Medical Policy
Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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Policy Number: 076
BCBSA Reference Number: 8.01.32
NCD/LCD: N/A

Related Policies
BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia, #612

Policy
Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

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.

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

Allogeneic HCT is considered MEDICALLY NECESSARY to treat relapsing ALL after a prior autologous HCT.

Relapse Risk Prognostic Factors
Childhood ALL
Adverse prognostic factors in children include the following: age younger than 1 year or more than 9 years, male gender, white blood cell (WBC) count at presentation above 50,000/μL, hypodiploidy (<45 chromosomes), t(9;22) or BCR/ABL fusion, t(4;11) or MLL/AF4 fusion, and ProB or T-lineage immunophenotype. Several risk stratification schema exist, but, in general, the following findings help define children at high risk of relapse: (1) poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/μL or greater, or poor treatment response to induction therapy at 6 weeks with high risk having ≥1% minimal residual disease measured...
by flow cytometry, (2) all children with T-cell phenotype, and (3) patients with either the t(9;22) or t(4;11) regardless of early response measures.

**Adult Acute Lymphoblastic Leukemia (ALL)**

Autologous HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in first complete remission but at high risk of relapse.

Allogeneic HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in first complete remission for any risk level.

Allogeneic HCT may be considered **MEDICALLY NECESSARY** to treat adult ALL in second or greater remissions, or in patients with relapsed or refractory ALL.

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

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

Allogeneic HCT is considered **MEDICALLY NECESSARY** to treat relapsing ALL after a prior autologous HCT.

**Adult ALL**

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/ìL (B-cell lineage) or greater than 100,000/ìL (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 HSCT could be curative may be considered candidates for RIC allogeneic HCT (see Description section). These 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.

The ideal allogeneic donors are HLA-identical siblings, matched at the HLA-A, B, and DR loci (6 of 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 GVHD and overall morbidity of the procedure may be severe, and experience with these donors is not as extensive as that with matched donors.

**Prior Authorization Information**

Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.

Yes indicates that prior authorization is required.

No indicates that prior authorization is not required.

N/A indicates that this service is primarily performed in an inpatient setting.
### Outpatient

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage</th>
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<tr>
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</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
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</tr>
<tr>
<td>Medicare HMO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
<td>N/A</td>
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<tr>
<td>Medicare PPO Blue&lt;sup&gt;SM&lt;/sup&gt;</td>
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</tr>
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</table>

**CPT Codes / HCPCS Codes / ICD Codes**

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The above medical necessity criteria MUST be met for the following codes to be covered for Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:

#### CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>38205</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; allogeneic</td>
</tr>
<tr>
<td>38206</td>
<td>Blood-derived hematopoietic progenitor cell harvesting for transplantation, per collection; autologous</td>
</tr>
<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38232</td>
<td>Bone marrow harvesting for transplantation; autologous</td>
</tr>
<tr>
<td>38240</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; allogeneic</td>
</tr>
<tr>
<td>38241</td>
<td>Bone marrow or blood-derived peripheral stem-cell transplantation; autologous</td>
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</table>

#### HCPCS Codes

<table>
<thead>
<tr>
<th>HCPCS codes:</th>
<th>Code Description</th>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived peripheral stem-cell harvesting and transplantation, allogeneic or autologous, including pheresis, high-dose chemotherapy, and the number of days of post-transplant care in the global definition (including drugs; hospitalization; medical surgical, diagnostic and emergency services)</td>
</tr>
</tbody>
</table>

