I. POLICY

CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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

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

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

ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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

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

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

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

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

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

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

**POLICY GUIDELINES**

**Relapse Risk Prognostic Factors**

**Childhood Acute Lymphoblastic Leukemia**

Adverse prognostic factors in children include the following: age less than 1 year or more than 9 years, male gender, white blood cell count at presentation above 50,000/µL, hypodiploidy (<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 6 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) regardless of early response measures.

**Adult Acute Lymphoblastic Leukemia**

Risk factors for relapse are less well-defined in adults, but a patient with any of the following may be considered at high risk for relapse: age greater than 35 years, leukocytosis at presentation of >30,000/µL (B cell lineage) or >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 reduced-intensity conditioning (RIC) allogeneic HCT. These include those whose age (typically >60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HCT, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

The ideal allogeneic donors are human leukocyte antigen (HLA) –identical siblings, matched at the HLA-A, -B, and DR (antigen-D related) loci on each arm of chromosome 6. Related donors mismatched at 1 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 3 of the 6 major histocompatibility antigens. Most patients will
have such a donor; however, the risk of graft-versus-host disease and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

*Cross-reference:*
  MP 2.317 BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

**II. PRODUCT VARIATIONS**

This policy is applicable to all programs and products administered by Capital BlueCross unless otherwise indicated below.

BlueJourney HMO*  BlueJourney PPO*  FEP PPO**

*Refer to the Centers for Medicare and Medicaid Services (CMS) National Coverage Determination (NCD) 110.23 Stem Cell Transplantation.

**The Federal Employee Program (FEP) may include specific conditions in which autologous and nonmyeloablative (reduced-intensity conditioning or RIC) allogeneic blood or marrow stem cell transplants may be considered eligible for coverage. Refer to the Service Plan Benefit Brochure for covered indications.

**III. DESCRIPTION/BACKGROUND**

**ACUTE LYMPHOBLASTIC LEUKEMIA**

**Childhood Acute Lymphoblastic Leukemia**

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years.\(^1\) Complete remission of disease is now typically achieved with pediatric chemotherapy regimens in 95% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.\(^2\) 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 variations resulting in distinct biologic subtypes. Patients are stratified by certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse.\(^3\) Two of the most important factors predictive of risk are patient age and white blood cell count at diagnosis.\(^3\) 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.\(^2\)

**Adult Acute Lymphoblastic Leukemia**

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve CR after induction chemotherapy; however, only 35% to 40% can be expected to survive 2 years.\(^4\) Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, 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/μL (B-cell lineage) or greater than 100,000/μL (T-cell lineage).

**CONDITIONING FOR HCT**

**Conventional 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 before undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections before engraftment, but not graft-versus-host disease.

The conventional (“classical”) practice of allo-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 preengraftment
opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-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 Allo-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 and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) when 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 of effects, from nearly totally 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, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**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.

**IV. RATIONALE**

This evidence review was updated with searches of the MEDLINE and EMBASE databases, most recently through November 9, 2016.

**CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA**

The evidence review of childhood acute lymphoblastic leukemia (ALL) was initially based on TEC Assessments completed in 1987 and 1990. In childhood ALL, conventional chemotherapy is associated with complete remission (CR) rates of approximately 95%, with long-term durable remissions up to 85%. Therefore, for patients in a first complete remission (CR1), hematopoietic cell transplantation (HCT) is considered only for those with unfavorable risk factors predictive of relapse.

Three randomized controlled trials (RCTs) comparing outcomes of HCT with outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC
Assessment.7-9 The children enrolled in these RCTs were being treated for high-risk ALL in CR1 or for relapsed ALL. These trials reported that overall outcomes after HCT were generally equivalent to overall outcomes after conventional-dose chemotherapy. While HCT administered in CR1 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 (OS) rates at a median follow-up of 78 months in children with very high risk ALL in CR1 who received allogeneic (allo-) or autologous HCT or standard chemotherapy with maintenance treatment.10 Similar results were observed using intention-to-treat (ITT) or per-protocol analyses. However, several limitations could have affected outcomes: the relatively small numbers of patients, variations across centers in the preparative regimen used before HCT and time elapsed between CR and undertaking of assigned treatment, and use of genetic randomization based on donor availability rather than true randomization for patients in the allo-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.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.

