



# Louisiana

## Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

**Policy #** 00048

**Original Effective Date:** 01/28/2002

**Current Effective Date:** 09/19/2018

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services Are Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

### **Children**

Based on review of available data, the Company may consider *allogeneic* or *autologous* hematopoietic cell transplantation (HCT) to treat childhood acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse to be **eligible for coverage**.

Based on review of available data, the Company may consider *autologous* or *allogeneic* hematopoietic cell transplantation (HCT) to treat childhood acute lymphoblastic leukemia (ALL) in second or greater remission or refractory acute lymphoblastic leukemia (ALL) to be **eligible for coverage**.

Based on review of available data, the Company considers *allogeneic* hematopoietic cell transplantation (HCT) to treat relapsing acute lymphoblastic leukemia (ALL) after a prior *autologous* hematopoietic cell transplantation (HCT) to be **eligible for coverage**.

### **Adults**

Based on review of available data, the Company may consider *autologous* hematopoietic cell transplantation (HCT) to treat adult acute lymphoblastic leukemia (ALL) in first complete remission but at high risk of relapse to be **eligible for coverage**.

Based on review of available data, the Company may consider *allogeneic* hematopoietic cell transplantation (HCT) to treat adult acute lymphoblastic leukemia (ALL) in first complete remission for any risk level to be **eligible for coverage**.

Based on review of available data, the Company may consider *allogeneic* hematopoietic cell transplantation (HCT) to treat adult acute lymphoblastic leukemia (ALL) in second or greater remissions, or in adults with relapsed or refractory acute lymphoblastic leukemia (ALL) to be **eligible for coverage**.

Based on review of available data, the Company may consider reduced-intensity conditioning (RIC) *allogeneic* hematopoietic cell transplantation (HCT) as a treatment of acute lymphoblastic leukemia (ALL) in patients who are in complete marrow and extramedullary first or second remission, and who, for medical

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reasons, would be unable to tolerate a standard myeloablative conditioning regimen to be **eligible for coverage**.

Based on review of available data, the Company considers *allogeneic* hematopoietic cell transplantation (HCT) to treat relapsing acute lymphoblastic leukemia (ALL) after a prior *autologous* hematopoietic cell transplantation (HCT) to be **eligible for coverage**.

### **When Services Are Considered Investigational**

*Note: Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers *autologous* hematopoietic cell transplantation (HCT) to treat adult acute lymphoblastic leukemia (ALL) in second or greater remission or those with refractory disease to be **investigational**.\*

## **Policy Guidelines**

### **Relapse Risk Prognostic Factors**

#### **Childhood Acute Lymphoblastic Leukemia**

Adverse prognostic factors in children include the following: age younger than 1 year or more than 9 years, male gender, white blood cell count at presentation above 50,000/ $\mu$ L, 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/ $\mu$ L or greater, or poor treatment response to induction therapy at 6 weeks with high risk having  $\geq$ 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 older than 35 years, leukocytosis at presentation of greater than 30,000/ $\mu$ L (B-cell lineage) or greater than 100,000/ $\mu$ L (T-cell lineage), "poor prognosis" genetic abnormalities like the Philadelphia chromosome (t[9;22]), extramedullary disease, and time to attain complete remission longer than 4 weeks.

### **Reduced-Intensity Conditioning**

Some patients for whom a conventional myeloablative allogeneic HCT could be curative may be considered candidates for reduced-intensity conditioning allogeneic HCT (see Background section). Such patients include those whose age (typically >60 years) or comorbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HSCT, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

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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.

### **Background/Overview**

#### **ACUTE LYMPHOBLASTIC LEUKEMIA**

##### **Childhood Acute Lymphoblastic Leukemia**

ALL is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years. 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. 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, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allogeneic HCT are unknown.

ALL is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified by certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse. Two of the most important factors predictive of risk are patient age and white blood cell count at diagnosis. Certain genetic characteristics of leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcomes and relapse risk are summarized in the Policy Guidelines section.

##### **Adult 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. 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

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sex, and leukocytosis at presentation of greater than 30,000/ $\mu$ L (B-cell lineage) or greater than 100,000/ $\mu$ L (T-cell lineage).