#### ICD-9 Procedure Codes

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<tr>
<th>ICD-9-CM procedure codes:</th>
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<tr>
<td>41.00</td>
<td>Bone marrow transplant, not otherwise specified</td>
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<tr>
<td>41.01</td>
<td>Autologous bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.02</td>
<td>Allogeneic bone marrow transplant with purging</td>
</tr>
<tr>
<td>41.03</td>
<td>Allogeneic bone marrow transplant without purging</td>
</tr>
<tr>
<td>41.04</td>
<td>Autologous hematopoietic stem cell transplant without purging</td>
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<tr>
<td>41.05</td>
<td>Allogeneic hematopoietic stem cell transplant without purging</td>
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<tr>
<td>ICD-10-PCS procedure codes:</td>
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<tr>
<td>30233G0</td>
<td>Transfusion of Autologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30233G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243G1</td>
<td>Transfusion of Nonautologous Bone Marrow into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30263G0</td>
<td>Transfusion of Autologous Bone Marrow into Central Artery, Percutaneous Approach</td>
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<tr>
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<td>Transfusion of Nonautologous Bone Marrow into Central Artery, Percutaneous Approach</td>
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<td>Introduction of Other Antineoplastic into Peripheral Vein, Percutaneous Approach</td>
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<td>3E04305</td>
<td>Introduction of Other Antineoplastic into Central Vein, Percutaneous Approach</td>
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<td>3E05305</td>
<td>Introduction of Other Antineoplastic into Peripheral Artery, Percutaneous Approach</td>
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<tr>
<td>3E06305</td>
<td>Introduction of Other Antineoplastic into Central Artery, Percutaneous Approach</td>
</tr>
<tr>
<td>30233Y0</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>30243Y0</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30233Y1</td>
<td>Transfusion of Autologous Hematopoietic Stem Cells into Peripheral Vein, Percutaneous Approach</td>
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<tr>
<td>30243Y1</td>
<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
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<td>Transfusion of Nonautologous Hematopoietic Stem Cells into Central Artery, Percutaneous Approach</td>
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<tr>
<td>30233X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Peripheral Vein, Percutaneous Approach</td>
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<td>Transfusion of Nonautologous Cord Blood Stem Cells into Central Vein, Percutaneous Approach</td>
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<tr>
<td>30263X1</td>
<td>Transfusion of Nonautologous Cord Blood Stem Cells into Central Artery, Percutaneous Approach</td>
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**Description**

Immunologic compatibility between infused hematopoietic cells and the recipient is not an issue in autologous hematopoietic cell transplantation (HCT). However, immunologic compatibility between donor and patient is a critical factor for achieving a good outcome with allogeneic HCT (allo-HCT). Compatibility is established by typing of human leukocyte antigen (HLA) using cellular, serologic, or molecular techniques. HLA refers to the tissue type expressed at the HLA-A, -B, and -DR (antigen-D related) loci on each arm of chromosome 6. Depending on the disease being treated, an acceptable donor will match the patient at all or most of the HLA loci (with the exception of umbilical cord blood).

**Conventional Preparative Conditioning for HCT**
The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient before undergoing bone marrow ablation. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient's disease is in complete remission (CR). 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 (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**
Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less intense regimens of cytotoxic drugs or radiation than are used in conventional full-dose myeloablative conditioning treatments. The goal of RIC is to reduce disease burden and to minimize as much as possible associated treatment-related morbidity and nonrelapse mortality (NRM) when the beneficial GVM effect of allogeneic transplantation develops. Although the definition of RIC remains arbitrary, with numerous versions employed, all seek to balance the competing effects of NRM and relapse due to residual disease. RIC regimens can be viewed as a continuum of effects, from nearly totally myeloablative, to minimally myeloablative with lymphoablation, with intensity tailored to specific diseases and patient condition. Patients who undergo RIC with allo-HCT initially demonstrate donor cell engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual malignant cells. For this evidence review, RIC will refer to all conditioning regimens intended to be nonmyeloablative, as opposed to fully myeloablative (conventional) regimens.

**Acute Lymphoblastic Leukemia**

**Childhood Acute Lymphoblastic Leukemia**

Acute lymphoblastic leukemia (ALL) is the most common cancer diagnosed in children; it represents nearly 25% of cancers in children younger than 15 years.\(^1\) CR of disease is now typically achieved with pediatric chemotherapy regimens in 95% of children with ALL, with up to 85% long-term survival rates. Survival rates have improved with the identification of effective drugs and combination chemotherapy through large randomized trials, integration of presymptomatic central nervous system prophylaxis, and intensification and risk-based stratification of treatment.\(^2\) The prognosis after first relapse is related to the length of the original remission. For example, leukemia-free survival is 40% to 50% for children whose first remission was longer than 3 years compared to only 10% to 15% for those who relapse less than 3 years after treatment. Thus, HCT may be a strong consideration in those with short remissions. At present, the comparative outcomes with autologous or allo-HCT are unknown.