Section Summary: Childhood Acute Lymphoblastic Leukemia
While the risks of treatment-related mortality 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), HCT remains a therapeutic option to manage childhood ALL.

ADULT ALL
The evidence review on adult ALL was initially based in part on a 1997 TEC Assessment of autologous HCT.12 This Assessment offered the following conclusions:

For patients in CR1, available evidence suggested survival was equivalent after autologous HCT or conventional-dose chemotherapy. For these patients, the decision between autologous HCT and conventional chemotherapy may reflect a choice between intensive therapy of short duration and longer but less intensive treatment.

In other settings, such as in second (CR2) or subsequent remissions, the evidence was inadequate to determine the relative effectiveness of autologous HCT compared with conventional chemotherapy.

Systematic Reviews
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 CR1.13 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. 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. Based on results from 3 RCTs, 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. 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 evidence review, 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 PETHEMA ALL-93 trial (N=222 patients), which was published after the ASBMT literature search. Among 183 high-risk patients in CR1, those with a human leukocyte antigen (HLA) – identical family donor were assigned to allo-HCT (n=84); the remaining cases were randomly assigned to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 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 ITT analyses. PETHEMA ALL-93 trial investigators pointed out several factors that could have affected outcomes: relatively small numbers of patients; variations among centers in the
preparative regimen used before HCT; differences in risk group assignment; and use of genetic randomization based on donor availability rather than true randomization for patients included in the allo-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). 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). 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. Although the difference in OS rates was not
statistically significant, this analysis demonstrated a moderate superiority of post-remission-matched sibling allo-HCT over chemotherapy in patients with high-risk ALL in CR1, in concordance with this evidence review.

The 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. 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 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%.

**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). Survival rates generally improved over time (i.e., 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. 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: Adult ALL**
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 evidence review that allo-HCT (matched sibling donor) is an effective postremission therapy in adults.

**REDUCED-INTENSITY CONDITIONING ALLO-HCT**
Use of reduced-intensity conditioning (RIC) regimens has been investigated as a means to extend the substantial GVL effect of postremission 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 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).

A 2007 multicenter, single-arm study of patients (N=43; median age, 19 years; range, 1-55 years) in CR2 reported a 3-year OS rate of 30%, with 100-day mortality and NRM rates of 15% and 21%, respectively.27 Despite achievement of complete donor chimerism in 100% of patients, 28 (65%) had leukemic relapse, with 67% ultimately dying.

A 2008 registry-based study included 97 adults (median age, 38 years; range, 17-65 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). With median follow-up of nearly 3 years, in the overall population, 2-year OS was 31%, with an NRM rate of 28% and a relapse rate of 51%. In patients with HCT in CR1, OS was 52%; in CR2 and CR3, OS was 27%; in patients with advanced or refractory ALL, OS was 20%. This evidence suggests RIC and allo-HCT have some efficacy as salvage therapy in high-risk ALL.

RIC for allo-HCT was investigated in a 2009 prospective phase 2 study of 37 consecutive adults (median age, 45 years; range, 15-63 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. Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Postremission 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, 121-96 months), 25 (67.6%) of patients were alive, 24 (96%) of whom remained in CR.

A 2009 multicenter prospective study involved 47 pediatric patients (median age, 11 years; range, 2-20 years) with hematologic cancers, including ALL (n=17), who underwent allo-HCT with a fludarabine-based RIC regimen. (This is the first large cooperative group study to be published in this setting.) 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 EFS of 35% and OS 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 suggests 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.

Section Summary: Reduced-Intensity Conditioning Allo-HCT
Based on currently available evidence, RIC allo-HCT may benefit patients who demonstrate complete marrow and extramedullary CR1 or CR2, could be expected to benefit from myeloablative allo-HCT, and who, for medical reasons, would be unable to tolerate a myeloablative conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allo-HCT.

Allogeneic Transplant After Failed Autologous Transplant
A 2000 TEC Assessment focused on allo-HCT, after a failed autologous HCT, in the treatment of a variety of malignancies, including ALL. The TEC Assessment found the evidence inadequate to permit conclusions about outcomes of this treatment strategy. Published evidence was limited to small, uncontrolled clinical series with short follow-up. Subsequent literature searches have not identified strong evidence to permit conclusions on this use of HCT.
Section Summary: Allogeneic Transplant After Failed Autologous Transplant
Small uncontrolled case series with short-term follow-up are inadequate to draw conclusions on the effect of all-HCT after a failed HCT on health outcomes in patients with ALL.

