**Policy Statement**

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

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

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

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

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

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

Autologous HCT is investigational to treat adult ALL in second or greater remission or those with refractory disease.

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

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 section), would be unable to tolerate a standard myeloablative conditioning regimen.

**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 sex, white blood cell count at presentation above 50,000/µL, hypodiploidy (<45 chromosomes), translocation involving chromosomes 9 and 22 (t(9;22)) or BCR-ABL fusion, translocation involving chromosomes 4 and 11 (t(4;11)) or MLL-AF4 fusion, and ProB or T-lineage immunophenotype. Several risk-stratification schema exist, but, in general, the following findings help define children at high-risk of relapse: (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% or higher 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 30000/µL (8-cell lineage) or greater than 100000/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 hematopoietic cell transplantation (HCT) could be curative may be considered candidates for reduced-intensity conditioning allogeneic HCT (see Background section). Such patients include those whose age (typically greater than 60 years) or comorbidities (e.g., liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HCT, low Karnofsky Performance Status score) preclude the 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 one locus are also considered suitable donors. A matched, unrelated donor identified through the National Marrow Donor Registry is typically the next option considered. Recently, there has been interest in haploidentical donors, typically a parent or a child of the patient, where usually there is sharing of only three of the six major histocompatibility antigens. Most patients will have such a donor. The risk of morbidity (e.g., graft-versus-host disease) may be higher than with HLA-matched donors; however, as medical treatments improve, the risks of graft-versus-host disease with haploidentical donors are approaching those similar to HLA-matched donors.

Description
Acute lymphoblastic leukemia (ALL) is a heterogeneous disease with different genetic variations resulting in distinct biologic subtypes. Patients are stratified to risk-adapted therapy according to certain clinical and genetic risk factors that predict an outcome. Therapy may include hematopoietic cell transplantation (HCT).

Related Policies

- BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia

Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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
Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

Research, under Code of Federal Regulation, title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

Rationale

Background

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. Remission of disease is now typically achieved with pediatric chemotherapy regimens in 98% 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 the first relapse is related to the length of the original remission. For example, leukemia-free survival is 40% to 50% for children whose first remission was longer than 3 years compared with 10% to 15% for those who relapse less than 3 years after treatment. Thus, hematopoietic cell transplantation (HCT) may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allogeneic HCT (allo-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 an 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 ALL

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve a complete response 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 vs childhood ALL help, in part, explain differences in outcomes between the two groups. For example, the “good prognosis” genetic abnormalities, such as hyperdiploidy and translocation of chromosomes 12 and 21, are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities such as the Philadelphia chromosome (translocation of chromosomes 9 and 22) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of greater than 30000/μL (B-cell lineage) or greater than 100000/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 the
subsequent graft-vs-malignancy effect that develops after engraftment of allogeneic stem cells within the patient's bone marrow space. While the slower graft-versus-malignancy effect is considered to be the potentially curative component, it may be overwhelmed by extant disease without the use of pretransplant conditioning. However, intense conditioning regimens are limited to patients who are sufficiently fit medically to tolerate substantial adverse effects that include pre-engraftment opportunistic infections secondary to loss of endogenous bone marrow function and organ damage and failure caused by the cytotoxic drugs. Furthermore, in any allo-HCT, immune suppressant drugs are required to minimize graft rejection and graft-versus-host disease, which also increases the 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 radiotherapy that 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 when the beneficial graft-versus-malignancy effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of nonrelapse mortality 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.

Literature Review
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 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.

Autologous and Allogeneic hematopoietic cell transplantation for Childhood ALL
Clinical Context and Test Purpose
The purpose of HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in children with ALL.

The question addressed in this evidence review is: does the use of HCT improve the net health outcomes of children with ALL?
The following PICOTS were used to select literature to inform this review.

**Patients**
The relevant population of interest are children with ALL.

**Interventions**
The therapy being considered is autologous and (allo-) HCT.

**Comparators**
Comparators of interest include conventional-dose chemotherapy.

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

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

**Setting**
Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

**Study Selection Criteria**
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

The evidence review of childhood ALL was informed by Blue Cross Blue Shield Association Technology Evaluation Center (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 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 (i.e., from treatment-related toxicity).

A 2007 randomized trial (PETHEMA ALL-93; n=106) demonstrated no significant differences in disease-free survival or OS rates at a median follow-up of 78 months in children with very high-risk ALL in CR1 who received autologous or 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.[11] The systematic review identified ten studies comparing HCT with chemotherapy for patients in CR1, including the PETHEMA trial. Reviewers identified a subset of patients at high-risk for whom allo-HCT would be indicated. Reviewers also identified 12 studies comparing HCT with chemotherapy for patients in second (CR2) or beyond, or relapsed disease.

