Introduction

Acute lymphocytic leukemia (ALL) is a cancer that starts from a certain form of early white blood cells known as lymphocytes. One way of treating ALL is to do a hematopoietic stem cell transplant.

Hematopoietic stem cells are cells that form within the bone marrow and can become many different types of blood cells. In a hematopoietic stem cell transplant, stem cells can be taken from a donor or the patient before the patient receives high dose chemotherapy. The harvested stem cells are then given to the patient, just like in a transfusion. It is hoped that these new stem cells will then settle into the bone marrow and start producing normal blood cells. If the hematopoietic stem cells are harvested from another person, it is called an allogeneic transplant. If the cells come from the patient, it is called an autologous stem cell transplant. This policy discusses when different types of hematopoietic stem cell transplants might be medically necessary to treat ALL.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Policy Coverage Criteria

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

<table>
<thead>
<tr>
<th>Service</th>
<th>Medical Necessity</th>
</tr>
</thead>
</table>
| Autologous or allogeneic HCT for children | Autologous or allogeneic hematopoietic cell transplantation (HCT) may be considered medically necessary to treat childhood acute lymphoblastic leukemia (ALL) for ANY of the following:  
  • First complete remission (CR1) but at high risk of relapse (see Related Information for high-risk factors)  
  OR  
  • Second or greater remission (CR2 or >2)  

  Allogeneic HCT may be considered medically necessary to treat relapsing ALL after a prior autologous HCT or prior chemotherapy. |
| Autologous or allogeneic HCT for adults | Autologous hematopoietic cell transplantation (HCT) may be considered medically necessary to treat adult acute lymphoblastic leukemia (ALL) in:  
  • First complete remission (CR1) for any relapse risk level (see Related Information for risk factors)  

  Allogeneic HCT may be considered medically necessary to treat adult ALL for ANY of the following:  
  • First complete remission (CR1) for any relapse risk level  
  OR  
  • Second or greater remission (CR2 or >)  
  OR  
  • Relapsing ALL after a prior autologous HCT or prior chemotherapy |
| Reduced-intensity                | Reduced-intensity conditioning (RIC) allogeneic HCT may be |
Service | Medical Necessity
--- | ---
conditioning allogeneic HCT | considered medically necessary as a treatment of ALL in patients who are in complete marrow and extramedullary first or second remission (CR1 or 2), and who for medical reasons (see Related Information), would be unable to tolerate a standard myeloablative conditioning regimen.

Service | Investigational
--- | ---
Autologous HCT for adults | Autologous HCT is considered investigational to treat adult ALL for the following:
- Second or greater remission (CR2 or >)
OR
- Those with refractory disease

Documentation Requirements

The patient’s medical records submitted for review should document that medical necessity criteria are met. The record should include clinical documentation of:
- Diagnosis/condition
- History and physical examination documenting the severity of the condition
- Number of remissions patient has had
- Risk factors for relapse

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>CPT</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38230</td>
<td>Hematopoietic progenitor cell (HPC); allogeneic transplantation per donor</td>
</tr>
<tr>
<td>38241</td>
<td>Hematopoietic progenitor cell (HPC); autologous transplantation</td>
</tr>
<tr>
<td>HCPCS</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
</tr>
<tr>
<td>S2140</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2142</td>
<td></td>
</tr>
<tr>
<td>Code</td>
<td>Description</td>
</tr>
<tr>
<td>-------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative service; and the number of days of pre- and post-transplant care in the global definition</td>
</tr>
</tbody>
</table>

**Note:** CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

**Related Information**

**Relapse Risk Prognostic Factors**

**Childhood ALL**

Adverse prognostic factors include the following: age younger than one year or more than nine years, male gender, white blood cell count at presentation above 50,000/μL, hypodiploidy (<45 chromosomes), 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 six 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 ALL**

Risk factors for relapse are less well defined, but an adult patient with any of the following may be considered at high risk for relapse: age older than 35 years, leukocytosis at presentation of greater than 30,000/μL (B-cell lineage) or greater than 100,000/μL (T-cell lineage), “poor prognosis” genetic abnormalities like the Philadelphia chromosome (t[9;22]), extramedullary disease, and time to attain complete remission longer than 4 weeks.
Reduced Intensity Conditioning (RIC)

Some patients for whom a conventional myeloablative allogeneic hematopoietic cell transplantation (HCT) could be curative may be considered candidates for RIC allogeneic HCT. Such patients include those whose age (typically older than 60 years) or co morbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy including autologous or allogeneic HCT, low Karnofsky Performance Status) preclude use of a standard myeloablative conditioning regimen.

