( $n=125$ ). (8) 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 compared allo-HCT treatment ( $n=101$ ) to chemotherapy ( $n=351$ ) in children with ALL in first remission. (9) 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 has 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. (10) 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 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 patients 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). (11) 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.

#### **Autologous 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 policy.

#### *Populations*

The relevant population of interest is adults with ALL.

#### *Interventions*

The therapy being considered is autologous 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 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 long-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.

### Systematic Reviews

The ASBMT (now the American Society for Transplantation and Cellular Therapy [ASTCT]) (2012) updated its 2005 guidelines for treatment of ALL in adults, covering literature to mid-October 2010. (7) The ASBMT indicated a grade A treatment recommendation for autologous HCT in patients who did not have a suitable allogeneic stem cell donor; the 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. (12) Among 183 high-risk adult patients in CR1, those with a human leukocyte antigen-identical family donor were assigned to allo-HCT (n=84); the remaining cases were randomized to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 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 3 arms by per-protocol or intention-to-treat 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., for patients in the allo-HCT arm).

### Section Summary: Autologous Hematopoietic Cell Transplantation for Adult Acute Lymphoblastic Leukemia

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 policy.

### *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 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 long-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.

### Systematic Reviews

A meta-analysis by Yanada et al. (2006) pooled evidence from 7 studies of allo-HCT published between 1994 and 2005 that included a total of 1274 patients with ALL in CR1. (13) 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. (7) 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. (14) 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). (15) 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 ( $n=588$ ) ( $p=.01$ ). (15) 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 nonrelapse 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. (16) 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 medical policy.

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. (17) 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-year OS 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 of 34% versus 41% and 61%, respectively, among those with no donor ( $n=3$ ;  $p=.50$ ). Nonrelapse mortality rates among standard-risk patients were 16% among those with a donor and 2% among those without a donor; in high-risk patients, NRM rates were 15% 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%. (17)

### 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). (18) 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. (19) Data were available on 1833 patients. Survival rates increased significantly over time in all age groups (18 to 24, 25 to 39, 40 to 59, 60 to 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. (20) 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 medical policy 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. (21) 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 Allogeneic Hematopoietic Cell Transplantation

A meta-analysis by Abdul Wahid et al. (2014) included data from 5 studies in which RIC (n=528) was compared with myeloablative conditioning regimens (n=2489) in adults with ALL who received allo-HCT mostly in CR1. (22) This analysis of data from nonrandomized studies suggested progression-free survival at 1 to 6 years is significantly lower after RIC (36%) than after myeloablative conditioning (41%; OR, 0.76; 95% CI, 0.61 to 0.93;  $p<.01$ ). 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;  $p=.76$ ). 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;  $p<.00001$ ).

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. (23) Despite the achievement of complete donor chimerism in 100% of patients, 28 (65%) had a leukemic relapse, with 67% ultimately dying. A registry-based study by Mohty et al. (2008) included 97 adults (median age, 38 years; range, 17 to 65 years) who underwent RIC and allo-HCT to treat ALL in CR1 (n=28), in CR2 and CR3 (n=26/5), and advanced or refractory disease (n=39). (24) With median follow-up of nearly 3 years, in the overall population, the 2-year rate OS was 31%, with an NRM rate of 28% and a relapse rate of 51%. In patients with HCT in CR1, the OS rate was 52%; in CR2 and CR3, the OS rate was 27%; in patients with advanced or refractory ALL, it was 20%. This evidence suggests RIC and allo-HCT have some efficacy as salvage therapy in high-risk ALL.

Reduced-intensity conditioning for allo-HCT was investigated in a prospective phase 2 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. (25) 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 3-year cumulative incidence of relapse was 19.7%; the NRM rate was 17.7%. The 3-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. (26) 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 NRM 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 the currently available evidence, RIC allo-HCT may also 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 Therapy Purpose

The purpose of allo-HCT 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 HCT.

