Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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**Policy**

**Children**

Autologous or allogeneic hematopoietic cell transplantation (HCT) may be considered medically necessary to treat childhood acute lymphoblastic leukemia (ALL) for ANY of the following:

- First complete remission but at high risk of relapse (see Policy Guidelines for high-risk factors); OR
- Second or greater remission; OR

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

**Adults**

Autologous HCT may be considered medically necessary to treat adult acute lymphoblastic leukemia (ALL) in:

- First complete remission for any relapse risk level (see Policy Guidelines for risk factors)

Allogeneic HCT may be considered medically necessary to treat adult ALL for ANY of the following:

- First complete remission for any relapse risk level; OR
- Second or greater remission; OR
- Relapsing ALL after a prior autologous HCT

Reduced-intensity conditioning (RIC) allogeneic HCT may be considered medically necessary as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission, and who for medical reasons (see Policy Guidelines), would be unable to tolerate a standard myeloablative conditioning regimen.

Autologous HCT is considered investigational to treat adult ALL for the following:

- Second or greater remission; OR
- Those with refractory disease

**Note:** The use of donor leukocyte infusions to treat relapse after high-dose chemotherapy (HDC) with allogeneic HCT for either children or adults is addressed in a separate medical policy. (See Related Policies.)
Related Policies

8.01.01     Adoptive Immunotherapy
8.01.26     Hematopoietic Stem-Cell Transplantation for Acute Myeloid Leukemia
8.01.30     Hematopoietic Cell Transplantation for Chronic Myelogenous Leukemia

Policy Guidelines

Relapse Risk Prognostic Factors

**Childhood ALL**
Adverse prognostic factors include the following: age younger than one year or more than nine years, male gender, white blood cell count at presentation above 50,000/μL, hypodiploidy (<45 chromosomes), t(9:22) or BCR/ABL fusion, t(4;11) or MLL/AF4 fusion, and ProB or T-lineage immunophenotype. Several risk stratification schema exist, but, in general, the following findings help define children at high risk of relapse: 1) poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/μL or greater, or poor treatment response to induction therapy at six weeks with high risk having ≥1% minimal residual disease measured by flow cytometry), 2) all children with T-cell phenotype and 3) patients with either the t(9;22) or t(4;11) are considered high risk regardless of early response measures.

**Adult ALL**
Risk factors for relapse are less well defined, but an adult patient with any of the following may be considered at high risk for relapse: age greater than 35 years, leukocytosis at presentation of >30,000/μL (B-cell lineage) and >100,000/μL (T-cell lineage), "Poor prognosis" genetic abnormalities like the Philadelphia chromosome (t(9;22)), extramedullary disease and time to attain complete remission longer than 4 weeks.

Reduced Intensity Conditioning
Some patients for whom a conventional myeloablative allogeneic HCT could be curative may be considered candidates for RIC allogeneic HCT. These include those whose age (typically older than 60 years) or co morbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

**Note:** Unless otherwise specified in the text of this Policy, it is assumed that the term "allogeneic HCT" refers to the use of a myeloablative pretransplant conditioning regimen.

The ideal allogeneic donors are HLA-identical siblings, matched at the LHA-A, B and DR loci (six of six). Related donors mismatched at one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. The majority of patients will have such a donor; however, the risk of GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

Coding

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<td>38230</td>
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Hematopoietic Cell Transplantation

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

Background
Immunologic compatibility between infused stem cells and the recipient is not an issue in autologous HCT. However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome of allogeneic HCT. Compatibility is established by typing of human leukocyte antigens (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA A, B, and DR loci on each leg of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci.

For individuals who have childhood ALL in first complete remission at high risk of relapse, subsequent remission, or refractory ALL who receive autologous or allogeneic 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, 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 first complete remission or subsequent remission, or refractory ALL who receive autologous or allogeneic 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 first complete remission, or myeloablative allogeneic HCT (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 ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence Street Assessments have identified only small case series with short-term follow-up, which were considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.
Allo-HCT after failed autologous HCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input has supported use of allogeneic HCT to treat relapsing ALL after a failed prior autologous HCT, particularly with RIC regimens, in adults or children. Thus, this indication may be considered medically necessary.