### **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 (GVHD).

The conventional (“classical”) practice of allo-HCT involves administration of cytotoxic agents (eg, 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**

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.

### **FDA or Other Governmental Regulatory Approval**

U.S. Food and Drug Administration (FDA)

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The U.S. FDA 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.

Centers for Medicare and Medicaid Services (CMS)

There is a national coverage determination (NCD) for stem cell transplantation (110.23; formerly 110.81), portions of which we highlight below:

### A. Nationally Covered Indications

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

- a) Effective for services performed on or after August 1, 1978, for the treatment of leukemia, leukemia in remission, or aplastic anemia when it is reasonable and necessary,
- b) Effective for services performed on or after June 3, 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
- c) Effective for services performed on or after August 4, 2010, for the treatment of Myelodysplastic Syndromes (MDS) pursuant to Coverage with Evidence Development (CED) in the context of a Medicare-approved, prospective clinical study.
- d) Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for multiple myeloma is covered by Medicare only for beneficiaries with Durie-Salmon Stage II or III multiple myeloma, or International Staging System (ISS) Stage II or Stage III multiple myeloma, and participating in an approved prospective clinical study that meets the criteria below. There must be appropriate statistical techniques to control for selection bias and confounding by age, duration of diagnosis, disease classification, International Myeloma Working Group (IMWG) classification, ISS stage, comorbid conditions, type of preparative/conditioning regimen, GVHD prophylaxis, donor type and cell source....
- e) Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for myelofibrosis (MF) is covered by Medicare only for beneficiaries with Dynamic International Prognostic Scoring System (DIPSSplus) intermediate-2 or High primary or secondary MF and participating in an approved prospective clinical study. All Medicare approved studies must use appropriate statistical techniques in the analysis to control for selection bias and potential confounding by age, duration of diagnosis, disease classification, DIPSSplus score, comorbid conditions, type of preparative/conditioning regimen, GVHD prophylaxis, donor type and cell source....
- f) Effective for claims with dates of service on or after January 27, 2016, allogeneic HSCT for sickle cell disease (SCD) is covered by Medicare only for beneficiaries with severe, symptomatic SCD who participate in an approved prospective clinical study....

#### II. Autologous Stem Cell Transplantation (AuSCT)

- a) Effective for services performed on or after April 28, 1989, AuSCT is considered reasonable and necessary under §1862(a)(1)(A) of the Act for the following conditions and is covered under Medicare for patients with:

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1. Acute leukemia in remission who have a high probability of relapse and who have no HLA-matched;
  2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
  3. Recurrent or refractory neuroblastoma; or,
  4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.
- b) Effective October 1, 2000, single AuSCT is only covered for Durie-Salmon Stage II or III patients that fit the following requirements:
- Newly diagnosed or responsive multiple myeloma. This includes those patients with previously untreated disease, those with at least a partial response to prior chemotherapy (defined as a 50% decrease either in measurable paraprotein [serum and/or urine] or in bone marrow infiltration, sustained for at least 1 month), and those in responsive relapse; and
  - Adequate cardiac, renal, pulmonary, and hepatic function.
- c) Effective for services performed on or after March 15, 2005, when recognized clinical risk factors are employed to select patients for transplantation, high dose melphalan (HDM) together with AuSCT is reasonable and necessary for Medicare beneficiaries of any age group with primary amyloid light chain (AL) amyloidosis who meet the following criteria:
- Amyloid deposition in 2 or fewer organs; and,
  - Cardiac left ventricular ejection fraction (EF) greater than 45%.”

### **Rationale/Source**

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

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

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### **AUTOLOGOUS AND ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION FOR CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA**

The evidence review of childhood ALL was informed by 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), HCT is considered only for those with unfavorable risk factors predictive of relapse.