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

**Adult Acute Lymphoblastic Leukemia**

ALL accounts for 20% of acute leukemias in adults. Between 60% and 80% of adults with ALL can be expected to achieve CR after induction chemotherapy; however, only 35% to 40% can be expected to survive 2 years.⁴ Differences in the frequency of genetic abnormalities that characterize adult ALL versus childhood ALL help, in part, explain the outcome differences between the 2 groups. For example, the “good prognosis” genetic abnormalities, such as hyperdiploidy and t(12;21), are seen much less commonly in adult ALL, whereas they are some of the most common in childhood ALL. Conversely, “poor prognosis” genetic abnormalities such as the Philadelphia chromosome (t[9;22]) are seen in 25% to 30% of adult ALL but infrequently in childhood ALL. Other adverse prognostic factors in adult ALL include age greater than 35 years, poor performance status, male sex, and leukocytosis at presentation of greater than 30,000/μL (B-cell lineage) or greater than 100,000/μL (T-cell lineage).

Note: The use of killer cells in the treatment of malignancies is addressed separately (policy #455 [adoptive immunotherapy]).

**Summary**

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

The evidence for autologous or allogeneic HCT (allo-HCT) in individuals who have childhood ALL in first complete remission but at high risk of relapse, or in second or greater remission, or with refractory ALL, includes randomized controlled trials (RCTs) and an evidence-based systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Studies suggest that while overall survival did not differ significantly after HCT compared with conventional-dose chemotherapy in most children with standard-risk ALL, HCT remains a therapeutic option for patients considered at high risk of relapse. This conclusion is further supported by an evidence-based systematic review of the literature sponsored by the American Society for Blood and Marrow Transplantation.

The evidence for autologous or allo-HCT in individuals who have adult ALL in first complete remission but at high risk of relapse, or in second or greater remission, or with refractory ALL, includes RCTs and an evidence-based systematic review. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Current evidence and clinical guidelines support the use of autologous HCT for adult patients with high-risk ALL in CR1, or myeloablative allo-HCT for adult patients with any risk level ALL, whose health status is sufficient to tolerate the procedure. Reduced-intensity conditioning (RIC) allo-HCT may be considered for patients who demonstrate complete marrow and extramedullary first or second remission and who could be expected to benefit from a myeloablative allo-HCT, but for medical reasons would not tolerate a myeloablative conditioning regimen. Additional evidence is necessary to determine whether some patients with ALL and residual disease may benefit from RIC allo-HCT.

The evidence for the use of allo-HCT individuals who have relapse after a prior autologous HCT is lacking. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. 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 supports this use, particularly with RIC regimens, in adults or children.

**Policy History**

<table>
<thead>
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<th>Date</th>
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<tr>
<td>2/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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5/2016  BCBSA National medical policy review. "Hematopoietic stem cell transplantation (HSCT)" was replaced with "hematopoietic cell transplantation (HCT)" in the policy statements and title. 5/1/2016

8/2015  Added coding language.

7/2015  New references added from BCBSA National medical policy.

5/2014  Updated Coding section with ICD10 procedure and diagnosis codes, effective 10/2015.

4/2014  Investigational indications for autologous hematopoietic stem-cell transplantation clarified; medically necessary indications for allogeneic hematopoietic stem-cell transplantation clarified.


12/2012  Updated to add new CPT code 38243.


Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References
10. Ribera JM, Ortega JJ, Oriol A, et al. Comparison of intensive chemotherapy, allogeneic, or autologous stem-cell transplantation as postremission treatment for children with very high risk


31. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Salvage high-dose chemotherapy with allogeneic stem-cell support for relapse or incomplete remission following high-dose chemotherapy with autologous stem-cell transplantation for hematologic malignancies. TEC Assessments. 2000;Volume 15:Tab 9. PMID