**Conventional Preparative Conditioning for HCT**

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

The conventional (“classical”) practice of allogeneic HCT involves administration of cytotoxic agents (e.g., cyclophosphamide, busulfan) with or without total-body irradiation at doses sufficient to destroy endogenous hematopoietic capability in the recipient. The beneficial treatment effect in this procedure is due to a combination of initial eradication of malignant cells and subsequent graft-versus-malignancy (GVM) effect that develops after engraftment of allogeneic stem cells within the patient’s bone marrow space. While the slower GVM effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allogeneic HCT, immune suppressant drugs are required to minimize graft rejection and GVHD, which also increases susceptibility of the patient to opportunistic infections.

**Reduced-Intensity Conditioning for Allogeneic HCT**

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to minimize as much as possible associated treatment-related morbidity and non-relapse mortality (NRM) in the period during which the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum in effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific disease and patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For the purposes of the Policy, the term “reduced-intensity conditioning” will refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully myeloablative (conventional) regimens.

**Acute Lymphoblastic Leukemia (ALL)**

**Childhood ALL**

ALL is the most common cancer diagnosed in children and represents almost 25% of cancers in children younger than 15 years. (1) Approximately 95% of children with ALL achieve remission with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large, randomized trials, integration of pre-symptomatic 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, the comparative outcomes with autologous or allogeneic HCT are unknown.

ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy
tailoring treatment based on the predicted risk of relapse. (3) Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis. (3) Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows: (2)

<table>
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<th>PROGNOSTIC FACTOR</th>
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<tr>
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<td>ProB, T lineage</td>
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**Adult ALL**

ALL accounts for approximately 20% of acute leukemias in adults. Approximately 60-80% of adults with ALL can be expected to achieve complete remission after induction chemotherapy; however, only 35-40% can be expected to survive two years. (4) Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, to explain the outcome differences between the two groups. For example, the “good prognosis” genetic abnormalities like hyperdiploidy and t(12;21) are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities like the Philadelphia chromosome (t(9;22)) are seen in 25-30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of >30,000/μL (B-cell lineage) and >100,000/μL (T-cell lineage).

Note: The use of killer (LAK) cells in the treatment of malignancies is addressed in a separate policy (See Related Policies.)

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

**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply.

**Benefit Application**

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health (NIH).
- Some plans may participate in voluntary programs offering coverage for patients participating in NIH-approved clinical trials of cancer chemotherapies, including autologous bone marrow transplantation.
• Some contracts or certificates of coverage (e.g., FEP) may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

### Rationale

#### Childhood ALL
The policy on childhood acute lymphoblastic leukemia (ALL) was initially based on TEC Assessments completed in 1987 and 1990.\(^\text{(5,6)}\) In childhood ALL, conventional chemotherapy is associated with complete remission rates of about 95%, with long-term durable remissions of 60%. Therefore, for patients in a first complete remission (CR1), cell transplantation (HCT) therapy is considered necessary only in those with risk factors predictive of relapse (see the Description section).

Three reports describing the results of randomized-controlled trials (RCTs) that compared outcomes of HDC with HCT in children with ALL were identified subsequent to the TEC Assessment.\(^\text{(7-9)}\) The children enrolled in the RCTs were being treated for high-risk ALL in first complete remission (1st CR) or for relapsed ALL. These studies reported that overall outcomes after HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HCT administered in 1st CR was associated with fewer relapses than conventional-dose chemotherapy, it was also associated with more frequent deaths in remission (i.e., from treatment-related toxicity).

A 2007 randomized trial (PETHEMA ALL-93, \(n = 106\)) demonstrated no significant differences in disease-free survival or overall survival rates at median follow-up of 78 months in children with very high-risk ALL in CR1 who received allogeneic or autologous HCT versus standard chemotherapy with maintenance treatment.\(^\text{(10)}\) Similar results were observed using either intention-to-treat (ITT) or per-protocol (PP) analyses. However, the authors point out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HCT and time elapsed between CR and undertaking of assigned treatment; and the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HCT arm.

A 2012 systematic evidence-based 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.\(^\text{(11)}\) 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 CR2 or beyond, or relapsed disease.