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

The ideal allogeneic donors are human leukocyte antigen (HLA)-identical siblings, matched at the HLA-A, -B and DR (antigen-D related) loci on each arm of the 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 (eg, 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.

Benefit Application

The following considerations may supersede this policy:

- State mandates requiring coverage for autologous bone marrow transplantation offered as part of clinical trials of autologous bone marrow transplantation approved by the National Institutes of Health.

- Some plans may participate in voluntary programs offering coverage for patients participating in clinical trials approved by the National Institutes of Health -for cancer chemotherapies, including autologous bone marrow transplantation.

- Some contracts may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.
**Evidence Review**

**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).

**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 35–40% 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 Preparative Conditioning for HCT**

The success of autologous HCT is predicated on the ability of cytotoxic chemotherapy with or without radiation to eradicate cancerous cells from the blood and bone marrow. This permits subsequent engraftment and repopulation of bone marrow space with presumably normal hematopoietic stem cells obtained from the patient prior to undergoing bone marrow ablation. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not graft-versus-host disease.

The conventional (“classical”) practice of allogeneic 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 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 allogeneic HCT, immune suppressant drugs are required to
minimize graft rejection and graft-versus-host disease, which also increases susceptibility of the
patient to opportunistic infections.

Reduced-Intensity Conditioning for Allogeneic HCT

Reduced-intensity conditioning (RIC) refers to the pretransplant use of lower doses or less
intense regimens of cytotoxic drugs or radiotherapy than are used in conventional full-dose
myeloablative conditioning treatments. The goal of RIC is to reduce disease burden, but also to
minimize as much as possible associated treatment-related morbidity and non-relapse mortality
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 in effects, from being nearly totally myeloablative, to
minimally myeloablative with lymphoablation, with intensity tailored to specific disease and
patient condition. Patients who undergo RIC with allogeneic HCT initially demonstrate donor cell
engraftment and bone marrow mixed chimerism. Most will subsequently convert to full-donor
chimerism, which may be supplemented with donor lymphocyte infusions to eradicate residual
malignant cells. For the purposes of the Policy, the term “reduced-intensity conditioning” will
refer to all conditioning regimens intended to be non-myeloablative, as opposed to fully
myeloablative (conventional) regimens.

Acute Lymphoblastic Leukemia (ALL)

Childhood ALL

ALL is the most common cancer diagnosed in children and represents almost 25% of cancers in
children younger than 15 years.1 Approximately 95% of children with ALL achieve remission with
up to 85% long-term survival rates. Survival rates have improved with the identification of
effective drugs and combination chemotherapy through large, randomized trials, integration of
pre-symptomatic central nervous system prophylaxis, and intensification and risk-based
stratification of treatment.2 The prognosis after first relapse is related to the length of the
original remission. For example, leukemia-free survival is 40% to 50% for children whose first
remission was longer than 3 years compared to only 10% to 15% for those who relapse less than
3 years after treatment. Thus, hematopoietic cell transplantation (HCT) may be a strong
consideration in those with short remissions. At present, the comparative outcomes with
autologous or allogeneic HCT are unknown.
ALL is a heterogeneous disease with different genetic alterations resulting in distinct biologic subtypes. Patients are stratified according to certain clinical and genetic risk factors that predict outcome, with risk-adapted therapy tailoring treatment based on the predicted risk of relapse. Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis. Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows:

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>1-9 years</td>
<td>&lt;1 or &gt;9 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>WBC count</td>
<td>&lt;50,000/μL</td>
<td>≥50,000/μL</td>
</tr>
<tr>
<td>Genotype</td>
<td>Hyperdiploidy (&gt;50 chromosomes)</td>
<td>Hypodiploidy (&lt;45 chromosomes)</td>
</tr>
<tr>
<td></td>
<td>t(12;21) or TEL/AML1 fusion</td>
<td>t(9;22) or BCR/ABL fusion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t(4;11) or MLL/AF4 fusion</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Common, preB</td>
<td>ProB, Tlineage</td>
</tr>
</tbody>
</table>

