Hematopoietic Cell Transplantation for Acute Lymphoblastic Leukemia

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 conditioning allogeneic HCT | **Reduced-intensity conditioning (RIC) allogeneic HCT may be considered medically necessary as a treatment of ALL in patients who are in complete marrow and extramedullary first** }
Service | Medical Necessity
--- | ---
Autologous HCT for adults | 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

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
</tr>
<tr>
<td>38240</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>38230</td>
<td>Bone marrow harvesting for transplantation; allogeneic</td>
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<td><strong>HCPCS</strong></td>
<td></td>
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<tr>
<td>S2140</td>
<td>Cord blood harvesting for transplantation, allogeneic</td>
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<tr>
<td>S2142</td>
<td>Cord blood-derived stem-cell transplantation, allogeneic</td>
</tr>
<tr>
<td>S2150</td>
<td>Bone marrow or blood-derived stem cells (peripheral or umbilical), allogeneic or autologous, harvesting, transplantation and related complications; including: pheresis and cell preparation/storage; marrow ablative therapy; drugs, supplies, hospitalization with outpatient follow-up; medical/surgical, diagnostic, emergency, and rehabilitative service; and the number of days of pre- and post-transplant care in the global definition</td>
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</tbody>
</table>

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Related Information

Relapse Risk Prognostic Factors

*Childhood ALL*

Adverse prognostic factors include the following: age younger than one year or older than nine years, male gender, white blood cell count at presentation above 50,000/μL, hypodiploidy (<45 chromosomes), t(9:22) or BCR/ABL fusion, t(4;11) or MLL/AF4 fusion, and ProB or T-lineage immunophenotype. Several risk stratification schema exist, but, in general, the following findings help define children at high risk of relapse: 1) poor response to initial therapy including poor response to prednisone prophase defined as an absolute blast count of 1000/μL or greater, or poor treatment response to induction therapy at six 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) are considered high risk 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 greater than 35 years, leukocytosis at presentation of >30,000/μL (B-cell lineage) and >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 HCT could be curative may be considered candidates for RIC allogeneic HCT. These include those whose age (typically older than 60 years) or co morbidities (eg, liver or kidney dysfunction, generalized debilitation, prior intensive chemotherapy, 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 HLA-identical siblings, matched at the LHA-A, B and DR loci (six of six). 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. The majority of 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.

**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 (NIH).

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

- Some contracts or certificates of coverage may include specific conditions in which autologous bone marrow transplantation would be considered eligible for coverage.

**Evidence Review**

**Description**

Hematopoietic stem-cell transplantation (HCT) refers to a procedure in which hematopoietic stem cells are infused to restore bone marrow function in cancer patients who receive bone-marrow-toxic doses of cytotoxic drugs, with or without whole-body radiation therapy. Bone-marrow stem cells may be obtained from the transplant recipient (ie, autologous HCT) or from a donor (ie, allogeneic HCT). They can be harvested from bone marrow, peripheral blood, or umbilical cord blood and placenta shortly after delivery of neonates. Although cord blood is an allogeneic source, the stem cells in it are antigenically “naïve” and thus are associated with a
lower incidence of rejection or graft-versus-host disease (GVHD). Cord blood is discussed in greater detail in a separate policy (see Related Policies).

Background

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

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 use of allogeneic HCT to treat relapsing ALL after a failed prior autologous HCT, particularly with RIC regimens, in adults or children. Thus, this indication may be considered medically necessary.

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. As a consequence, autologous HCT is typically performed as consolidation therapy when the patient’s disease is in complete remission. Patients who undergo autologous HCT are susceptible to chemotherapy-related toxicities and opportunistic infections prior to engraftment, but not GVHD.