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

#### *Populations*

The relevant population of interest is patients with ALL who relapse after a prior autologous HCT.

#### *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 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 long-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.

Published evidence is limited to small, uncontrolled clinical series with short follow-up. Literature searches have not identified strong evidence to permit conclusions on this use of allo-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 allo-HCT after a failed autologous HCT on health outcomes in patients with ALL.

#### **Summary of Evidence**

For individuals who have childhood acute lymphoblastic leukemia (ALL) in first complete remission (CR1) at high-risk of relapse, remission, or refractory ALL who receive autologous hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival (OS), disease-specific survival (DSS), and treatment-related mortality (TRM) 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 (ASBMT). The evidence is sufficient to determine that the technology results in an 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 allogeneic HCT (allo-HCT), the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, DSS, and TRM 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 ASBMT. The evidence is sufficient to determine that the technology results in an 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 OS,

DSS, and TRM 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 an 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, systematic reviews, and observational studies. Relevant outcomes are OS, DSS, and TRM 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 an 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. Relevant outcomes are OS, DSS, and TRM and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which was considered inadequate evidence of benefit. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## **Clinical Input From Physician Specialty Societies and Academic Medical Centers**

### **2013 Input**

Clinical input supports the use of allo-HCT to treat relapsing ALL after a failed, prior autologous HCT, particularly with reduced-intensity conditioning regimens, in adults or children. Thus, these indications may be considered medically necessary.

## **Practice Guidelines and Position Statements**

### **The American Society for Transplantation and Cellular Therapy**

In 2020, the 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 allo-HCT. Recommendations were intended to describe the current consensus on the use of HCT in and out of the clinical trial setting.

(27) 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	N
First complete response, high-risk	S	N	S	N

Second complete response	S	N	S	N
At least third complete response	C	N	S	N
Not in remission	C	N	S	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 (v.2.2025) for ALL indicate allo-HCT is appropriate for consolidation treatment of most poor risk (e.g., the Philadelphia chromosome-positive, relapsed, or refractory) patients with ALL. (28) The guidelines state that for appropriately fit older adults with ALL who are achieving remission, consideration of allogeneic HCT 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 NCCN guidelines (v.1.2026) for pediatric ALL say that "Allogeneic HCT 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. (29)

### **Medicare National Coverage**

There is a national coverage determination for stem cell transplantation (110.23; formerly 110.81), (30) portions of which are highlighted below:

#### Nationally Covered Indications

##### "I. Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

- a) Effective ... 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 ... 1989, AuSCT is considered reasonable and necessary ... 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;
  2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
  3. Recurrent or refractory neuroblastoma; or,
  4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor."

### **Ongoing and Unpublished Clinical Trials**

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

**Table 2. Summary of Key Trials**

NCT Number	Trial Name	Planned Enrollment	Completion Date
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	1800	Apr 2030
NCT04232241	Matched Unrelated Donor vs Haploidentical Donor for Allogeneic 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	63	Apr 2025
NCT01700946	A Phase II Study of Therapy for Pediatric Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia and Lymphoma	80	Jul 2021

NCT: national clinical trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	36511, 38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38220, 38221, 38222, 38230, 38232, 38240, 38241, 38242, 38243, 81265, 81266, 81267, 81268, 81370, 81371, 81372, 81373, 81374, 81375, 81376, 81377, 81378, 81379, 81380, 81381, 81382, 81383, 86805, 86806, 86807, 86808, 86812, 86813, 86816, 86817, 86821, 86822, 86825, 86826, 86828, 86829, 86830, 86831, 86832, 86833, 86834, 86835, 86849, 86950, 86985, 88240, 88241
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<b>HCPCS Codes</b>	S2140, S2142, S2150
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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