#### Adult ALL
The policy on adult ALL was initially based on a 1997 TEC Assessment of HDC and autologous (not allogeneic) stem cell support.\(^\text{(12)}\) This Assessment offered the following conclusions:

- For patients in CR1, the data suggest survival is equivalent after high-dose therapy plus autologous HCT or conventional chemotherapy. For these patients the decision between HDC and conventional chemotherapy may reflect a choice between an intensive therapy of short duration and longer but less-intensive treatment.
- In other settings such as in second (CR2) or subsequent remission, data were inadequate to determine the relative effectiveness of high-dose therapy plus autologous stem-cell support compared to conventional chemotherapy.

#### Systematic Reviews
A 2006 meta-analysis pooled evidence from 7 studies of allo-HCT published between 1994 and 2005 that included a total of 1274 patients with ALL in CR1.\(^\text{(13)}\) Results showed that, regardless of risk category, allo-HCT was associated with a significantly longer OS (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.02 to 1.63; \(p=0.037\)) for all patients who had a suitable donor versus patients without a donor who received chemotherapy or autologous HCT. Pooled evidence from patients with high-risk disease showed an increased survival advantage...
for allo-HCT compared to those without a donor (HR=1.42; 95% CI, 1.06 to 1.90; p=0.019). 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.

In 2012, ASBMT updated its 2005 guidelines for treatment of ALL in adults, covering literature to mid-October 2010.(11) The evidence available at that time 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. Further, 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 postremission chemotherapy, the shorter treatment duration with the former is an advantage. Finally, ASBMT concluded that allo-HCT was recommended over chemotherapy for adults with ALL in CR2 or beyond.

In an earlier review (2006), ASBMT had reviewed evidence through January 2005 on HCT in adults with ALL and recommended HCT as consolidation therapy for adults with high-risk disease in CR1 but not for standard-risk patients and for patients in CR2.(14) Based on results from 3 RCTs,(15-17) ASBMT further concluded that myeloablative allo-HCT is superior to autologous HCT in adult patients in CR1, although available evidence did not permit separate comparisons of high-risk versus low-risk patients.

A 2013 individual patient data meta-analysis included 13 studies (total N=2962 patients), several of which are evaluated herein.(18) 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 to chemotherapy in CR1 (odds ratio [OR], 1.18; 95% CI, 0.99 to 1.41; p=0.06), primarily due to higher transplant-related mortality in the autograft patients than in chemotherapy recipients. The results did not change the conclusions of our current policy, but indicate further study is needed to determine the optimal therapy for adult ALL patients.

**Randomized Controlled Trials**

In 2005, Ribera et al reported results from the multicenter (35 Spanish hospitals) randomized trial (PETHEMA ALL-93; n=222) published after the ASBMT literature search.(19) Among 183 high-risk patients in CR1, those with an HLA-identical family donor were assigned to allogeneic HCT (n=84); the remaining cases were randomized to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to two years in CR (n=48). At median follow-up of 70 months, the study did not detect a statistically significant difference in outcomes among all three arms by both per-protocol and ITT analyses. The PETHEMA ALL-93 trial investigators pointed out several study limitations that could have affected outcomes, including the relatively small numbers of patients; variations among centers in the preparative regimen used prior to HCT; differences in risk group assignment; and the use of genetic randomization based on donor availability rather than true randomization for patients included in the allogeneic HCT arm.

While the utility of allo-HCT for postremission therapy in patients with high-risk ALL has been established, its role in standard-risk patients has been less clear. This question has been 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).(20) The 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 an HLA-matched sibling donor (n=443) were assigned to receive an 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, OS 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=0.01). (20) Analysis of Ph-negative patient outcomes by disease risk showed a 5-year OS of 41% among patients with high-risk ALL and a sibling donor versus 35% of high-risk patients with no donor (p=0.2). In contrast, OS 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=0.02). Among Ph-negative patients with 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<0.001). Among Ph-negative patients with high-risk ALL, the rate of relapse at 10-year follow-up was 37% following allo-HCT versus 63% without a transplant (p<0.001), demonstrating the potent graft-versus-leukemia (GVL) effect in an allogeneic transplantation. This evidence clearly showed a significant long-term survival benefit associated with postremission 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 a high nonrelapse mortality (NRM) rate at 1 and 2 years, mostly due to graft-versus-host-disease (GVHD) and infections. At 2 years, NRM 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, ITT 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.(21) Although the difference in OS rates was not statistically significant, this analysis demonstrated a moderate superiority of postremission-matched sibling allo-HCT over chemotherapy in patients with high-risk ALL in CR1, in concordance with this policy.