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 (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 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 GVHD, 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 radiation 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 (NRM) in the period during which 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 in effects. They range from being nearly totally myeloablative, to minimally myeloablative with lymphoablation, with the 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.\(^3\) Two of the most important factors predictive of risk are patient age and white blood cell count (WBC) at diagnosis.\(^3\) Certain genetic characteristics of the leukemic cells strongly influence prognosis. Clinical and biologic factors predicting clinical outcome can be summarized as follows\(^2\):

<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) t(12;21) or TEL/AML1 fusion</td>
<td>Hypodiploidy (&lt;45 chromosomes) t(9;22) or BCR/ABL fusion t(4;11) or MLL/AF4 fusion</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>Common, preB</td>
<td>ProB, T lineage</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.\(^4\) 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, subsequent remission, or refractory ALL who receive autologous or allogeneic hematopoietic cell transplantation (HCT), the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. For children with high risk ALL in first complete remission (CR1) or with relapsed ALL, studies have suggested that HCT is associated with fewer relapses but higher death rates due to treatment-related toxicity. However, for a subset of high-risk patients in second complete remission or beyond or with relapsed disease, HCT is a treatment option. This conclusion is further supported by an evidence-based systematic review and position statement from the American Society for Blood and Marrow Transplantation. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

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

For individuals who have relapse after a prior autologous HCT for ALL who receive allo-HCT, the evidence includes case series and systematic reviews. Relevant outcomes are overall survival, disease-specific survival, and treatment-related mortality and morbidity. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcome.

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>
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<tbody>
<tr>
<td>NCT02042690</td>
<td>Haplo-identical HCT Versus Chemotherapy for Adult Acute Lymphoblastic Leukemia Patients</td>
<td>300</td>
<td>Dec 2018</td>
</tr>
<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>
</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 provide appropriate reviewers who collaborate with and make recommendations during this process, 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, clinical 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. Evidence on this point is scare but evolving and substantial trials are likely to be slow in forthcoming. Given this background, reduced-intensity conditioning allo-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.

National Comprehensive Cancer Network Guidelines

The 2013 National Comprehensive Cancer Network clinical practice guidelines for acute lymphoblastic leukemia indicate allogeneic HCT is appropriate for consolidation treatment of most poor-risk (eg, Ph1+, relapsed or refractory) patients with ALL. These guidelines are
generally consistent with this policy. However, the NCCN guidelines now stratify treatment according to the categories of adolescent and young adult (age 15-39 years) and adult (age 40 or more years), rather than the more traditional categories of children (18 years or younger) and adults (18 or more years).

**American Society for Blood and Marrow Transplantation**

In 2015, the American Society for Blood and Marrow Transplantation published guidelines on indications for autologous and allogeneic HCT. Recommendations were intended to describe the current consensus on the use of HCT within and outside 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>Allogeneic HCT</th>
<th>Autologous HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>First complete response, standard risk</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>First complete response, high risk</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>Second complete response</td>
<td>S</td>
<td>N</td>
</tr>
<tr>
<td>At least third complete response</td>
<td>C</td>
<td>N</td>
</tr>
<tr>
<td>Not in remission</td>
<td>C</td>
<td>N</td>
</tr>
</tbody>
</table>

ASBMT: American Society for Blood and Marrow Transplantation; C: clinical evidence available; HCT: hematopoietic cell transplantation; N: not generally recommended; S: standard of care.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**Regulatory Status**

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

References


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


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<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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<tr>
<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>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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<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</td>
</tr>
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<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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<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: &quot;Hematopoietic Stem Cell Transplantation for Acute Lymphocytic Leukemia&quot;. Reviewed and recommended by the OAP on February 19, 2009.</td>
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<td>12/08/09</td>
<td>Code Update - 86817 added back to the policy.</td>
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<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>
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<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>
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<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>
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<td>Update Related Policies. Change title to policy 8.01.31.</td>
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<td>10/18/13</td>
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<td>12/03/13</td>
<td>Coding Update. Add ICD-10 codes.</td>
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<td>03/21/14</td>
<td>Update Related Policies. Remove 8.01.514 as it was deleted.</td>
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<tr>
<td>04/18/14</td>
<td>Update Related Policies. Delete 8.01.20 and replace with 8.01.529.</td>
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<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>
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<tr>
<td>03/13/15</td>
<td>Update Related Policies. Add 8.01.01</td>
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<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</td>
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<td>Date</td>
<td>Comments</td>
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<td>------------</td>
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<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>
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<tr>
<td>09/30/16</td>
<td>Coding Update. Remove CPT 86817 from coding section.</td>
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<tr>
<td>11/04/16</td>
<td>Coding update. Removed codes that are transplant benefit related.</td>
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<tr>
<td>06/09/17</td>
<td>Coding update; updated description for CPT codes 38230, 38240, and 38241.</td>
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<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>
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**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). ©2018 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
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  - Information written in other languages