**Adult ALL**

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

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

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

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

For individuals who have relapse after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. Evidence reviews have identified only small case series with short term follow-up which was considered inadequate evidence of benefit. However, allo-HCT after failed auto-HCT has been shown to be of clinical benefit in other hematologic malignancies and is potentially curative. In addition, clinical input has supported use of allo-HCT to treat relapsing ALL after a failed, prior, auto-HCT particularly with RIC allo-HCT use in both adults and children. Thus, this indication may be considered medically necessary.
Ongoing and Unpublished Clinical Trials

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

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>NCT02042690</td>
<td>Haplo-identical HCT Versus Chemotherapy for Adult Acute Lymphoblastic Leukemia Patients</td>
<td>300</td>
<td>Dec 2018 (unknown)</td>
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<tr>
<td>NCT01597778</td>
<td>A Multi-Center, Phase III, Randomized Trial of Reduced Intensity Conditioning (RIC) and Transplantation of Double Unrelated Umbilical Cord Blood (dUCB) Versus HLA-Haploidentical Related Bone Marrow (Haplo) for Patients With Hematologic Malignancies</td>
<td>410</td>
<td>Jun 2020</td>
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<tr>
<td>NCT01700946</td>
<td>Therapy for Pediatric Relapsed or Refractory Precursor B-Cell Acute Lymphoblastic Leukemia and Lymphoma</td>
<td>40</td>
<td>Oct 2021</td>
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<tr>
<td>NCT03314974</td>
<td>Myeloablative Allogeneic Hematopoietic Cell Transplantation Using a Related or Unrelated Donor for the Treatment of Hematological Diseases</td>
<td>40</td>
<td>Nov 2023</td>
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<tr>
<td>NCT01949129</td>
<td>Allogeneic Stem Cell Transplantation for Children and Adolescents With Acute Lymphoblastic Leukaemia</td>
<td>1000</td>
<td>Apr 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 medical society, 2 academic medical centers, and 3 physicians from Blue Distinction Centers while this policy was under review in 2013. In general, 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 reflect this for children and adults.

Practice Guidelines and Position Statements

*National Comprehensive Cancer Network*

Current National Comprehensive Cancer Network guidelines (v.1.2018) for acute lymphoblastic leukemia indicate allogeneic HCT is appropriate for consolidation treatment of most poor-risk (eg, 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 2.

**Table 2. ASBMT Guidelines for Autologous and Allogeneic HCT**

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

<table>
<thead>
<tr>
<th>Children (Age &lt;18 Years)</th>
<th>Adults (Age ≥18 Years)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Allogeneic</td>
</tr>
<tr>
<td></td>
<td>HCT</td>
</tr>
<tr>
<td>At least third complete response</td>
<td>C</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
</tr>
</tbody>
</table>

C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

### 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**

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

   a. Effective ... 1978, for the treatment of leukemia, leukemia in remission, or aplastic 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%.

**Regulatory Status**

The U.S. Food and Drug Administration regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation title 21, parts 1270 and 1271. Hematopoietic stem cells are included in these regulations.