Three RCTs comparing outcomes of HCT with outcomes with conventional-dose chemotherapy in children with ALL were identified subsequent to the TEC Assessment. 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 (ie, 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 autologous or allogeneic (allo-) HCT or standard chemotherapy with maintenance treatment. Similar results were observed using intention-to-treat or per-protocol analyses. However, several limitations could have affected outcomes: the relatively small numbers of patients, variations across centers in the preparative regimen used before HCT and time elapsed between CR and undertaking of assigned treatment, and use of genetic randomization based on donor availability rather than true randomization 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. 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: Autologous and Allogeneic Hematopoietic Cell Transplantation for 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 (eg, those at very high-risk of relapse or following relapse HCT), autologous HCT and allo-HCT remains a therapeutic option to manage childhood ALL.

### **AUTOLOGOUS AND ALLOGENEIC HCT FOR ADULT ALL**

The evidence review on adult ALL was informed by a 1997 TEC Assessment of autologous HCT. 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

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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. 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 vs patients without a donor who received chemotherapy or autologous HCT. Pooled evidence from patients who had high-risk disease showed an increased survival advantage for allo-HCT compared with those without a donor (HR=1.42; 95% CI, 1.06 to 1.90;  $p=0.019$ ). 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 then available supported a grade A treatment recommendation (at least 1 meta-analysis, systematic review, or RCT) that myeloablative allo-HCT would be an appropriate treatment for adult ALL in CR1 for all risk groups. 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 recommended allo-HCT over chemotherapy for adults with ALL in CR2 or beyond.

In an earlier evidence-based review (2006), ASBMT had reviewed the literature through January 2005 on use of 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 adults in CR1, although available evidence did not permit separate comparisons of high-risk and 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 with 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.

### 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

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patients in CR1, those with a HLA-identical family donor were assigned to allo-HCT (n=84); the remaining cases were randomized to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 years in CR (n=48). At a 70-month median follow-up, the trial did not detect a statistically significant difference in outcomes among all 3 arms by per-protocol or intention-to-treat analyses. PETHEMA ALL-93 trial investigators pointed out several factors that could have affected outcomes: relatively small numbers of patients; variations among centers in the preparative regimen used before HCT; differences in risk group assignment; and use of genetic randomization based on donor availability rather than true randomization 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 was addressed by the International ALL Trial, a collaborative effort conducted by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States (MRC UKALL XII/ECOG 2993). 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 allo-HCT. Patients with the Ph chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HCT. Patients who did not have a matched sibling donor or were older than 55 years (n=588) were randomized to a single autologous HCT or consolidation and maintenance chemotherapy.

In ECOG 2993, the OS rate at 5-year follow-up of all 1913 patients was 39%; it reached 53% for Ph-negative patients with a donor (n=443) compared with 45% without a donor (n=588) (p=0.01).<sup>20</sup> Analysis of Ph-negative patient outcomes by disease risk showed a 5-year OS rate of 41% among patients with high-risk ALL and a sibling donor vs 35% of high-risk patients with no donor (p=0.2). In contrast, the OS rate at 5-year follow-up was 62% among standard-risk Ph-negative patients with a donor and 52% among those with no donor, a statistically significant difference (p=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 relapse rate at 10-year follow-up was 37% following allo-HCT vs 63% without a transplant (p<0.001), demonstrating the potent graft-versus-leukemia effect with 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 high nonrelapse mortality (NRM) rate at 1 and 2 years, mostly due to GVHD and infections. At 2 years, the NRM rate was 36% among high-risk patients with a donor compared with 14% among those who did not have a donor. Among standard-risk cases, the NRM rates at 2 years were 20% in patients who underwent allo-HCT and 7% in those who received autologous HCT or continued chemotherapy.

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In a separate 2009 report on the Ph-positive patients in the ECOG 2993 trial, intention-to-treat analysis (N=158) showed 5-year OS rates of 34% (95% CI, 25% to 46%) for those who had a matched sibling donor and 25% (95% CI, 12% to 34%) for those with no donor who received consolidation and maintenance chemotherapy. 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 (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% vs 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 the direct comparison of their outcomes. The HOVON data were reanalyzed by donor availability from diagnosis to facilitate a meaningful comparison. This reanalysis showed a 5-year OS rate of 60% in standard-risk patients with a donor in the HOVON trial, which is very similar to the 62% OS rate observed in standard-risk patients with a donor in the ECOG 2993 trial. Collectively, these results suggest that patients with standard-risk ALL can expect to benefit from allo-HCT in CR1, provided the NRM risk is less than 20% to 25%.