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Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can also 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:

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Oromo (Cushite):

Français (French):

Kreyòl ayisyen (Creole):
Avi sila a gen Enfòmasyon Enpòtan Iadann. Avi sila a kapab genyen enfòmasyon enpòtan konsènan aplikasyon y’i lan oswa konvènt kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou pran kék aksyon avan sèten dat limit pou ka kenbe kouvèti asirans sante w la oswa pou yo ka ede w avèk depans yo. Se dwa w pou resewva enfòmasyon sa a ak asistans nan lang ou pa pale a, san ou pa gen pou peye pou pe sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

Deutsche (German):

Hmoob (Hmong):

Ilokano (Ilocano):
Daytoy a Pakdaar ket naglaon iti Napateg nga Impormasion. Daytoy a pakdaar mabal hag tiitad ket naglaon nga ita napateg nga impormasion maipanggepp iti aplikasyon yonno coverage baban iti Premera Blue Cross. Daytoy ket mabal dagiti importante a palsa iti daytoy a pakdaar. Mabal hag tiitad nga adda rumbeng a hag aramidenyo nga ita adda sakbay dagiti partikular a naitading nga adlaw tapno mapagtalainedyo ti coverage ti salun-atyo wenno tulong kadagiti gastos. Adda karbenganyo a mangala iti daytoy nga impormasion ken tulong iti bukodyo a pagasao nga awan ti bayadanyo. Tumawag ti numero nga 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要的日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請接電話 800-722-1471 (TTY: 800-842-5357)。

037338 (07-2016)
Este Aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

ไทย (Thai):
ประกาศนี้มีข้อมูลที่สำคัญเกี่ยวกับการขอสินไหมทดแทนประกันสุขภาพของคุณด้วย Premera Blue Cross และให้คุณรู้สึกว่าคุณควร notas in the paunawa. เพื่อจะรักษาการประกันสุขภาพของคุณหรือการช่วยเหลือที่มีค่าใช้จ่าย โปรดติดต่อ 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В этом уведомлении могут быть ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

Español (Spanish):
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud de cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Português (Portuguese):
Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir datas importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde e ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e em custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Polski (Polish):
To ogłoszenie może zawierać ważne informacje. To ogłoszenie może zawierać ważne informacje odnośnie Polski wizyty lub zakresu świadczeń poprzez Premera Blue Cross. Prosimy zwrócić uwagę na kluczowe daty, które mogą być zawarte w tym ogłoszeniu aby nie przekroczyć terminów w przypadku utraty polisy ubezpieczeniowej lub pomocy związanej z kosztami. Macie prawo do bezpłatnej informacji we własnym języku. Zadzwoń pod 800-722-1471 (TTY: 800-842-5357).

Français (French):

日本語 (Japanese):
この通知には重要な情報が含まれています。この通知には、Premera Blue Crossの申請または補償範囲に関する重要な情報が含まれている場合があります。この通知には記載されている可能性がある重要な日付をご確認ください。健康保険や有料サポートを維持するには、特定の期間までに行動を取りなければなりません。この言語による情報とサポートが無料で提供されます。800-722-1471 (TTY: 800-842-5357)までお電話ください。

한국어 (Korean):
이 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 공통의 Premera Blue Cross를 통해 커버리지에 관한 정보를 포함하고 있습니다. 이 통지서에는 빅이 되는 날짜들이 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계획을 유지하거나 이를 점검하기 위해서 일정한 마감일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하가 이러한 정보에 도움을 귀하의 언어와 사용 부담없이 얻을 수 있는 권리가 있습니다. 800-722-1471 (TTY: 800-842-5357)로 전화하시십시오.