## Policy History/Revision

Date	Description of Change
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12/15/2025	Document updated. The following change was made to Coverage: Definition of high-risk factors moved to Policy Guidelines section. Added references 28-30; others updated. Title changed from: Hematopoietic Cell Transplantation as a Treatment for Acute Lymphoblastic Leukemia (ALL).
04/01/2025	Reviewed. No changes.
09/15/2024	Document updated with literature review. Coverage unchanged. Added/updated the following references: 1, 3, 4, and 21. Title changed from: "Hematopoietic Cell Transplantation as a Treatment of Acute Lymphoblastic Leukemia (ALL)."
12/15/2023	Reviewed. No changes.
05/15/2022	Document updated with literature review. Editorial changes made to Coverage without change to intent. Added/updated the following references: 1, 4, 28, and 30-32.
06/15/2021	Reviewed. No changes.
04/15/2020	Document updated with literature review. Coverage unchanged. The following references were added/updated: 25, 27-32, and 34-35. Title changed from: "Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia (ALL)".
06/15/2018	Reviewed. No changes.
06/01/2017	Document updated with literature review. Coverage unchanged.
07/01/2016	Reviewed. No changes.
06/15/2015	Document updated with literature review. The following coverage changed for children and adults was: "Allogeneic HSCT may be considered medically necessary to treat relapsing ALL after a prior autologous HSCT." Title changed from Stem-Cell Transplant for Acute Lymphoblastic Leukemia (ALL).
06/01/2014	Document updated with literature review. The following was added: 1) expanded coverage to consider a) donor leukocyte infusion (DLI) as medically necessary for childhood acute lymphoblastic leukemia (ALL) that has relapsed following an AlloSCS procedure, to prevent relapse in the setting of a high-risk relapse, or to convert a patient from mixed to full chimerism; b) DLI is considered experimental, investigational and/or unproven following an AlloSCS treatment for childhood ALL that was originally considered experimental, investigational and/or unproven for the treatment of childhood ALL OR as a treatment prior to AlloSCS; 2) Expanded coverage as follows a) donor leukocyte infusion (DLI) and hematopoietic progenitor cell (HPC) boost may be considered medically necessary for adult ALL that has relapsed following an AlloSCS procedure, to prevent relapse in the setting of a high-risk relapse, or to convert a patient from mixed to full chimerism; b) DLI and HPC boost are considered experimental, investigational and/or unproven following an AlloSCS treatment for adult ALL that was originally considered experimental, investigational and/or unproven for the treatment of adult ALL OR as a treatment prior to AlloSCS and 3) Expanded coverage as follows a) short tandem repeat (STR) markers



	<p>may be considered medically necessary when used in pre- or post-stem-cell support testing of the donor and recipient DNA profiles as a way to assess the status of donor cell engraftment following AlloSCS for ALL; b) all other uses of STR markers are considered experimental, investigational and/or unproven, if not listed in the coverage section. Title changed from Stem-Cell Transplant for Acute Lymphocytic Leukemia (ALL). Description and Rationale substantially revised.</p>
04/01/2010	<p>New medical document originating from: SUR703.017, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies; SUR703.018, Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies; SUR703.022, Cord Blood as a Source of Stem Cells (CBSC); SUR703.023, Donor Leukocyte Infusion (DLI); and SUR703.024, Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies. Stem cell transplant continues to be medically necessary when stated criteria are met.</p> <p>[NOTE: A link to the medical policies with the following titles can be found at the end of the medical policy SUR703.002, Stem-Cell Reinfusion or Transplantation Following Chemotherapy (General Donor and Recipient Information):</p> <ul style="list-style-type: none"> <li>• Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Non-Malignancies;</li> <li>• Peripheral/Bone Marrow Stem Cell Transplantation (PSCT/BMT) for Malignancies;</li> <li>• Cord Blood as a Source of Stem Cells;</li> <li>• Donor Leukocyte Infusion (DLI); and</li> <li>• Tandem/Triple High-Dose Chemoradiotherapy with Stem Cell Support for Malignancies.</li> </ul>