### Observational Studies

Several recent studies have evaluated changes in survival rates over time. A 2017 multicenter clinical trial from Europe reported on 4859 adults with ALL in 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 (ie, from 1993-2002 to 2008-2012). For the period 2008 to 2012, 2-year OS rates after matched sibling donor HCT were 76% for 18- to 25-year-olds, 69% for 26- to 35-year-olds and 36- to 45-year-olds, and 60% for 46- to 55-year-olds. During that time, 2-year OS rates after unrelated donor HCT were 66% for 18- to 25-year-olds, 70% for 26- to 35-year-olds, 61% for 36- to 45-year-olds, and 62% for 46- to 55-year-olds. Also, 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

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age groups (18-24, 25-39, 40-59, 60-69, and  $\geq 70$  years old). For the most recent period (2007-2012), 5-year relative survival rates by age group were 75%, 57%, 37%, 22%, and 5%, respectively.

Pavlu et al (2017) conducted a retrospective study to examine the outcome of HCT among adults with primary refractory ALL who failed to achieve a CR after 2 or more courses of chemotherapy. Among 86 eligible patients who underwent their first HCT for primary refractory ALL between 2000 and 2012, following a median follow-up of 106 months, the probability of survival was 36% at 2 years and 23% at 5 years. At 2 and 5 years, the probability of leukemia-free survival rates were 28% and 17%, respectively, and the probability of nonrecurrence mortality rates were 20% and 29%, respectively. For 66 patients who achieved a CR (77%), the survival rates at 2 years and 5 years were 36% and 29%, respectively. The authors incorporated these findings into a scoring system that identified 3 groups (those with 2, 1, or no prognostic factors) with survival rates of 57%, 22%, and 8%, respectively.

### Donor Source

A 2011 Cochrane review evaluated the evidence for the efficacy of matched sibling stem cell donor vs no donor status for adults with ALL in CR1. 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.

### Section Summary: Autologous and Allogeneic HCT for 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 the use of allo-HCT, particularly for older patients. For adults who survive HCT, there is a significant relapse rate. The current evidence supports the use of 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.

### REDUCED-INTENSITY CONDITIONING ALLO-HCT

Use of RIC regimens has been investigated as a means to extend the substantial graft-versus-leukemia 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. 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

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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.<sup>28</sup> Despite the achievement of complete donor chimerism in 100% of patients, 28 (65%) had a 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, the 2-year rate OS was 31%, with an NRM rate of 28% and a relapse rate of 51%. In patients with HCT in CR1, the rate OS was 52%; in CR2 and CR3, the OS rate was 27%; in patients with advanced or refractory ALL, it was 20%. This evidence suggests RIC and allo-HCT have some efficacy as salvage therapy in high-risk ALL.

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. Among the 17 ALL cases, 4 were in CR2, 12 in CR3, and 1 had secondary ALL. All patients were heavily pretreated, which included previous myeloablative allo- or autologous HCT, but these treatments were not individually reported. While most data were aggregated, some survival findings were specified, showing an event-free survival rate of 35% and an OS rate of 37% at 2-year follow-up for the ALL patients. Although most patients lived only a few months after relapse or rejection, some were long-term survivors (>3 years after HCT) after further salvage treatment. Neither transplant-related mortality nor HCT-related morbidities were reported by disease. However, this evidence would suggest allo-HCT with RIC can be used in children with high-risk ALL and can facilitate long-term survival in patients with no therapeutic recourse.

Rosko et al (2017) used Center for International Blood and Marrow Transplant Research registry data to examine the effectiveness of RIC HCT in adults 55 years or older with B-cell ALL and explored prognostic

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factors associated with long-term outcomes. The authors evaluated 273 participants with B-cell ALL with disease status in CR1 (71%), CR2 or beyond (17%), and primary induction failure/relapse (11%) who underwent RIC HCT between 2001 and 2012. Among patients with available cytogenetic data, 50% were Ph-positive. The 3-year OS rate was 38% (95% CI, 33% to 44%). The 3-year cumulative incidences of nonrelapse mortality and relapse were 25% (95% CI, 20% to 31%) and 47% (95% CI, 41% to 53%), respectively.