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

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

The question addressed in this evidence review is: does the use of HCT improve the net health outcomes of adults with ALL?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest are adults with ALL.

Interventions
The therapy being considered is autologous and allo-HCT.

Comparators
Comparators of interest include conventional-dose chemotherapy.

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

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

Setting
Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

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

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

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

A meta-analysis by Yanada et al (2006) pooled evidence from 7 studies of allo-HCT published between 1994 and 2005 that included a total of 1274 patients with ALL in CR1. Results showed that, regardless of risk category, allo-HCT was associated with a significantly longer OS (hazard ratio, 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 (hazard ratio=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.

The ASBMT (2012) 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 one 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, the ASBMT indicated a grade A treatment recommendation for autologous HCT in patients who did not have a suitable allogeneic stem cell donor; the ASBMT suggested that although survival outcomes appeared similar between autologous HCT and post-remission chemotherapy, the shorter treatment duration with the former is an advantage. Finally, the ASBMT recommended allo-HCT over chemotherapy for adults with ALL in CR2 or beyond.

In an earlier evidence-based review (2006), the 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 three RCTs, the 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.

An individual patient data meta-analysis by Gupta et al (2013) 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**

Ribera et al (2005) reported results from the multicenter (35 Spanish hospitals), randomized PETHEMA ALL-93 trial (n=222 patients), which was published after the ASBMT literature search. Among 183 high-risk patients in CR1, those with a human leukocyte antigen–identical family donor were assigned to allo-HCT (n=84); the remaining cases were randomized to autologous HCT (n=50) or to delayed intensification followed by maintenance chemotherapy up to 2 years in CR (n=48). At a 70-month median follow-up, the trial did not detect a statistically significant difference in outcomes among all 3 arms by per-protocol or intention-to-treat analyses. PETHEMA ALL-93 trial investigators pointed out several factors that could have affected outcomes: relatively small numbers of patients; variations among centers in the preparative regimen used before HCT; differences in risk group assignment; and use of genetic randomization based on donor availability rather than true randomization for patients included in the allo-HCT arm.

While the utility of allo-HCT for post-remission therapy in patients with high-risk ALL has been established, its role in standard-risk patients has been less clear. This question was addressed by the International ALL Trial, a collaborative effort conducted by the Medical Research Council (MRC) in the United Kingdom and the Eastern Cooperative Oncology Group (ECOG) in the United States (MRC UKALL XII/ECOG 2993). 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 a human leukocyte antigen-matched sibling donor (n=443) were assigned to allo-HCT. Patients with the Ph chromosome (n=267) who did not have a matched sibling donor could receive an unrelated donor HCT. Patients who did not have a matched sibling donor 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). 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 the standard-risk disease who underwent allo-HCT, the relapse rate was 24% at 10 years compared with 49% among those who did not undergo HCT (p<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 post-remission allo-HCT in standard-risk Ph-negative patients, an effect previously not demonstrated in numerous smaller studies. Failure to demonstrate a significant OS benefit in high-risk Ph-negative cases can be attributed to high nonrelapse mortality (NRM) rate at 1 and 2 years, mostly due to graft-versus-host-disease (GVHD) and infections. At 2 years, the NRM rate was 36% among high-risk patients with a donor compared with 14% among those who did not have a donor. Among standard-risk cases, the NRM rates at 2 years were 20% in patients who underwent allo-HCT and 7% in those who received autologous HCT or continued chemotherapy.

In a separate 2009 report on the Ph-positive patients in the ECOG 2993 trial, intention-to-treat analysis (n=158) showed 5-year OS rates of 34% (95% CI, 25% to 46%) for those who had a matched sibling donor and 25% (95% CI, 12% to 34%) for those with no donor who received consolidation and maintenance chemotherapy.21 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 a human leukocyte antigen-matched sibling donor, irrespective of risk category.22 The 433 eligible patients included 288 who were younger than 55 years, in CR1, and eligible to receive consolidation treatment using autologous HCT or allo-HCT. Allo-HCT was performed in 91 (95%) of 96 with a compatible sibling donor. OS rates at 5-year follow-up were 61% among all patients with a donor and 47% among those without a donor (p=0.08). The cumulative incidences of relapse at 5-year follow-up among all patients were 24% in those with a donor and 55% in those (n=161) without a donor (p<0.001). Among patients stratified by disease risk, those in the standard-risk category with a donor (n=50) had a 5-year OS rate of 69% and a relapse rate at 5 years of 14% compared with 49% and 52%, respectively, among those (n=88) without a donor (p=0.05). High-risk patients with a donor (n=46) had a 5-year OS rate of 53% and relapse rate at 5 years of 34% 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 CR1 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 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 60% for 46- to 55-year-olds. During that time, 2-year OS rates after unrelated donor HCT were 66% for 18- to 25-year-olds, 70% for 26- to 35-year-olds, 61% for 36- to 45-year-olds, and 62% for 46- to 55-year-olds. Also Dinmohamed et al (2016) reviewed survival trends among adults with ALL who underwent HCT between 1989 and 2012. Data were available on 1833 patients. Survival rates increased significantly over time in all age groups (18-24, 25-39, 40-69, ≥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 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 nonrelapse 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 (hazard ratio = 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, 0.53; 95% CI, 0.37 to 0.76; p < 0.001) and significantly increased NRM (relative risk = 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 post-remission therapy in adults.