The 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 an HLA-matched sibling donor, irrespective of risk category.(22) 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. OS rates at 5-year follow-up were 61% among all patients with a donor and 47% among those without a donor (p=0.08). 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=0.001). 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=0.05). 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=0.50). NRM rates among standard-risk patients were 16% among those with a donor and 2% among those without a donor; in high-risk patients, 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 direct comparison of their outcomes. To facilitate a meaningful comparison, the HOVON data were reanalyzed by donor availability from diagnosis. 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%.(22)

**Observational Studies**

Several studies published in 2016 have evaluated changes in survival rates over time. A 2017 multicenter clinical trial from Europe reported on 4859 adults with ALL in first remission treated with allo-HCT from either a matched sibling donor (n=2681) or an unrelated donor (n=2178).(23) Survival rates generally improved over time (ie, from 1993-2002 to 2008-2012). For the time 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 period, 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, in 2016, Dinmohamed et al 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 time period (2007-2012), 5-year relative survival rates by age group were 75%, 57%, 37%, 22%, and 5%, respectively.

**Section Summary**
The evidence indicates postremission myeloablative autologous or 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 use of allo-HCT, particularly for older patients. For adults who survive HCT, there is a significant relapse rate. The current evidence support the use of autologous HCT for adults with high-risk ALL in CR1, or myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure.

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 (total N=3157 patients) 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=0.01). 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<0.001) and significantly increased NRM (RR=2.8; 95% CI, 1.66 to 4.73; p=0.001). These results support the conclusions of this policy that allo-HCT (matched sibling donor) is an effective postremission therapy in adults.

Reduced-Intensity Conditioning Allogeneic HCT
The use of RIC regimens has been investigated as a means to extend the substantial GVL effect of post remission allogeneic HCT to patients who could expect to benefit from this approach but who are ineligible or would not tolerate a fully myeloablative procedure.

A 2014 meta-analysis 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.(26) 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<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).

In a 2007 multicenter single-arm study of patients (n=43, median age 19 years; range: one to 55) in second complete remission (CR2), a three-year OS rate of 30% was achieved, with 100-day and NRM rates of 15% and 21%, respectively. Despite achievement of complete donor chimerism in 100% of the patients, 28 (65%) had leukemic relapse, with 67% ultimately succumbing to their disease.(29)

A 2008 registry-based study included 97 adult patients (median age 38 years, range 17–65) 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).(28) With median follow-up of about three years, in the overall population two-year OS was 31%, with non-relapse mortality of 28% and relapse rate of 51%. In patients transplanted in CR1, OS was 52%; in CR2/CR3, it was 27%; in patients with advanced or refractory ALL, OS was 20%. These data suggest RIC and allogeneic HCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allogeneic HCT was investigated in a 2009 prospective Phase II study that included 37 consecutive adults (median age 45 years; range 15–63 years) with high-risk ALL (43% Ph-positive, 43% high WBC) in CR1 (81%) or CR2 (19%) who were ineligible to receive a myeloablative allogeneic HCT because of age, organ dysfunction, low Karnofsky performance status (<50%), or the presence of infection.(29) Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Post remission RIC conditioning consisted of fludarabine and melphalan, with GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib prior to HCT. The three-year cumulative incidence of relapse was 19.7% ± 6.9%, that of NRM was 17.7% ± 6.9%. The three-year cumulative OS rate was 64.1% ± 8.6%, with DFS rate of 62.6% ± 8.5% at the same point. After a median follow-up of 36 months (range: 121–96 months), 25 (67.6%) of patients remained alive, among whom 24 (96%) remained in continuous CR.