### **Section Summary: Reduced-Intensity Conditioning Allo-HCT**

Based on the 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 allo-HCT.

### **Section Summary: Allogeneic Transplant After Failed Autologous Transplant**

Small uncontrolled case series with short-term follow-up are inadequate to draw conclusions on the effect of all-HCT after a failed autologous HCT on health outcomes in patients with ALL.

### **SUMMARY OF EVIDENCE**

For individuals who have childhood ALL in first CR1 at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, autologous HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have childhood ALL in CR1 at high-risk of relapse, remission, or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in

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second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1, subsequent remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have adult ALL in CR1 or subsequent remission or refractory ALL who receive allo-HCT, the evidence includes RCTs and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have relapsed after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which were considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

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|------------|--|
| 12/06/2001 | Medical Policy Committee review  |
| 03/25/2002 | Managed Care Advisory Council approval   |
| 06/24/2002 | Format revision. Policy addresses only Acute Lymphocytic Leukemia. Replaces High Dose Chemotherapy with Hematopoietic Stem Cell Support. |
| 03/31/2004 | Medical Director review  |
| 04/20/2004 | Medical Policy Committee review. Format revision. No changes to coverage eligibility.  |
| 04/26/2004 | Managed Care Advisory Council approval   |
| 04/05/2005 | Medical Director review  |
| 04/19/2005 | Medical Policy Committee review. Format revisions only. Coverage eligibility unchanged.  |
| 05/23/2005 | Managed Care Advisory Council approval   |
| 09/06/2006 | Medical Director review  |
| 09/20/2006 | Medical Policy Committee approval. Format changes only. Coverage eligibility unchanged.  |
| 07/11/2007 | Medical Director review  |

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07/18/2007	Medical Policy Committee approval. Format revision only. Coverage eligibility unchanged.
07/02/2008	Medical Director review
07/16/2008	Medical Policy Committee approval. No change to coverage eligibility.
07/02/2009	Medical Director review
07/22/2009	Medical Policy Committee approval. Title changed to Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia. Revised policy based on updated research.
07/01/2010	Medical Policy Committee approval.
07/21/2010	Medical Policy Implementation Committee approval. Policy statement regarding treatment of adult ALL in first complete remission but at high risk of relapse split to address allogeneic and autologous transplant separately.
07/07/2011	Medical Policy Committee approval.
07/20/2011	Medical Policy Implementation Committee approval. No change to coverage eligibility.
06/28/2012	Medical Policy Committee review.
07/27/2012	Medical Policy Implementation Committee approval. No change to coverage eligibility.
03/04/2013	Coding updated
08/01/2013	Medical Policy Committee review
08/21/2013	Medical Policy Implementation Committee approval. Revised coverage statements so that allogeneic HSCT may be considered eligible for coverage following a failed autologous HSCT in children or adult patients.
09/04/2014	Medical Policy Committee review
09/17/2014	Medical Policy Implementation Committee approval. No change to coverage.
09/03/2015	Medical Policy Committee review
09/23/2015	Medical Policy Implementation Committee approval. No change to coverage.
09/08/2016	Medical Policy Committee review
09/21/2016	Medical Policy Implementation Committee approval. No change to coverage.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
09/07/2017	Medical Policy Committee review
09/20/2017	Medical Policy Implementation Committee approval. The word stem was removed from title and body of policy.
09/06/2018	Medical Policy Committee review
09/19/2018	Medical Policy Implementation Committee approval. No change to coverage.
Next Scheduled Review Date:	09/2019

### **Coding**

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	38204, 38205, 38206, 38207, 38208, 38209, 38210, 38211, 38212, 38213, 38214, 38215, 38230, 38240, 38241, 38242, 38243
HCPCS	S2140, S2142, S2150
ICD-10 Diagnosis	C91.00-C91.02

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  - 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  - 3. Reference to federal regulations.

\*\*Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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