**Section Summary: Autologous and Allogeneic HCT for Adult ALL**

The evidence indicates post-remission 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 have been investigated as a means to extend the substantial graft-versus-leukemia effect of post-remission allo-HCT to patients who could expect to benefit from this approach but who are ineligible or would not tolerate a fully myeloablative procedure.

A meta-analysis by Abdul Wahid et al (2014) included data from 5 studies in which RIC (n=528) was compared with myeloablative conditioning regimens (n=2489) in adults with ALL who received a allo-HCT mostly in CR1.27 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 multicenter, single-arm study (Gutierrez-Aguirre et al, 2007) 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.28 Despide the achievement of complete donor chimerism in 100% of patients, 28 (65%) had a leukemic relapse, with 67% ultimately dying.

A registry-based study by Mohty et al (2008) included 97 adults (median age, 38 years; range, 17-65 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).29 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 prospective phase 2 study (Cho et al, 2009) 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 Kafosky Performance Status score (<50%), or the presence of infection.30 Patients received stem cells from a matched sibling (n=27) or matched unrelated donor (n=10). Post-remission RIC consisted of fludarabine and melphalan, with GVHD prophylaxis (cyclosporine or tacrolimus, plus methotrexate). All Ph-positive patients also received imatinib before HCT. The 3-year cumulative incidence of relapse was 19.7% the NRM rate was 17.7%. The 3-year cumulative OS rate was 64.1% with a disease-free survival rate of 62.6% at the same point. After a median follow-up of 36 months (range, 121-96 months), 25 (67.6%) of patients were alive, 24 (96%) of whom remained in CR.

A multicenter prospective study by Pulsipher et al (2009) 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.31 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 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 NRM and relapse were 25% (95% CI, 20% to 31%) and 47% (95% CI, 41% to 53%), respectively.

**Section Summary: RIC 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**

**Clinical Context and Test Purpose**

The purpose of allo-HCT is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with ALL who relapse after a prior autologous HCT.

The question addressed in this evidence review is: does the use of allo-HCT improve the net health outcomes of patients with ALL who relapse after a prior autologous HCT?

The following PICOTS were used to select literature to inform this review.

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

**Interventions**
The therapy being considered is allo-HCT.

**Comparators**
Comparators of interest include conventional-dose chemotherapy.

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

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

**Setting**
Patients are actively managed by hematologists/oncologists in an inpatient and outpatient clinical setting.

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

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 is inadequate to draw conclusions on the effect of allo-HCT after a failed autologous HCT on health outcomes in patients with ALL.
Summary of Evidence
For individuals who have childhood ALL in first CR1 at high-risk of relapse, remission, or refractory ALL who receive autologous HCT, the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in CR2 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 ASBMT. 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 allogeneic HCT (allo-HCT), the evidence includes RCTs and systematic reviews. The relevant outcomes are OS, DSS, and TRM and morbidity. For children with high-risk ALL in CR1 or with relapsed ALL, studies have suggested that allo-HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, allo-HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the 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. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of autologous HCT for adults with high-risk ALL in CR1, whose health status is sufficient to tolerate the procedure. The evidence is sufficient to determine that the technology results in 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. The relevant outcomes are OS, DSS, and TRM and morbidity. Current evidence supports the use of myeloablative allo-HCT for adults with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. The evidence is sufficient to determine that the technology results in 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. The relevant outcomes are OS, DSS, and TRM and morbidity. Evidence reviews have identified only small case series with short-term follow-up, which was considered inadequate evidence of benefit. The evidence is insufficient to determine the effects of the technology on health outcome.

Allo-HCT after failed autologous HCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input has supported the use of allo-HCT to treat relapsing ALL after a failed, prior autologous HCT, particularly with reduced-intensity conditioning regimens, in adults or children. Thus, this indication may be considered medically necessary.