A 2009 multicenter prospective study published in 2010 involved 47 pediatric patients (median age 11 years, range: 2-20 years) with hematologic cancers, including ALL (n=17), who underwent allogeneic HCT with a fludarabine-based RIC regimen.(30) It represents the first large cooperative group study to be published in this setting. Among the 17 cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily
pretreated, including previous myeloblastic allogeneic or autologous HCT, but these were not individually reported. While most data were presented in aggregate, some survival findings were specified, showing EFS of 35% and OS of 37% at 20-year follow-up for the ALL patients. Although most patients lived only a few months after relapse or rejection, some were long-term survivors after further salvage treatment. Among those, 1 ALL patient received chemotherapy and donor lymphocyte infusion (DLI) for low chimerism and relapse and was reported alive 1 year following DLI and 3 years from HCT. A second ALL case, who rejected an initial mismatched unrelated donor graft, underwent a second RIC regimen using the same donor and was alive with moderate chronic GVHD more than 3 years after HCT. Treatment-related mortality was not reported by disease, nor was HCT-related morbidity. However, these data do suggest allogeneic HCT with RIC can be used in children with high-risk ALL and achieve some long-term survival in patients with no therapeutic recourse.

Thus, based on currently available data and clinical input as noted in the following section, RIC allogeneic HCT may be considered medically necessary in patients who demonstrate complete marrow and extramedullary first or second remission; could be expected to benefit from a myeloablative allogeneic HCT; and, who for medical reasons, could not tolerate a myeloablative conditioning regimen. Additional data are necessary to determine whether some patients with ALL and residual disease may benefit from RIC allogeneic HCT.

**Allogeneic Transplant after Prior Failed Autologous Transplant**

A 2000 TEC Assessment focused on allogeneic SCT after a prior failed autologous SCT in the treatment of a variety of malignancies, including ALL. (31) The TEC Assessment found that data were inadequate to permit conclusions about outcomes of this treatment strategy. Published evidence was limited to small, uncontrolled clinical series with short follow-up. Updated literature searches have not identified any additional evidence to permit conclusions on this use of HCT.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 1.

**Table 1. Summary of Key Trials**

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02042690</td>
<td>Haplo-identical HCT Versus Chemotherapy for Adult Acute Lymphoblastic Leukemia Patients</td>
<td>300</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01700946</td>
<td>Therapy for Pediatric Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia and Lymphoma</td>
<td>40</td>
<td>Oct 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

**Summary**

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, 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 first complete remission or subsequent remission, or refractory ALL who receive autologous or allogeneic 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 first complete remission, or myeloablative allogeneic HCT (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 ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence Street Assessments have identified only small case series with short-term follow-up, which were considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

Clinical Input Received through Physician Specialty Society and Academic Medical Center Input
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.

In response to requests, input was received from 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, 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.

National Comprehensive Cancer Network Guidelines
The 2013 National Comprehensive Cancer Network clinical practice guidelines for acute lymphoblastic leukemia indicate allogeneic HCT is appropriate for consolidation treatment of most poor-risk (e.g., Ph1+, relapsed or refractory) patients with ALL.(32) These guidelines are generally consistent with this policy. However, the NCCN guidelines now stratify treatment according to the categories adolescent and young adult (age 15-39 years) and adult (age 40 or more years), rather than in more traditional children (18 years or younger) and adult categories (18 or more years).

American Society for Blood and Marrow Transplantation
In 2015, guidelines from 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 within and outside of the clinical trial setting.(33) Recommendations on ALL are listed in Table 2.

<table>
<thead>
<tr>
<th>Table 2. ASBMT Guidelines for Autologous and Allogeneic HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>First complete response, standard risk</td>
</tr>
<tr>
<td>First complete response, high risk</td>
</tr>
<tr>
<td>Second complete response</td>
</tr>
<tr>
<td>At least third complete response</td>
</tr>
<tr>
<td>Not in remission</td>
</tr>
</tbody>
</table>

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

U.S. Preventive Services Task Force Recommendations
Not applicable.
Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