SUMMARY OF EVIDENCE
For individuals who have childhood acute lymphoblastic leukemia (ALL) in first complete remission at high risk of relapse, subsequent remission, or refractory ALL who receive autologous or allogeneic hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high risk ALL in first complete remission (CR1) or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, 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 FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.
PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
Current National Comprehensive Cancer Network (NCCN) guidelines (v.2.2016) for acute lymphoblastic leukemia (ALL) indicate allogeneic hematopoietic cell transplantation (allo-HCT) is appropriate for consolidation treatment of most poor risk (e.g., the Philadelphia chromosome positive, relapsed or refractory) patients with ALL. The guidelines do not include specific recommendations on the use of autologous HCT. 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.

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. Recommendations on ALL are listed in Table 1.

### Table 1. ASBMT Guidelines for Autologous and Allogeneic HCT

<table>
<thead>
<tr>
<th>Indication</th>
<th>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First complete response, standard risk</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>First complete response, high risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Second complete response</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>At least third complete response</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 2.
V. DEFINITIONS

ALLOGENEIC refers to having a different genetic constitution but belonging to the same species, i.e., involves a donor and a recipient. These cells are harvested from a donor, after verifying the donor and the recipient are well matched with respect to human leukocyte antigens (HLA). Allogeneic cells provide two (2) theoretical advantages: the lack of tumor contamination associated with autologous stem cells, and the possibility of a beneficial graft-versus-tumor effect. Their disadvantage is the risk of graft-versus-host disease (GVHD), which increases with great HLA disparity and recipient age.

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

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

VI. BENEFIT VARIATIONS

The existence of this medical policy does not mean that this service is a covered benefit under the member's contract. Benefit determinations should be based in all cases on the applicable contract language. Medical policies do not constitute a description of benefits. A member’s individual or group customer benefits govern which services are covered, which are excluded, and which are subject to benefit limits and which require preauthorization. Members and providers should consult the member’s benefit information or contact Capital for benefit information.

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

**VIII. CODING INFORMATION**

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

**Covered when medically necessary:**

<table>
<thead>
<tr>
<th>CPT Codes ®</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>38204</td>
<td>38205</td>
</tr>
<tr>
<td>38212</td>
<td>38213</td>
</tr>
<tr>
<td>38240</td>
<td>38241</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation, and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative services; and the number of days of pre and post-transplant care in the global definition</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICD-10-CM Diagnosis Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C91.00</td>
<td>Acute lymphoblastic leukemia not having achieved remission</td>
</tr>
<tr>
<td>C91.01</td>
<td>Acute lymphoblastic leukemia, in remission</td>
</tr>
<tr>
<td>C91.02</td>
<td>Acute lymphoblastic leukemia, in relapse</td>
</tr>
</tbody>
</table>

*If applicable, please see Medicare LCD or NCD for additional covered diagnoses.*
IX. REFERENCES

13. Yanada M, Matsuo K, Suzuki T, et al. Allogeneic hematopoietic stem cell transplantation as part of postremission therapy improves survival for adult patients...
<table>
<thead>
<tr>
<th><strong>Policy Title</strong></th>
<th><strong>Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Policy Number</strong></td>
<td>MP-9.041</td>
</tr>
</tbody>
</table>


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


Other:

Mosby’s Medical, Nursing & Allied Health Dictionary 6th edition
Taber’s Cyclopedic Medical Dictionary 21st edition

X. POLICY HISTORY

<table>
<thead>
<tr>
<th>MP 9.041</th>
<th>CAC 5/20/14 Minor. Information on HCST for Acute Lymphoblastic Leukemia extracted from MP 9.037 Autologous and Allogeneic Stem Cell Transplantation (which was retired) and this new separate policy created. No change to policy statements. References updated. Policy guidelines and rationale sections added. Policy coded.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC 6/2/15 Consensus review. No changes to the policy statements. References and rationale updated. No changes in coding.</td>
</tr>
<tr>
<td></td>
<td>1/1/17 Administrative-variations reformatted.</td>
</tr>
<tr>
<td></td>
<td>CAC 5/23/17 Consensus review. No changes to the policy statements. Background, rationale and references updated. Coding reviewed.</td>
</tr>
</tbody>
</table>