Supplemental Information
Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate
In response to requests from Blue Cross Blue Shield Association, input was received from 1 medical society, 2 academic medical centers, and 3 physicians from Blue Distinction Centers in 2013. In general, input supported most existing policy statements. However, most reviewers disagreed that allogeneic hematopoietic cell transplantation (allo-HCT) is considered investigational to treat relapsing acute lymphoblastic leukemia (ALL) after a prior autologous HCT in either children or adults. Given a scarcity of evidence on this topic, with no substantial trials likely to be forthcoming, and that reduced-intensity conditioning allogeneic HCT is considered medically necessary to treat ALL in second or greater remission or relapsed or refractory ALL, the policy statements were revised to medical necessity for this indication in children and adults.

Practice Guidelines and Position Statements
National Comprehensive Cancer Network
Current National Comprehensive Cancer Network guidelines (v.1.2018) for ALL indicate allo-HCT is appropriate for consolidation treatment of most poor risk (e.g., the Philadelphia chromosome-positive, relapsed, or refractory) patients with ALL. The guidelines state that for appropriately fit older adults with ALL who are achieving remission, “consideration of autologous or reduced-intensity allogeneic stem cell transplantation may be appropriate.” In addition, the guidelines note that chronologic age is not a good surrogate for fitness for therapy and that patient should be evaluated on an individual basis.

American Society for Blood and Marrow Transplantation
The guidelines from the American Society for Blood and Marrow Transplantation (2015) were published on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on the use of HCT in and out of the clinical trial setting. Recommendations on ALL are listed in Table 1.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Children (Age &lt;18 Years)</th>
<th>Adults (Age ≥18 Years)</th>
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<tr>
<td></td>
<td>Allogeneic HCT</td>
<td>Autologous HCT</td>
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<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>
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</table>

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 a national coverage determination for stem cell transplantation (110.23; formerly 110.81), portions of which are highlighted below:
Nationally Covered Indications
  1. “Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)
     a) Effective ... 1978, for the treatment of leukemia, leukemia in remission, or a plastic anemia when it is reasonable and necessary,
     b) Effective ... 1985, for the treatment of severe combined immunodeficiency disease (SCID) and for the treatment of Wiskott-Aldrich syndrome.
     c) Effective ... 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, graft vs. host disease (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, graft vs. host disease (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 ... 1989, AuSCT is considered reasonable and necessary ... for the following conditions and is covered under Medicare for patients with:
   1. Acute leukemia in remission who have a high probability of relapse and who have no human leucocyte antigens (HLA)-matched;
   2. Resistant non-Hodgkin's lymphomas or those presenting with poor prognostic features following an initial response;
   3. Recurrent or refractory neuroblastoma; or,
   4. Advanced Hodgkin's disease who have failed conventional therapy and have no HLA-matched donor.

b. Effective ... 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 ... 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%.”

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
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<td>NCT01597778</td>
<td>A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated</td>
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<td>NCT03314974</td>
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<td>40</td>
<td>Nov 2023</td>
</tr>
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</table>

NCT: national clinical trial.

References


33. 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.

**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- Referring physician history and physical
- Bone marrow transplant consultation report and/or progress notes documenting:
  - Diagnosis (including disease staging) and prognosis
  - Synopsis of alternative treatments performed and results
  - Specific transplant type being requested
- Surgical consultation report and/or progress notes
- Results of completed transplant evaluation including:
  - Clinical history
  - Specific issues identified during the transplant evaluation
  - Consultation reports/letters (when applicable)
  - Correspondence from referring physicians (when applicable)
  - Identification of donor for allogeneic related bone marrow/stem cell transplant (when information available)
• Medical social service/social worker and/or psychiatric (if issues are noted) evaluations including psychosocial assessment or impression of patient’s ability to be an adequate candidate for transplant
• Radiology reports including:
  o Chest x-ray (CXR)
  o PET scan, CT scan and bone survey (as appropriate)
• Cardiology procedures and pulmonary function reports:
  o EKG
  o Echocardiogram
  o Pulmonary function tests (PFTs)
• Biopsy/Pathology reports including:
  o Bone marrow biopsy
  o Lymph node biopsy (as appropriate)
• Laboratory reports

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

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<td>38207</td>
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<td>Transplant preparation of hematopoietic progenitor cells; thawing of previously frozen harvest, without washing, per donor</td>
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### Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

#### Type

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#### ICD-10 Procedure

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</table>

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>01/07/2011</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>04/04/2014</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>06/01/2016</td>
<td>Policy title change from Hematopoietic Stem-Cell Transplantation for Acute Lymphoblastic Leukemia</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/01/2018</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>03/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>03/01/2019</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>
Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Transplant Case Management Department. Please call 1-800-637-2066 ext. 3507708 or visit the Provider Portal www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.