31. 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. PMID 18245655

Appendix
**History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/27/00</td>
<td>Add to Therapy Section - New Policy — replaces 8.01.15, original master policy on HDC for miscellaneous malignancies. However, policy statement is unchanged.</td>
</tr>
<tr>
<td>12/21/00</td>
<td>Replace Policy - Policy statement revised to state that allogeneic transplant after a prior failed autotransplant is considered investigational, based on 2000 Tec Assessment.</td>
</tr>
<tr>
<td>06/17/03</td>
<td>Replace Policy - Policy updated w/expanded rationale and new references; policy statement unchanged.</td>
</tr>
<tr>
<td>08/12/03</td>
<td>Replace Policy - Reviewed and recommended for adoption without any changes by Company Oncology Advisory Panel July 22, 2003.</td>
</tr>
<tr>
<td>12/14/04</td>
<td>Replace Policy - Policy reviewed w/literature search; update added on clinical trials and NCCN guidelines; policy statement unchanged.</td>
</tr>
<tr>
<td>01/10/06</td>
<td>Replace Policy - Policy reviewed with literature search; no change to policy statement.</td>
</tr>
<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes.</td>
</tr>
<tr>
<td>10/09/07</td>
<td>Replace Policy - Policy reviewed with BCBSA literature update through March 2007. NCI clinical trials updated; NCCN guidelines information unchanged. New references added; Policy statement unchanged.</td>
</tr>
<tr>
<td>11/12/07</td>
<td>Code updated - CPT code 86817 removed as directed by RPIW.</td>
</tr>
<tr>
<td>05/13/08</td>
<td>New PR status - Policy statement regarding HDC and allogeneic SCT to treat relapsing ALL after a prior course of HDC and autologous SCT changed from investigational to medically necessary for children and adults. Reviewed and recommended by the OAP on February 21, 2008. Replaces BC.8.01.32, status changed from BC to PR.</td>
</tr>
<tr>
<td>05/12/09</td>
<td>Replace Policy - Policy revised with literature search. Clinical input received. New policy statement added that RIC allogeneic SCT may be considered medically necessary in select patients in complete remission. Policy titles changed to: “Hematopoietic Stem Cell Transplantation for Acute Lymphocytic Leukemia”. Reviewed and recommended by the OAP on February 19, 2009.</td>
</tr>
<tr>
<td>12/08/09</td>
<td>Code Update - 86817 added back to the policy.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Code Update - New 2010 codes added.</td>
</tr>
<tr>
<td>09/15/11</td>
<td>Replace Policy – Policy updated with literature review; no change in policy statement.</td>
</tr>
<tr>
<td>03/23/12</td>
<td>Replace policy. Policy updated with literature review; no change in policy statement. References added, removed and reordered. Reviewed and recommended by OAP on February 16, 2012.</td>
</tr>
<tr>
<td>08/01/12</td>
<td>Update Related Policies Titles: 8.01.21, 8.01.22, 8.01.29, 8.01.30, 8.01.31, 8.01.35, 8.01.514. Policy 8.01.507 was changed to 8.01.17.</td>
</tr>
<tr>
<td>02/01/13</td>
<td>Update Related Policies, change title of policy 8.01.21.</td>
</tr>
<tr>
<td>03/20/13</td>
<td>The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.</td>
</tr>
<tr>
<td>09/30/13</td>
<td>Update Related Policies. Change title to policy 8.01.31.</td>
</tr>
<tr>
<td>10/18/13</td>
<td>Update Related Policies. Change title to policy 8.01.17.</td>
</tr>
<tr>
<td>12/03/13</td>
<td>Coding Update. Add ICD-10 codes.</td>
</tr>
<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.30.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Remove 8.01.514 as it was deleted.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and replace with 8.01.529.</td>
</tr>
<tr>
<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements. Related Policies updated; only those related to leukemia remain; all others removed.</td>
</tr>
<tr>
<td>03/13/15</td>
<td>Update Related Policies. Add 8.01.01</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature search; no change to policy statement. References updated. ICD-9 and ICD-10 procedure codes removed; they were listed for informational purposes only.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Annual Review, approved June 14, 2016. Literature review. No change to policy statement.</td>
</tr>
</tbody>
</table>
Discussion wording updated. Clinical trial reviews updated.

09/30/16 Coding Update. Remove CPT 86817 from coding section.
11/04/16 Coding update. Removed codes that are transplant benefit related.
06/09/17 Coding update; updated description for CPT codes 38230, 38240, and 38241.

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