**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.


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>06/27/00</td>
<td>Add to Therapy Section - New Policy — replaces 8.01.15, original master policy on HDC for miscellaneous malignancies. However, policy statement is unchanged.</td>
</tr>
<tr>
<td>12/21/00</td>
<td>Replace Policy - Policy statement revised to state that allogeneic transplant after a prior failed autotransplant is considered investigational, based on 2000 Tec Assessment.</td>
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<td>06/17/03</td>
<td>Replace Policy - Policy updated w/expanded rationale and new references; policy statement unchanged.</td>
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<td>Date</td>
<td>Comments</td>
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<tr>
<td>08/12/03</td>
<td>Replace Policy - Reviewed and recommended for adoption without any changes by Company Oncology Advisory Panel July 22, 2003.</td>
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<tr>
<td>12/14/04</td>
<td>Replace Policy - Policy reviewed w/literature search; update added on clinical trials and NCCN guidelines; policy statement unchanged.</td>
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<td>01/10/06</td>
<td>Replace Policy - Policy reviewed with literature search; no change to policy statement.</td>
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<tr>
<td>06/02/06</td>
<td>Disclaimer and Scope update - No other changes</td>
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<tr>
<td>10/09/07</td>
<td>Replace Policy - Policy reviewed with BCBSA literature update through March 2007. NCI clinical trials updated; NCCN guidelines information unchanged. New references added; Policy statement unchanged.</td>
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<td>11/12/07</td>
<td>Code updated - CPT code 86817 removed as directed by RPIW.</td>
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<tr>
<td>05/13/08</td>
<td>New PR status - Policy statement regarding HDC and allogeneic SCT to treat relapsing ALL after a prior course of HDC and autologous SCT changed from investigational to medically necessary for children and adults. Reviewed and recommended by the OAP on February 21, 2008. Replaces BC.8.01.32, status changed from BC to PR.</td>
</tr>
<tr>
<td>05/12/09</td>
<td>Replace Policy - Policy revised with literature search. Clinical input received. New policy statement added that RIC allogeneic SCT may be considered medically necessary in select patients in complete remission. Policy titles changed to: “Hematopoietic Stem Cell Transplantation for Acute Lymphocytic Leukemia”. Reviewed and recommended by the OAP on February 19, 2009.</td>
</tr>
<tr>
<td>12/08/09</td>
<td>Code Update - 86817 added back to the policy.</td>
</tr>
<tr>
<td>02/09/10</td>
<td>Code Update - New 2010 codes added.</td>
</tr>
<tr>
<td>09/15/11</td>
<td>Replace Policy – Policy updated with literature review; no change in policy statement.</td>
</tr>
<tr>
<td>03/23/12</td>
<td>Replace policy. Policy updated with literature review; no change in policy statement. References added, removed and reordered. Reviewed and recommended by OAP on February 16, 2012.</td>
</tr>
<tr>
<td>08/01/12</td>
<td>Update Related Policies Titles: 8.01.21, 8.01.22, 8.01.29, 8.01.30, 8.01.31, 8.01.35, 8.01.514. Policy 8.01.507 was changed to 8.01.17.</td>
</tr>
<tr>
<td>02/01/13</td>
<td>Update Related Policies, change title of policy 8.01.21.</td>
</tr>
<tr>
<td>03/20/13</td>
<td>The following codes were removed from the policy, as they were not suspending and just informational: HCPCS J9000-J9999 and Q0083 – Q0085.</td>
</tr>
<tr>
<td>09/30/13</td>
<td>Update Related Policies. Change title to policy 8.01.31.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>10/18/13</td>
<td>Update Related Policies. Change title to policy 8.01.17.</td>
</tr>
<tr>
<td>12/03/13</td>
<td>Coding Update. Add ICD-10 codes.</td>
</tr>
<tr>
<td>02/27/14</td>
<td>Update Related Policies. Change title to 8.01.30.</td>
</tr>
<tr>
<td>03/21/14</td>
<td>Update Related Policies. Remove 8.01.514 as it was deleted.</td>
</tr>
<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and replace with 8.01.529.</td>
</tr>
<tr>
<td>07/31/14</td>
<td>Annual Review. Policy updated with literature review; no change in policy statements. Related Policies updated; only those related to leukemia remain; all others removed.</td>
</tr>
<tr>
<td>03/13/15</td>
<td>Update Related Policies. Add 8.01.01</td>
</tr>
<tr>
<td>07/14/15</td>
<td>Annual Review. Policy updated with literature search; no change to policy statement. References updated. ICD-9 and ICD-10 procedure codes removed; they were listed for informational purposes only.</td>
</tr>
<tr>
<td>07/01/16</td>
<td>Annual Review, approved June 14, 2016. Literature review. No change to policy statement. Discussion wording updated. Clinical trial reviews updated.</td>
</tr>
<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding section.</td>
</tr>
<tr>
<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
</tr>
<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT codes 38230, 38240, and 38241.</td>
</tr>
<tr>
<td>11/10/17</td>
<td>Policy moved into new format; no change to policy statements.</td>
</tr>
<tr>
<td>05/01/18</td>
<td>Annual Review, approved April 3, 2018. Policy updated with literature review through November 2017; references updated. Reference 35* added. Policy statements unchanged.</td>
</tr>
<tr>
<td>05/01/19</td>
<td>Annual Review, approved April 18, 2019. Policy updated with literature review through November 2018; no references added. Policy statements unchanged.</td>
</tr>
</tbody>
</table>

**Disclaimer**: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2019 Premera All Rights Reserved.

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PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:
U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

You can also file a grievance with the U.S. Department of Health and Human Services, Office for Civil Rights, by mail, phone, fax, or email at:
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Email AppealsDepartmentInquiries@Premera.com

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